ADOLESCENT STRESS-SENSITIVE PERIODS AND DOPAMINE SYSTEM HYPERACTIVITY: IMPLICATIONS FOR SCHIZOPHRENIA ETIOLOGY AND PREVENTION

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Schizophrenia arises from interacting risk factors. Emerging evidence indicates childhood and adolescence are potential sensitive periods for stress to confer psychosis risks, but how early stress modulates pathophysiological factors, namely hippocampal hyperactivity and ventral tegmental area (VTA) hyperdopaminergic activity, is unclear. Current antipsychotic treatments have unmet therapeutic needs. As potential alternative treatments, the preventative efficacy of environmental enrichment (EE) and antioxidant treatment (N-acetylcysteine) have been moderately indicated in humans. In animals whether they positively modulate schizophrenia pathophysiological factors in the hippocampus and the VTA was undetermined.

Our previous study indicated that combined foot-shock and restraint stress during adolescence [postnatal day (PD) 31-40] and adulthood (PD65-74) of male rats can induce distinct activity disruptions to VTA dopamine and ventral hippocampus (vHipp) pyramidal neurons. Specifically, adolescent stress uniquely induced persistent hyperdopaminergic states, accompanied by vHipp hyperactivity and decreased markers of parvalbumin interneurons (PVIs) and their maturation (perineuronal nets). These effects contrasted with the transient hypodopaminergic state induced by adult stress, indicating stress-sensitive periods. To define the temporal boundaries of sensitive periods and elucidate sex differences, this dissertation compared consequences of prepubertal (PreP-S) and postpubertal stress (PostP-S) (at PD21-30 or PD41-50, respectively). Males were selectively vulnerable to PreP-S, exhibiting adult hyperdopaminergic activity, vHipp

hyperactivity, and vHipp PVI impairments. In contrast, females were vulnerable to PostP-S in these outcome measures. Persistent male-selective activation of the basolateral amygdala (BLA) was found after PreP-S, suggesting that PreP-S and PostP-S might engage sexually dimorphic mechanisms to lead to similar adult neurophysiological outcomes relevant to schizophrenia.

The preventative potentials of early EE and N-acetylcysteine were determined in the methylazoxymethanol acetate (MAM) model. In MAM rats, PD21-40 EE prevented VTA hyperdopaminergic activity and vHipp hyperactivity but failed to prevent anxiety and related BLA hyperactivity. PD11-25 N-acetylcysteine treatment prevented adult hyperdopaminergic states, as well as the abnormal prefrontal regulation of dopamine neurons. This effect was accompanied by prevention of PVI oxidative impairments in the thalamic reticular nucleus.

Altogether, these results suggest that stress during age- and sex-dependent adolescent sensitive periods can lead to schizophrenia-related electrophysiological alterations. Moreover, EE and N-acetylcysteine could be promising prophylactic approaches for at-risk individuals.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

8-oxo-dG	8-oxo-7, 8-dihydro-20-deoxyguanosine
3-NT	3-Nitrotyrosine
AIH	Amphetamine-Induced Hyperlocomotion
ARMS	At Risk Mental State
BLA	Basolateral Amygdala
ChABC	Chondroitinase ABC
chondroitinase ABC	Chabc
CHR	Clinical High Risk
DA	Dopamine
dPBS	Dulbecco's PBS
EE	Environmental Enrichment
EPM	Elevated Plus Maze
FEP	First Episode of Psychosis
FS	Footshock
GD	Gestational Day
GSH	Glutathione
HDAC	Histone Deacetylase
HFS	High-Frequency Electric Stimulation
Hipp	Hippocampus
HPA	Hypothalamic-Pituitary–Adrenal
ilPFC	Infralimbic PFC
LTD	Long-Term Depression
MAM	Methylazoxymethanol Acetate
NAC	N-Acetyl Cysteine
N-acetylcysteine	Nac
NOR	Novel Object Recognition
PBS	Phosphate Buffered Saline
PD	Postnatal Day
PFC	Prefrontal Cortex
PFC	Prefrontal Cortex
plPFC	Prelimbic PFC
PNN	Perineuronal Net
PNNs	Perineuronal Nets
PostP-S	Postpubertal Stress
PreP-S	Prepubertal Stress
PV	Parvalbumin
PVI	Parvalbumin Interneuron

RE	Regular Environment
RS	Restraint Stress
SAHA	Suberoylanilide Hydroxamic Acid
SAL	Saline
SN	Substantia Niagra
TRN	Thalamic Reticular Nucleus
TTX	Tetrodotoxin
UHR	Ultra-High Risk
Veh	Vehicle
vHipp	Ventral Hippocampus
VP	Ventral Pallidum
VPA	Sodium Valproate
vSub	Ventral Subiculum
VTA	Ventral Tegmental Area
WFA	Wisteria floribunda agglutinin

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1.0 **GENERAL INTRODUCTION**

Parts of the materials in Chapter 1 are adapted from previous reviews:

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Zhu, X., Gomes, F. V., & Grace, A. A. (2017). The methylazoxymethanol acetate rat model: molecular and epigenetic effect in the developing prefrontal cortex: An Editorial Highlight for 'Epigenetic mechanisms underlying NMDA receptor hypofunction in the prefrontal cortex of juvenile animals in the MAM model for schizophrenia' on page 320. *Journal of Neurochemistry*, 143(3), 264–267. https://doi.org/10.1111/jnc.14133

Zhu, X., Uliana, D.L., and Grace, A.A. (2022). The MAM model to study the role of dopamine in schizophrenia. *Neuromethods*; Humana Press, New York, NY. *Accepted*

1.1 SCHIZOPHRENIA: A BRIEF OVERVIEW

Schizophrenia is a severe psychiatric disorder with profound adverse health effects and enormous economic and societal burdens (Salomon et al., 2012). Schizophrenia symptomatology is characterized by positive and negative symptoms, as well as cognitive impairments (Owen et al., 2016). Positive symptoms, or psychosis, are prevalent and considered a disease-defining feature of schizophrenia, characterized by delusions and hallucinations (Breier & Berg, 1999). The

first episode of psychosis (FEP) usually appears in late adolescence or early adulthood (Millan et al., 2016). After FEP, the affected individual could enter various fluctuating trajectories containing periods of relapse or remission and residual long-term psychotic symptoms (Millan et al., 2016). Before FEP, schizophrenia is frequently characterized by an immediately preceding prodromal phase (from weeks to several months) that typically contains attenuated forms of psychosis and other symptoms. However, some individuals may experience a sudden or no transition (Wood et al., 2011). This period is also known as ultra-high risk (UHR) state (Miller et al., 2003), clinical high risk (CHR) state (Fusar-Poli et al., 2013), or at risk mental state (ARMS) for psychosis (Yung & McGorry, 1996). The developmental periods ranging from gestation to early adolescence before the prodromal phase are the premorbid phase, during which affected individuals typically have non-specific anomalies such as poor motor coordination, social deficits, and mood disruptions (Howes & Murray, 2014; Lieberman et al., 2001).

The etiology of schizophrenia is largely elusive. One predominant theory is that cumulative interactions between genetic and environmental risk factors can alter underlying neurodevelopmental processes in the premorbid and the prodromal stages, leading to the manifestation of psychosis (Davis et al., 2016). The pathophysiology of schizophrenia, on the other hand, is relatively better understood, at least for psychosis. In this context, dysfunctions in the dopamine (DA) system have been strongly linked to the positive symptoms of schizophrenia (Howes & Kapur, 2009), although their relevance to other domains of symptoms is still debated (Kesby et al., 2018; Moncrieff, 2009). Notably, evidence also suggests that genetic and environmental risk factors may to some extent converge onto DA system dysfunction to lead to psychosis (McCutcheon et al., 2020).

1.2 THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

1.2.1 Dopamine system dysregulations in schizophrenia

DA system dysregulation has long been proposed to underlie psychosis, a defining feature of schizophrenia. These theories have been generally referred to as the "dopamine hypothesis" (Howes & Kapur, 2009). Historically, early versions of the dopamine hypothesis emerged from two lines of evidence. First, DA system agonists can induce psychosis in healthy individuals. In addition, antipsychotics targeting DA D2 receptors effectively reduced psychosis (Seeman, 2021). Direct support for DA dysfunctions in schizophrenia first emerged from postmortem studies showing elevated DA, DA metabolites, and DA receptor expression in the striatum of schizophrenia patients (Lee & Seeman, 1980; Seeman & Kapur, 2000). Later, substantial support for the "dopamine hypothesis" was established by *in vivo* human molecular imaging studies (Howes et al., 2012). These techniques measure radiotracer binding to DA receptors or uptake to presynaptic terminals, allowing researchers to pinpoint presynaptic vs. postsynaptic mechanisms (Abi-Dargham, 2004). Replicating post-mortem findings, baseline synaptic DA levels, indexed by D2/3 receptors binding, were found to be elevated in the striatum of schizophrenia patients, so as the stimulant-induced DA release (Howes et al., 2012). Furthermore, terminal uptake of radiolabeled l-dihydroxyphenylalanine (L-DODA) was found to be elevated in the striatum (McCutcheon et al., 2019). These findings collectively indicate heightened presynaptic DA synthesis capacity in schizophrenia, now considered a disease phenotype (Tamminga & Holcomb, 2005). Importantly, longitudinal imaging studies of CHR groups have also shown elevated DA synthesis capacity, especially in people who later convert to clinical psychosis (Howes et al., 2011). Furthermore, in CHR individuals actively transitioning from prodrome to diagnostic

psychosis, DA synthesis capacity was positively correlated with psychosis severity (Egerton et al., 2013; Howes et al., 2009). Thus, these findings in schizophrenia at-risk individuals indicate a putative pathogenic role of DA system dysregulation in schizophrenia.

Dysregulated DA system functions are linked to positive symptoms of schizophrenia via an "aberrant salience" framework (Howes et al., 2020; Kapur, 2003). In this model, aberrant firing of ventral tegmental area (VTA) DA neurons could lead to excessive, uncoordinated, or sensitized striatal DA release. This heightened dopaminergic signaling is proposed to contribute to false attribution of motivational salience to normally irrelevant stimuli, which consequently could attract attention, lead to inappropriate associations, and/or generate maladaptive inference of causality. These are cognitive features that are commonly present in psychosis episodes (Roiser et al., 2013).

1.2.2 Hippocampal dysfunctions in schizophrenia

Besides DA dysfunctions, disruptions to hippocampus (Hipp) structure and functions are another set of the most robust and replicated findings in schizophrenia. Indeed, numerous studies reported volume reduction and shape anomalies in the medial temporal lobe structures (e.g., anterior subiculum and the CA1) of schizophrenia patients, especially in the more chronic cases (Chakos et al., 2005; Csernansky et al., 1998; Schobel, Kelly, et al., 2009). On the other hand, aberrant hippocampal activity, indexed by increased cerebral blood volume, glucose metabolism, and/or glutamate levels, has been widely described by functional imaging studies (Gur et al., 1995; Kraguljac et al., 2013; Tregellas et al., 2014). Increased Hipp activity is positively associated with psychotic symptoms, such as delusions and suspiciousness (Schobel, Lewandowski, et al., 2009). Moreover, there appears to be a sequential mechanism in hippocampal structural and functional

deficits in high-risk subjects progressing towards psychosis, with limbic anterior Hipp hyperactivity (indexed by increased cerebral blood volume in the anterior subiculum) preceding local atrophy (Lieberman et al., 2018a). In preclinical models, it has been experimentally demonstrated that surges in extracellular glutamate levels in the Hipp can damage local parvalbumin interneurons (PVI), which might directly contribute to the volume loss and indirectly cause hippocampal hyperactivity via disinhibition (Lieberman et al., 2018a).

Substantial clinical evidence from prodromal and early cases of schizophrenia also supports the hypothesis that hippocampal hyperactivity is a driving factor for schizophrenia. Notably, anterior limbic Hipp hyperactivity is present in the early phases of schizophrenia (McHugo et al., 2019), and many hippocampal structural and functional abnormalities are already present in the prodrome (Provenzano et al., 2020; Schobel et al., 2013; Vargas et al., 2018). These temporal associations suggested that Hipp functional disruptions are involved in the pathogenesis of schizophrenia (Lieberman et al., 2018a). Supporting this, several studies reported that in prodromal patients that later converted to clinical psychosis (approximately 40%), elevated baseline Hipp cerebral blood volume was positively associated with psychosis conversion (Schobel et al., 2013; Schobel, Lewandowski, et al., 2009). DA system hyperactivity has been shown to underlie psychosis; thus, hippocampal disruptions could interact with the overactive DA system to drive psychosis. Unfortunately, in humans, the precise temporal relationship between DA system hyperactivity and hippocampal disruptions in schizophrenia has not been systematically determined by longitudinal association studies, nor causally determined due to apparent feasibility and ethical concerns. Nevertheless, concurrent increases in resting cerebral blood flow in the midbrain and the hippocampus (Allen et al., 2018), as well as linked dysfunctions between Hipp glutamate levels and striatal DA synthesis capacity (Stone et al., 2010), have been

reported in prodromal psychosis. This line of evidence indicates that hippocampal glutamate and midbrain DA systems are at least co-activated in schizophrenia development, with the hippocampus likely being an upstream driver.

There are several theories explaining the Hipp dysfunctions in schizophrenia, and multiple lines of evidence suggested that Hipp hyperactivity is due to reduced inhibitory regulation from the PVIs (Benes & Berretta, 2001). Molecularly, PV or PVI loss has been partially attributed to oxidative stress-related mechanisms (Do et al., 2015). Excitotoxicity from chronic oxidative stress and glutamate accumulation has been hypothesized to cause loss of PVI that contributes to volumetric reduction observed in neuroimaging studies (Boley et al., 2014; Heckers & Konradi, 2015).

1.3 DEVELOPMENT OF DA SYSTEM DYSFUNCTION FROM HIPPOCAMPAL HYPERACTIVITY: INSIGHT FROM THE MAM MODEL

In vivo electrophysiological evidence from our lab has established that the rat limbic Hipp (i.e., ventral hippocampus, vHipp) is a predominant modulator of the midbrain DA neuron activity. Precisely, the ventral subiculum (vSub) of the vHipp predominantly controls the tonic activity of VTA DA neurons (i.e., the number of spontaneously active neurons; "population activity") via a polysynaptic circuit that involves nucleus accumbens (NAc) and the ventral pallidum (VP) (Floresco et al., 2001; Grace, 2016; Lodge & Grace, 2006). Tonic activity is an essential index of the overall responsivity of the DA system, because only spontaneously active DA neurons can engage in NMDA receptor-mediated phasic firing (high-frequency action potential bursts) to produce high levels of intrasynaptic DA transients. In this way, tonic DA activity functionally

controls the level of amplification of the DA system reactivity to external stimuli (Grace, 2016). In rats, we have previously demonstrated that pharmacological activation of the vHipp increased VTA DA population activity and striatal DA release (Floresco et al., 2003). This basic science finding mechanistically linked anterior Hipp hyperactivity and presynaptic DA neuron hyperfunction observed in schizophrenia.

Schizophrenia is now widely considered a neurodevelopmental disorder (Insel, 2010; Owen & O'Donovan, 2017). Pathological neurodevelopmental processes in schizophrenia begin as early as gestation, modified by a complex interplay between genetic and environmental risk factors throughout one's lifespan (Murray et al., 2017). To study neurodevelopmental risks for schizophrenia, researchers have devised various animal models based on manipulations of perinatal environments to produce long-lasting neurodevelopmental changes (Jones et al., 2011). The methylazoxymethanol acetate (MAM) rodent model stands out as a valuable tool in schizophrenia research. Specifically, prenatal exposure to MAM, a neural-specific mitotoxin, on gestational day (GD) 17 can lead to anatomical and behavioral abnormalities in adults resembling distinct pathologies and symptom domains of schizophrenia (Lodge & Grace, 2009). Crucially, hyperactivity of the Hipp and DA system, two of the most robust pathophysiological features, is recapitulated by the MAM model (Modinos et al., 2015). Indeed, in adult MAM rats, there are increased VTA DA neuron population activity and aberrant vHipp pyramidal neuron firing rate, and pharmacological inhibition of the vHipp completely prevents the hyperactivity of VTA DA neurons (Lodge & Grace, 2007). These findings linked Hipp hyperactivity to DA dysregulation, therefore, building a framework to understand schizophrenia development (Grace, 2016; Heckers & Konradi, 2015). Similar to human findings in schizophrenia (Heckers & Konradi, 2015), MAM rats also show decreased expression of PV in the vHipp (Lodge et al., 2009), resulting in a baseline

hyperactive firing state due to disinhibition of pyramidal neurons (Lodge & Grace, 2007). It has been postulated that loss of PV can be an upstream mechanism leading to sequential hippocampal dysfunction and DA hyperactivity through the above-described afferent pathway from the NAC and the VP (Boley et al., 2014; Grace, 2016).

1.4 STRESS AND SCHIZOPHRENIA

Schizophrenia arises from the complex interaction between genetic disposition and environmental risk factors. Although schizophrenia is highly heritable (Lichtenstein et al., 2009; Sullivan et al., 2003), accumulating evidence indicates that the genetic vulnerability is polygenic (Purcell et al., 2009). Indeed, each putative risk gene for schizophrenia is predicted to only confer a small effect on the phenotypes, and only a proportion of risk gene carriers eventually convert to clinical psychosis (Henriksen et al., 2017; Jagannath et al., 2017). Furthermore, twin studies revealed that, despite identical genetic backgrounds, the concordance rate for schizophrenia is only approximately 50% (Cardno & Gottesman, 2000). This line of evidence indicates that schizophrenia is not entirely genetically determined, and a significant proportion of schizophrenia liability might therefore be contributed by environmental factors (Dean & Murray, 2005).

1.4.1 Evidence for the association between stress and schizophrenia

One of the most consistent epidemiologically validated environmental risk factors for schizophrenia is exposure to psychosocial stress in childhood and adolescence (Bendall et al., 2008; R. van Winkel et al., 2008). Indeed, in early human life, psychosocial stress in the forms of

developmental adversity or trauma has been associated with increased risks of adult psychosis (Varese et al., 2012). Notably, not all trauma victims eventually develop psychosis. Thus, it has been hypothesized other risk factors, such as genetic predisposition (Daskalakis & Binder, 2015), may interact with psychosocial stress to cause schizophrenia pathophysiological changes. However, there is also evidence supporting that childhood adversity might contribute independently to schizophrenia liabilities without interacting with genetic risks (Trotta et al., 2016).

Studies from prodromal groups have further shed light on the specificity of early life stress on schizophrenia symptoms. Exposure to childhood trauma is highly prevalent in CHR populations, estimated by a meta-analysis to be 86.8% (Kraan et al., 2015). Furthermore, longitudinal studies have established that prodromal patients with a trauma history are more likely to convert to FEP (Bechdolf et al., 2010). In addition to trauma exposure, altered stress vulnerability/sensitivity has also been linked to psychosis. In particular, CHR patients tend to have increased levels of cortisol and hypothalamic-pituitary-adrenal (HPA) axis hyperactivity (Aiello et al., 2012), and CHR individuals with heightened stress reactivity to chronic stress tend to later convert to overt psychosis (Pruessner et al., 2011; Walker et al., 2013). Intriguingly, emerging evidence suggests that traumatic events are not equipotent to confer risks to psychosis. A recent large-scale birth cohort study identified that during childhood development (up to age 17 years), adolescent trauma is more predictive of psychotic experience in adults (Croft et al., 2019). This finding supports the existence of 'sensitive periods' during which stress exposure could maximally or specifically confer psychosis risk. Despite the established strong associations between early stress and psychosis risks, the underlying neurobiological mechanisms are still unknown (Mayo et al., 2017).

Stress has been hypothesized to convey psychosis risks by directly modulating DA system functions. Supporting this, human imaging studies have found that in healthy individuals, a history of childhood trauma increased presynaptic DA synthesis in the striatum (Egerton et al., 2016). Consistently, subjects who report a greater number of developmental traumatic events have increased DA release induced by adult stress or amphetamines (Oswald et al., 2014; Pruessner et al., 2004). Intriguingly, a cohort study also found significant positive associations between childhood trauma exposure and hippocampal hyperperfusion (Allen et al., 2018). Collectively, these findings suggest that severe early stress can induce schizophrenia-like dysregulations of the DA system, potentially via hippocampal hyperactivity. Notably, not all trauma victims develop adult DA dysregulation in these studies. The biological mechanism contributing to such selective vulnerability and resilience is unknown.

1.4.2 Deleterious effects of stress driving schizophrenia development: insight from the mam model

Most of the schizophrenia-like changes in the MAM model appear during late adolescence/early adulthood (Gomes et al., 2016). As with individuals at genetic risks for schizophrenia (Jones et al., 2016), MAM rats exhibit increased stress reactivity and heightened anxiety in early adolescence. Thus, we found that MAM rats in the juvenile period [postnatal day (PD) 22] are more responsive to stress. Specifically, in response to acute footshock, juvenile MAM rats emitted more ultrasonic vocalizations, vocalized for a longer duration, and spent more time in freezing behavior than controls and adult 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 & Grace, 2013), which was associated with hyperactivity

of the basolateral amygdala (BLA) (Du & 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 of schizophrenia, indicating that those showing greater sensitivity to stress and increased anxiety tended to be those who converted to psychosis later in life (Devylder et al., 2013; Owens et al., 2005).

Since anxiety and abnormal stress responses occurred early in adolescence and appeared to precede adult DA dysregulation in MAM rats, we next tested whether alleviating these early phenotypes may prevent the emergence of DA dysfunction. We treated MAM rats with daily administration of an anxiolytic drug, diazepam, during peripuberty (PD31–40) at a dose sufficient to normalize anxiety responses and amygdala activity (Du & Grace, 2013, 2016). Consequently, peripubertal diazepam administration prevented the development of anxiety-like behaviors and higher neuronal firing rates within the BLA of MAM rats at adulthood (Du & Grace, 2016), as well as prevented the development of the hyperdopaminergic state observed in adult MAM rats (Du & Grace, 2013). These findings indicate that relieving stress in MAM rats around puberty circumvents the transition to the schizophrenia-like phenotypes in adults. It is likely that other stress-relieving nonpharmacological interventions will also be effective. This is important because early diazepam treatment in children may have safety concerns. In human translation, environment-based protective factors (e.g., enhanced physical activity and social support) engaged in adolescence (age 12-18 years) have been shown to reduce the transition to psychosis in at-risk individuals (Crush et al., 2018).

Interpreting these findings in MAM rats, we propose that MAM, and perhaps other prenatal predisposing factors, including genetic liability, do not independently “cause” schizophrenia.

Instead, it could increase sensitivity to stressors during critical developmental stages, during which the interaction with other environmental risks would eventually cause schizophrenia development. This idea 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). Accordingly, if this model is accurate, one could predict that exposing normal rats to sufficiently strong stressors in development would lead to pathophysiology in the adult that recapitulates the results from the MAM treatment. We demonstrated this by implementing a compound stressor consisting of footshock and restraint in PD31-40 in normal rats (Gomes & Grace, 2017). We found that when these stressed rats reach adulthood, they display schizophrenia-relevant hyperdopaminergic activity and behavioral abnormalities similar to those of MAM rats. Some key questions remained, including (1) whether the observed stress effects depend on stress timing and (2) whether sex is a modulatory factor. These questions merit extensive research effort because in humans, age-dependent childhood adversity is differentially associated with psychosis risk (Alameda et al., 2016; Croft et al., 2019; Devylder et al., 2013), and sex differences in schizophrenia symptom development are well-documented (Abel et al., 2010; Aleman et al., 2003; S. Ochoa et al., 2012).

1.4.3 Sensitive period of stress vulnerability in schizophrenia development

Adversity most strongly affects the developing brain. Based on this consensus and in light of the findings indicating a significant association between childhood (frequently defined by exposure age up to 18 years) adversity/trauma and many psychopathologies, including schizophrenia, increasing attention has been given to the early life stress (ELS) models. In rodents, ELS is a broad term that describes adverse experiences before adulthood, encompassing prenatal,

neonatal/perinatal, early postnatal, and adolescent periods (Molet et al., 2014). Numerous ELS studies have established that stress timing can profoundly influence adult consequences, ranging from somatic/hormonal stress response to various brain functions. In humans, late childhood and adolescence, approximately 8-17 years of age (Baker et al., 2013; Cohen et al., 1993), are particularly relevant to schizophrenia pathogenesis and pathophysiology, as numerous environmental risk factors in these periods are highly associated with increased adult development of psychosis (Mennigen & Bearden, 2020; Millan et al., 2016). These risk factors are collectively classified as 'second wave hits', chronologically distinguished from genetic predisposition and perinatal risk factors ('first wave hits') (Fusar-Poli et al., 2017). In rodents, the precise definitions of late childhood and adolescence vary among studies but generally refer to a period between PD20-60. This prolonged period has also been divided into different stages, either based on chronological age [e.g., early, mid and late adolescence (Wilkin et al., 2012)] or by maturational events such as puberty onset [e.g., prepuberty, peri-puberty, and post-puberty; (Romeo, 2010)]. In both humans and rodents, adolescent development is characterized by distinct developmental plasticity, structural maturation, and generally immature capacity emotional and cognitive coping skills (Crews et al., 2007; Semple et al., 2013; Spear, 2013). Many of the ongoing developmental changes occur at the most dynamic rates during adolescence and can be maximally disrupted by chronic stress (Sheth et al., 2017). Thus, adolescence has been widely characterized as a stress vulnerable period.

Stress timing can profoundly influence its consequences, an effect highly dependent on biological sex, outcome measures, and stressor-related parameters (intensity, duration, etc.) (Bale & Epperson, 2015; Molet et al., 2014). The time during which stress can maximally disrupt a specific brain region, circuit, neural function, or behavior is often referred to as "sensitive periods

of stress exposure" (Andersen, 2019). This is derived from the concept of a "sensitive period" in developmental neurobiology that describes a time when standard or expected environmental experiences have the most significant impact on brain circuitry (Hensch & Bilimoria, 2012). In contrast, the term “critical period” is a more stringent concept, which describes a time when a specific environmental stimulus is required to properly develop a particular circuit (Hensch & Bilimoria, 2012). Several recent human association studies preliminarily indicate the existence of early sensitive periods for trauma to increase adult psychosis risks. Indeed, the largest birth cohort to date discovered that adolescent trauma (age 11-17 years) is most strongly associated with psychosis experience at age 18 (Croft et al., 2019). However, other studies indicate that earlier trauma is more predictive of higher levels of symptoms (Alameda et al., 2016) or higher risks of developing psychosis (Arseneault et al., 2011). These seemingly opposite results are possibly attributable to methodological differences. Nevertheless, these studies convergently indicate the existence of unique stress-sensitive periods to increase developmental psychosis risk. The neurobiological basis of this effect is currently unknown. In addition, whether there are sex differences in the putative sensitive periods for stress to modulate schizophrenia pathophysiological mediators (such as the vHipp and VTA DA system) has not been systematically assessed. Addressing these questions would significantly advance our current understanding of the pathogenic mechanisms of schizophrenia. Moreover, despite increasing research efforts in psychosis prevention, the most productive approach to date is avoiding risk factors (Murray et al., 2021). In this respect, identifying the sensitive periods of stress in schizophrenia-relevant regions would offer critical insights to devise novel need-based prevention strategies (Fusar-Poli et al., 2020) and to enhance the efficacy of illness phase-specific therapy (Krystal & Anticevic, 2015).

1.4.4 Alterations in stress response systems in schizophrenia

Exposure to stress can elicit a wide range of interacting central and peripheral stress responses, prominently in the autonomic nervous system (ANS) and the HPA axis (Chrousos, 2009). Stress responses mediated by these systems occur on timescales ranging from milliseconds to days and are capable of inducing permanent neural and behavioral consequences when chronically engaged and/or insufficiently controlled (Godoy et al., 2018). In principle, once a stressor is centrally detected by distinct brainstem and hypothalamic circuits, temporally the first phase of the stress response (starting within seconds) is within the sympatho-adrenal medullary (SAM) axis that primarily leads to rapid release of epinephrine and norepinephrine into the bloodstream (De Kloet et al., 2005; Joëls & Baram, 2009). This SAM effect results typically in immediate yet transient responses to overall promote alertness, vigilance, and appraisal of stressful situations necessary for effective stress coping (Ulrich-Lai & Herman, 2009). The second phase of stress response emerges more slowly after the exposure, which is mediated by the HPA axis and is thought to ensure more protracted and amplified stress responses (Ulrich-Lai & Herman, 2009). In particular, these systems are complementary and engaged by stress in a coordinated manner, with extensive cross-talk activities that enable appropriate cognitive processing of stress responses and facilitate complex coping behaviors (Godoy et al., 2018).

Of relevance to schizophrenia, alterations in both autonomic and endocrine stress responses have been discovered. In clinical settings, one of the most popular approaches to estimate ANS dynamics is heart rate variability (HRV), a measure that indicates the output balance between the sympathetic and the parasympathetic nervous systems (SNS and PSNS, respectively) (Stogios et al., 2021). HRV deficits are a robust finding in schizophrenia, and the most comprehensive meta-analysis to date on this topic concluded that schizophrenia patients have significantly reduced HRV

in high-frequency bandwidths and root mean square of the successive differences (Clamor et al., 2016), which indicate imbalanced ANS output potentially attributable to lower efferent vagal activity of the PSNS (Billman, 2011). Moreover, HRV indices for increased SNS output, for example, increased LF/HF ratio, were found to increase in schizophrenia patients (Akar et al., 2015; Chang et al., 2010; Chang et al., 2009), although there is also contradictory evidence (Stogios et al., 2021). Furthermore, in addition to HRV measures, other methods that evaluate peripheral indicators of ANS activity, such as salivary alpha-amylase activity and skin conductance, have established SNS hyperactivation in schizophrenia (Ieda et al., 2014; Inagaki et al., 2010; Zahn et al., 1997). Whether ANS abnormalities represents an epiphenomenon, or a feature of schizophrenia pathophysiology, is unclear.

Despite the robust correlation between schizophrenia (with overt psychosis) and ANS dysregulations, literature investigating the presence of ANS deficits in at-risk populations is limited (Guccione et al., 2019). Nonetheless, the available evidence preliminarily points to autonomic dysregulations in the early phases of the illness, which is postulated to be linked to genetic risk factors of schizophrenia. Specifically, the offspring of schizophrenia patients display reduced HRV markers as compared to the siblings (Bär et al., 2010). This finding is consistent with another study reporting HRV deficits in deep breathing conditions in patients and first-degree relatives (Liu et al., 2016), which points to a putative link between schizophrenia genetic liability and ANS dysregulations (Guccione et al., 2019). Beyond studies on genetic risks, whether ANS dysfunctions are present in other at-risk populations are even more understudied. In one study, individuals in the early phases of psychotic disorders (i.e., UHR individuals and FEP patients) were found to show decreased HRV at rest or when exposed to socially challenging situations, compared to healthy controls and unaffected siblings of psychotic patients (Counotte et al., 2017).

Therefore, it is possible that non-genetic risk factors, such as developmental stress or trauma, could also contribute to autonomic disruptions involved in schizophrenia.

On the other hand, structural and functional HPA axis alterations have been widely observed across illness stages of schizophrenia. In FEP patients, there is a specific pattern of HPA axis disruption that overall indicates system hyperfunction, manifesting as larger pituitary volume, higher baseline cortisol levels, and blunted cortisol awakening responses (which are specific to males). Notably, increasing evidence in UHR individuals suggests that higher cortisol levels are associated with prodromal psychosis (Mittal and Walker, 2011, Corcoran et al., 2012), and that a larger pituitary at baseline is predictive of later transition to overt psychosis (Garner et al., 2005, Buschlen et al., 2011). Thus, HPA axis alterations are postulated to be strong vulnerability markers rather than disease consequences in schizophrenia.

The increased SNS tone and hyperactive HPA axis in schizophrenia could be linked to early stress exposure, such as childhood trauma (Ruby et al., 2014), which is associated with sensitization of stress responses (Heim et al., 2008). At the system level, these changes could contribute to DA system hyperactivity in schizophrenia. As part of the SAM stress response system, chronic increase in SNS activation can increase circulating catecholamine (e.g., epinephrine and norepinephrine) levels. Although these peripheral signaling molecules cannot cross the blood-brain barrier (Kostrzewa, 2007), they activate the intermedial lateral column of the spinal cord to stimulate the vagus nerve, which in turn activates the nucleus tractus solitarius and/or the locus coeruleus (LC) through norepinephrine (NE) signaling (Tank & Lee Wong, 2015). Activation of these nuclei enhances norepinephrine neurotransmission in the afferent regulators of VTA DA neurons, such as the BLA and the vHipp (Sara & Bouret, 2012), and alters their activity states (Bacon et al., 2020; Giustino et al., 2020), which could in turn affect the output of VTA DA

neurons. Comparatively, hyperactivation of the HPA axis could more directly influence the firing of the DA neuron through enhanced glucocorticoid signaling in afferent regulator regions, due to the ability of circulating glucocorticoid to cross the blood-brain barrier (Karssen et al., 2005). Moreover, it is known that HPA axis activation modulates hippocampal and BLA activity and excitability via mineralocorticoid (MRs) and glucocorticoid receptors (GRs) (de Kloet et al., 2005), and these regulations change in time- and dose-dependent manners (Schwabe et al., 2010). Moreover, evidence also suggests that when stress exposure occurs early in development, the induced HPA axis hyperactivation could be more pronounced compared with adults (Romeo et al., 2016). In addition, slice electrophysiology demonstrated that glucocorticoid signaling can strengthen glutamate synapses at DA neurons, and therefore might influence their activity patterns (Daftary et al., 2009). Taken together, these neurophysiological and molecular effects of HPA axis activation could lead to pathological modification of the circuits that control the output of VTA DA neurons, possibly mediating the pathophysiology related to childhood trauma in schizophrenia. Notably, early stress can have age- and sex-dependent programing effects on the reactivities of both stress response systems, leading to enduring hyper- or hypo-activation (Agorastos et al., 2019; Fogelman & Canli, 2019; Romeo et al., 2016). Thus, stress during sensitive windows may elicit differential physiological stress responses, which could possibly lead to differential downstream consequences in DA neuron electrophysiology.

1.5 SCHIZOPHRENIA TREATMENT FROM A PREVENTATIVE PSYCHIATRY PERSPECTIVE

1.5.1 Novel treatment and potential interventions for schizophrenia

Current pharmacological treatments, i.e., antipsychotics, for schizophrenia primarily operate as post-synaptic DA receptor antagonists. Decades of antipsychotic research have proven their efficacy in acutely alleviating episodes of psychosis and in preventing symptom recurrence (Leucht et al., 2009). Antipsychotic treatments are considered symptomatic and do not target the primary pathophysiological factors of schizophrenia (Lieberman et al., 2019). Thus, antipsychotic-based treatment is often used as lifetime maintenance therapy, which in combination with its limited efficacy on other domains and considerable effects, can often lead to relapses (Leucht et al., 2012). These unmet therapeutic needs with current antipsychotic treatment have prompted the search for alternative multimodal approaches from a preventative psychiatry perspective, with the ultimate goal of providing indicated interventions based on efficient risk detection and accurate prognosis (Fusar-Poli et al., 2019).

Since the 1980's, accumulating evidence on the interacting risks factors and the progressive nature of schizophrenia disease trajectories has led to a significant reconceptualization of the disease (Lieberman et al., 2019; Millan et al., 2016). It is now widely accepted that overt psychosis or FEP in schizophrenia is not the beginning of the disease, but rather a downstream consequence. This view has raised the possibility that timely treatment or intervention could limit the morbidity of the disease or even prevent its onset (Perkins et al., 2005). Under this framework, numerous putative disease-modifying strategies have been studied for their potentials to alter the course of schizophrenia. Currently, one primary focus in schizophrenia intervention research is to prevent

FEP, which is based on the findings that untreated psychosis episodes are associated with worse disease progression and long-term outcomes in later life (Lieberman et al., 2001; Marshall et al., 2005; Perkins et al., 2005).

Heuristically, late childhood and adolescence (i.e., the prodromal stages) are considered as "windows of opportunity" for targeted interventions to confer enduring benefits to the pathophysiological processes underlying psychosis (Millan et al., 2016). However, some researchers propose that preemptive interventions should take place perinatally or in early premorbid phases (Liu et al., 2015). In a practical sense, interventions in the prodromal stages might be comparatively more optimal for several reasons. First, numerous environmental risk factors are already present in the prodromal phase. Moreover, most progressive maturational anomalies in brain structure, connectivity, functions, neurochemistry tend to initiate or change most dynamically in childhood/adolescent stages (Karlsgodt et al., 2010; Pettersson-Yeo et al., 2011; Van Den Heuvel & Fornito, 2014). Furthermore, although not all prodromal individuals convert to full-blown psychosis (estimated 24%-40%), our approaches to accurately detect attenuated psychotic signs and predict long-term prognosis in CHR individuals have been substantially advanced (Fusar-Poli et al., 2020). This provides an advantage for "prodromal" over early "premorbid" targeted preventions because the latter is less predictive of schizophrenia. Therefore, interventions in premorbid phases could face more iatrogenic, safety, and ethical concerns (Sommer et al., 2016).

The designing and testing of novel therapies rely on scientifically validated animal models. Schizophrenia pathogenesis and pathophysiology are highly complex. As a result, each animal model for schizophrenia generally can recapitulate only a subset of risk factors and phenotypes. Notably, schizophrenia-related subjective mental states, such as hallucinations and delusions,

cannot be measured in research animals (Arguello and Gogos, 2006; Powell and Miyakawa, 2006). Considering these factors, useful preclinical models should allow the screening of early interventions based on well-defined endpoints that are closely related to schizophrenia pathology/pathophysiology. In this sense, the MAM model is an ideal tool for testing new interventions and generating testable hypotheses for human translation.

1.5.2 The potential of environmental enrichment in preventing psychosis

Environmental enrichment (EE) has been established to convey broad benefits to neurodevelopment and therefore may be efficacious in neurodevelopmental disorders. Notably, although its underlying concepts have already been translated into human aspects of prevention, it has remained largely a laboratory phenomenon. The first human study that directly evaluated the use of EE in the prevention of schizophrenia symptoms was in the early 2000s in a general population cohort (Raine et al., 2003). In this longitudinal study, an environmental enrichment program at ages 3-5, including nutritional, educational, and physical exercise enhancement, was associated with lower levels of schizotypal features in early adulthood (Raine et al., 2003). Although schizotypal personalities are not *bona fide* psychosis and in schizophrenia patients they only weakly correlated with psychosis symptoms (Lenzenweger, 2021), this measure has been widely used in the CHR/UHR groups as it has high independent predictive potentials for psychosis conversion (conversion rate ranging from 25-48%) (Debbané et al., 2015). High levels of schizotypy traits also share genetic and environmental risk factors, brain activity patterns, and pathophysiological factors (e.g., increased DA system activity) with diagnosed schizophrenia (Abi-Dargham et al., 2004; Ettinger et al., 2014). Thus, this initial finding that EE reduced

schizotypy has a far-reaching impact, as it built a foundation for future investigations in preclinical models of schizophrenia.

Despite sparse attempts to directly translate EE into practical human psychosis interventions (Crush et al., 2018; Kühn et al., 2017; Raine et al., 2003), this approach is still a laboratory phenomenon in schizophrenia preclinical models. Relatively strong preclinical evidence suggests that certain variations of EE paradigms can broadly counteract shared risk factors and thus positively alter the trajectories of many neurodevelopmental disorders, such as autism, attention deficit/hyperactivity disorder, and fragile X syndrome (Ball et al., 2019). Comparatively, EE in schizophrenia risk models has been more limited. However, considering the shared genetic (Owen & O'Donovan, 2017; Rees et al., 2021) and environmental risk factors (Schmitt et al., 2014) between schizophrenia and these disorders, it is plausible that EE may positively modulate schizophrenia courses. In preclinical models of schizophrenia risk factors, the available studies convergently indicate that EE might be broadly beneficial in modulating schizophrenia-related behaviors. For example, in PCP and MK-801 models based on NMDA receptor antagonism that models human NMDAR hypofunction in schizophrenia, EE rescued pre-pulse inhibition, social interaction, and cognitive (i.e., recognition memory) deficits (Koseki et al., 2012; Nozari et al., 2015). Furthermore, in models based on specific genetic risks, such as phospholipase C knockout and PACAP-deficient animals, EE has also been shown to reduce sensorimotor gating deficits, spontaneous hyperlocomotion, and abnormal social interactions (Ishihama et al., 2010; C. E. McOmish et al., 2008). In schizophrenia neurodevelopmental models based on hippocampal pathologies, such as the MAM model, overall similar behavioral benefits were also observed, including preventions of sensorimotor deficits, social abnormalities, and short-term memory dysfunctions (Bator et al., 2018), as well as improved cognitive control deficits in

two-frame avoidance tasks (Lee et al., 2012). These studies indicated that early EE is sufficient to chronically modulate common behavioral phenotypes related to schizophrenia, with benefits spanning all domains of symptoms. However, these behavioral phenotypes, although related, are not specific to schizophrenia. Whether these effects represent true prevention or merely symptom relief are unclear. Thus, a missing mechanistic link has been the underlying DA pathophysiology related to schizophrenia symptoms. Given the strong evidence linking presynaptic DA hyperactivity and psychosis, elucidating whether early EE modifies DA system function in preclinical models would give unequivocal insights into the possibility of successful human EE-based interventions.

1.5.3 Targeting oxidative stress in schizophrenia

The term 'oxidative stress' broadly describes the imbalance between the excessive accumulation of toxic reactive oxygen and nitrogen species and the organism's inability to clear it. Chronic oxidative stress can lead to cellular damages or even cell death (Schiavone et al., 2013). Compared to other organs, the brain is highly vulnerable for oxidative stress due to its intense oxidative metabolisms and, therefore, increased production of reactive oxygen species (Salim, 2017). In the brain, oxidative stress is primarily controlled by glutathione (GSH)-mediated redox reactions, which is the most abundant endogenous antioxidant (Forman et al., 2009).

PVIs are especially vulnerable to oxidative stress due to their fast-spiking ability and therefore high metabolic demands (Do et al., 2009; Steullet et al., 2017). In fact, when the GSH system is genetically weakened, oxidative stress markers accumulate prominently in PVIs (Morishita et al., 2015). Furthermore, accumulation of oxidative stress markers appears to precede PV reduction (Steullet et al., 2010), and early antioxidant treatment, for example, N-acetylcysteine

(NAC), prevents this effect (Cabungcal, Steullet, Kraftsik, et al., 2013). Thus, these findings demonstrate that chronic oxidative stress can directly cause structural impairments of PVI, which include PV or PVI loss. Notably, PVIs are normally protected from chronic oxidative stress by a specialized extracellular matrix structure, perineuronal nets (PNNs) (Cabungcal, Steullet, Morishita, et al., 2013). However, excessive levels of reactive chemical species can themselves damage PNNs. PNNs accumulate around PVIs through a prolonged developmental process, which completes at different timing not only to protect PVIs but also to act as a maturational marker to stabilize developmental sensitive periods or critical periods of neuroplasticity (Do et al., 2015; Wen et al., 2018a). Therefore, the deleterious effects of chronic oxidative stress involve both reduced PV expression and maturational deficits in PV-associated PNNs.

Oxidative stress is a strong candidate pathological mechanism integrating genetic and early environmental risk factors for schizophrenia (Steullet et al., 2017). The first clinical observation linking oxidative stress with schizophrenia was established in the 1990s, in which altered GSH metabolism was found in the cerebral spinal fluid of schizophrenia patients (Cuenod et al., 2021; Do et al., 1995). Since then, oxidative damage and antioxidant deficits (e.g., GSH) have been widely detected in patients, ranging from biospecimen to in vivo magnetic resonance spectroscopy studies (Perkins et al., 2020). Oxidative stress is purported to contribute to the development of schizophrenia primarily via damaging PVIs and PV networks (Steullet et al., 2017), which depending on the affected regions, can, in turn, lead to diverse schizophrenia symptoms.

Oxidative PVI impairments in schizophrenia preclinical models have been predominantly studied in cortical regions, especially the prefrontal cortex (PFC) and the anterior cingulate cortex (Steullet et al., 2017). Comparatively, little is known about the effects of oxidative stress in the subcortical structures (J. H. Cabungcal et al., 2019). However, a recent study in patients with

schizophrenia has pinpointed a new location, the thalamic reticular nucleus (TRN), for PVI impairments that could be attributed to oxidative stress (Steullet et al., 2018). Moreover, in mice with a genetically weakened GSH system, TRN was the first region (at PD20) to manifest observable oxidative PVI impairments, which preceded the structural deficits in the amygdala and the hippocampus (J. H. Cabungcal et al., 2019). Thus, this spatiotemporal pattern of PVI loss to broad redox dysregulation raised the possibility that the TRN might be increasingly vulnerable to oxidative stress. How such newly observed TRN deficits in schizophrenia patients are functionally related to schizophrenia pathophysiology, specifically DA system dysregulations, is unknown. We recently discovered a TRN-mediated DA neuron control pathway (Zimmerman & Grace, 2016; Zimmerman & Grace, 2018), which operates by providing feedforward inhibition from infralimbic PFC (ilPFC) to midline thalamic output nuclei that project to vHipp. Thus, TRN impairment could eventually alter the modulation of VTA DA neurons by altering vHipp activity. Redox dysregulation and oxidative stress have been postulated to be prophylactic targets for schizophrenia (Sawa & Seidman, 2014). Indeed, previous studies using early NAC treatment prevented PFC deficits in the neonatal hippocampal lesion model of schizophrenia development (Cabungcal et al., 2014). Given the newly discovered oxidative PVI impairment in the TRN and its possible involvement in regulating DA system function, it would be informative to determine whether early antioxidant treatment could prevent DA system dysregulation in the MAM model via this pathway.

1.6 PURPOSES OF STUDIES

1.6.1 Rationale

Schizophrenia pathophysiology is complex and remains to be fully understood. Substantial research has identified Hipp and VTA DA system hyperactivities as core pathophysiology mechanisms underlying psychosis. These changes can be studied electrophysiologically in MAM rats, a neurodevelopmental model of schizophrenia. Strong epidemiological evidence indicates childhood adversity increases psychosis risks in schizophrenia development. Emerging human evidence also suggests that traumatic stress during adolescence exerts non-linear effects on the risk of adult psychosis, highlighting the possibility of age-defined stress-sensitive periods with a unique risk association for the pathophysiology of schizophrenia. We aim to determine this relationship in rats by systemically studying the sex- and exposure age-dependent effects of adolescent stress. Moreover, in light of the generally promising findings of EE in preventing schizophrenia-related behaviors across animal models, it would be useful to test whether EE prevents vHipp and VTA DA hyperactivity in MAM rats, as these electrophysiological measures are more closely related to psychosis. Furthermore, propelled by recent advances in schizophrenia biomarker research, specifically the novel finding of TRN PVI oxidative impairments, we aim to functionally determine such thalamic pathology in MAM rats, emphasizing DA neuron function and prefrontal control pathways. Furthermore, it would also be informative to test the preventative potential of early antioxidant, NAC, treatment on TRN pathology and DA system dysfunctions. Our goals are to provide novel etiological insights and to test novel prophylactic approaches, as these remain critical knowledge gaps in schizophrenia research.

1.6.2 Research objectives

In this dissertation, we hypothesize that adolescent stress (broadly defined as stress in PD21-50) drives adult hyperdopaminergic states as observed in schizophrenia in a sensitive-period-like manner. Our previous study indicates that stress during a selective window of rat adolescence (i.e., PD31-40) in males is sufficient to increase adult VTA DA system activity (Gomes & Grace, 2017; Gomes et al., 2020). This effect is age-dependent, as the same stressor administered in adult males (i.e., PD65-74) failed to elicit similar changes in the VTA(Gomes et al., 2020). In contrast, females showed resilience to long-term stress-induced dysregulation of DA after both stress from PD31-40 and adult stress from PD65-74 (Klinger et al., 2019). In Chapter 2, we aim to extend these previous findings and systematically identify/characterize adolescent sensitive periods for stress-induced DA system dysregulations, emphasizing on age and sex dependences. In Chapter 3, we test whether targeting early stress processes through EE could prevent the later development of DA dysregulation in the MAM model. Finally, in Chapter 4, we determine whether targeting redox dysregulation in MAM rats through early antioxidant treatment prevents later life DA abnormalities, emphasizing the functional importance of TRN PVI oxidative impairments.

2.0 SEX- AND EXPOSURE AGE-DEPENDENT EFFECTS OF ADOLESCENT STRESS ON VENTRAL TEGMENTAL AREA DOPAMINE SYSTEM AND ITS AFFERENT REGULATORS

Chapter 2 is a modified version of a manuscript:

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(Supplementary figures and detailed methods of this chapter are in **Appendix A Supplementary Materials for Chapter 2**)

2.1 INTRODUCTION

Converging epidemiologic evidence indicates exposure to early developmental stress (such as childhood adversity or trauma) is strongly associated with adult risks for psychotic disorders (Bailey et al., 2018; Varese et al., 2012). In this context, emerging studies implicate age-dependent sensitive periods during which developmental stress specifically modulates later-life psychosis risks (Alameda et al., 2016; Croft et al., 2019). Childhood adversity is linked to the adult manifestation of elevated presynaptic dopamine (DA) function (Dahoun et al., 2019; A. Egerton et al., 2016), a hallmark of psychosis in schizophrenia (O. D. Howes & R. M. Murray, 2014). At present, the pathophysiological mechanisms linking early developmental stress exposure to adult DA dysfunction are unclear.

Preclinical research indicates stress exposure can induce dynamic changes in presynaptic DA functions, including abnormal DA release and dysfunctional ventral tegmental area (VTA) DA neuron firing (Baik, 2020; Douma & de Kloet, 2020; Holly & Miczek, 2016). Comparatively, more intense research effort has been given to DA release-related measures, and relatively consistent microdialysis evidence indicates most acute stressors immediately increase extracellular mesolimbic DA levels for tens of minutes, followed by a gradual decrease to baseline (reviewed in (Holly & Miczek, 2016)). Our previous electrophysiological study is consistent with this finding, indicating stress can increase DA neuron firing during stress or immediately after stress termination (Valenti et al., 2011). In contrast, the effects of chronic stress on DA release (Imperato et al., 1992; Miczek et al., 2011) and the associated DA neuron activation appear to be more long-lasting, which in some cases can last for weeks (Cao et al., 2010; Friedman et al., 2014), albeit more heterogeneous and displaying stressor dependence (Chang & Grace, 2014; Tye et al., 2013). Notably, chronic stress exposure was shown to sensitize DA release to future challenges (Jordan et al., 1994; Naef et al., 2013), although these results are inconsistent and again display stressor dependence (Holly et al., 2015). This line of evidence predicts chronic stress can modulate DA neuron firing properties over the long term. As a potential caveat, previous findings on the physiological effects of stress were obtained mainly from adult and male animals. Consequently, the developmental relevance and potential sex difference in stressor response is largely unknown. In developing brains, although sporadic evidence suggests that early life stress during the first 2-3 postnatal weeks can lead to adult DA release cross-sensitization (Brake et al., 2004; Jezierski et al., 2007) and an increase in VTA DA neuron excitability (Oh et al., 2021; Spyrka et al., 2020), the ensuing windows such as adolescence were largely unexplored. Given that in humans it is the late childhood or adolescent trauma that mostly strongly correlates with psychosis risks (Croft et

al., 2019), studying how stress during the corresponding windows in rodents [i.e., postnatal day (PD), 21-60 (Sheth et al., 2017)] affects DA neurons firing could have substantial translational value.

We have reported recently that, in male rats, chronic stress during adolescence at PD31-40 can induce long-term tonic activation of VTA DA neurons (Gomes & Grace, 2017). Moreover, this effect appears to be age- and sex-dependent, as adult male stress (PD65-74 (Gomes et al., 2020)) and adolescent or adult female stress (Klinger et al., 2019) all failed to elicit any sustained VTA firing abnormalities. Noteworthy, adolescence is a prolonged period, with puberty being a hallmark event (Sinclair et al., 2014). In terms of behavioral or hormonal responses, adolescence could be further divided into separate windows, defined by chronological age and relative temporal relationship to puberty (i.e., pre-adolescence/prepuberty vs. post-adolescence/postpuberty) (Romeo et al., 2016). Despite our recent substantial findings in PD31-40 rats (Gomes et al., 2020; Klinger et al., 2019), whether stress during other temporally defined adolescent windows may affect adult DA neuron firing properties has been unexplored. We aimed to address these questions in the present study.

In sum, based on the emerging human and animal literature linking developmental stress to adult DA dysfunction, we sought to determine the long-term neurophysiological effects of two adolescent stress paradigms on adult VTA DA neuron firing. In particular, we emphasized age- and sex dependence of stress exposure, and tested whether a 10-day stress paradigm can lead to distinct later-life schizophrenia-relevant electrophysiological alterations in VTA DA neurons and their afferent regulators, specifically the ventral hippocampus (vHipp) and the basolateral amygdala (BLA) (Grace, 2016). Furthermore, we also determined the age- and sex-specific effects of adolescent stress on the maturation of parvalbumin interneurons (PVIs) in these regions, given

their functional importance in regulating regional neurophysiological output and clinical relevance to schizophrenia (Gomes et al., 2019b). Altogether, our data indicate discrete adolescent windows of sex-specific vulnerability to stress-induced DA system physiological alterations.

2.2 RESULTS

2.2.1 PreP-S and PostP-S are associated with sex-selective effects on adult VTA DA neuron activity

We first explored sex differences in the physiological effects of PD21-30 footshock (FS) and restraint (RS) combined stress, which is defined as prepubertal stress (PreP-S), on adult VTA DA neuron activity and behaviors (Figure 1A). With respect to DA neuron population activity, a two-way ANOVA detected a significant sex and PreP-S interaction [$F(1,31)=12.30$, $p<0.01$] and a significant main effect of PreP-S [$F(1,31)=9.852$, $p<0.01$]. Tukey's post hoc analyses revealed PreP-S selectively increased population activity in males ($p<0.01$) (Figure 1B). This male-selective increase in population activity is limited to the medial VTA [two-way repeated measure (RM) ANOVA; sex:stress condition: $F(3,93)=7.165$, $p<0.001$; PreP-S:Males, $p<0.05$] (Figure 1C). No significant effect was found on DA neuron phasic firing (i.e., average firing rate and spikes in burst) (Figure 1D-E). At PD65-71, stress-induced behavioral changes were evaluated using the elevated plus maze (EPM), novel object recognition (NOR), and amphetamine-induced hyperlocomotion (AIH). PreP-S:Males selectively exhibited less time spent in the open arms [interaction: $F(1,38)=6.228$, $p<0.05$; PreP-S:Males, $p<0.05$] in EPM (Figure 1F) and reduced discrimination index [interaction, $F(1,37)=6.884$, $p<0.01$; PreP-S:Males, $p<0.01$] in NOR (Figure 1H). Although a two-way RM ANOVA on post-amphetamine locomotion revealed significant main effects of time [$F(5.031,181.1)=16.51$; $p<0.0001$] and stress:sex conditions [$F(3,36)=9.573$, $p<0.0001$] (Figure 1I), Tukey's post hoc analysis did not reveal any significant stress-related differences within sex.

In contrast, the effects of PD41-50 postpubertal stress (PostP-S) were highly female-specific (Figure 2). For VTA DA recordings, a female-selective elevation in adult DA neuron population activity was observed [interaction: $F(1,31)=11.47$; $p<0.01$; sex: $F(1,31)=13.32$, $p<0.01$; PostP-S:Females, $p<0.01$] (Figure 2B), which was again selective for the medial aspect of the VTA [stress:sex condition: [$F(3,93)=6.714$, $p<0.001$; PostP-S:Females, $p<0.05$] (Figure 2C). PostP-S did not alter the phasic firing of DA neurons (Figure 2D and E). Behaviorally, no significant effect was found in EPM or NOR (Figure 2F-H). In AIH, despite significant main effects of time [$F(4.326,164.4)=17.93$; $p<0.0001$] and stress:sex conditions [$F(3,38)=11.49$; $p<0.0001$], post hoc comparisons did not reveal significant stress-related effects (Figure 2I). Collectively, this dataset indicates dramatic sex and exposure-time differences in stress-induced adult DA neuron firing alterations.

We also monitored body weight development (Appendix A, Table S1), which did not show prominent stress-related differences. Moreover, to control for potential confounds from behavioral testing or differential recovery time, we performed DA recordings at 1-2 weeks or 5-6 weeks after stress in another set of behavioral testing-naive rats (Appendix A, Figure S1). We found that both stresses uniformly increased DA firing in the short term, but the long-term stress impact on DA neurons was sex- and exposure-time-specific; consistent with the above-reported findings. Furthermore, we determined singular FS or RS on adult DA system function (Appendix A, Figure S2). Consistent with our previous findings (Gomes & Grace, 2017; Klinger et al., 2019), RS alone did not induce any effect on adult DA neuron activity. Interestingly, prepubertal FS alone recapitulated the above described male-selective stress vulnerability to PreP-S. This result contrasted with our previous finding that only PD31-40 combinational FS+RS is sufficient to alter adult DA neuron firing, therefore suggesting that at a younger age males might be increasingly

vulnerable to a broader range of stressors. Nonetheless, given that prominent sex differences were only observable in the long-term DA system response to stress, in the subsequent experiments we focused on the combined stress and adult stress consequences.

2.2.2 Sex and exposure-age differences in adult vHipp pyramidal neuron firing response to stress

VTA DA neuron tonic and phasic firing modes are regulated by distinct circuits (Floresco et al., 2003). The vHipp, precisely the ventral subiculum (vSub), predominantly controls the tonic activity of VTA DA neurons (i.e., population activity) via a polysynaptic circuit that involves the nucleus accumbens (NAc) and the ventral pallidum (VP) (Floresco et al., 2001; Lodge & Grace, 2006). Developmental stress can alter chronically the firing properties and oscillatory activity of hippocampal pyramidal neurons (Ali et al., 2013; Murthy et al., 2019). Consistently, our previous study showed adolescent stress during PD31-40 leads to vHipp pyramidal neuron hyperactivity in adults (Gomes et al., 2020). Nonetheless, the precise age and sex dependence of this effect was unclear. To test this, we next explored whether stress-induced DA system activation was accompanied by abnormal vHipp activity.

Putative vHipp pyramidal neurons were recorded in adult animals and identified by electrophysiological signatures as previously described (Gomes et al., 2020) (Figure 3A). No effect of stress on vHipp pyramidal neuron population activity was detected (Figure 3B). Significant group median differences were detected in vHipp pyramidal neuron firing rate (data non-normally distributed, Kruskal–Wallis test, $H=24.80$, $p<0.001$). Dunn's multiple-comparison tests revealed a male-selective increase in vHipp activity by PreP-S ($p<0.05$) and a female-selective increase by PostP-S ($p<0.01$) (Figure 3C). Significant group median differences in spikes that occurred in

bursts were also observed (Kruskal-Wallis, $H=16.34$, $p<0.01$), and post hoc Dunn's tests revealed a sex-selective increase only in PreP-S:Males ($p<0.05$) (Figure 3D). Altogether, this dataset indicates distinct sex- and expose-age-dependent stress effects on adult vHipp functions, a vulnerability pattern corresponding highly to VTA DA neurons.

2.2.3 Sex and exposure-age differences in BLA pyramidal neuron firing response to stress

The BLA projects strongly to the vHipp (Felix-Ortiz et al., 2013; Pikkarainen et al., 1999), and stress exposure is known to increase BLA pyramidal neuron firing rate (Blume et al., 2019; Zhang & Rosenkranz, 2012) and excitability (Rosenkranz et al., 2010). Notably, abnormal activation or disinhibition of the BLA can have long-term deleterious effects on hippocampal structure and function, manifesting as interneuron deficits (Berretta et al., 2004) and synaptic plasticity disruptions (Vouimba & Richter-Levin, 2005). Thus, in parallel to vHipp and VTA activation, we propose that adolescent stress might also chronically activate BLA neurons, which could be upstream to the emergence of vHipp hyperactivity and VTA hyperdopaminergic state (Gomes et al., 2019b). Early life stress-induced persistent activation of the BLA has been explored immunohistochemically by c-fos staining in rodents and by neuroimaging in humans (Malter Cohen et al., 2013), but few studies have directly explored this effect electrophysiologically. Thus, two studies using adolescent repeated restraint stress reported increased BLA pyramidal neuron spontaneous firing and excitability approximately two days after stress exposure (Hetzel & Rosenkranz, 2014; Zhang & Rosenkranz, 2012). Consistently, another study reported that continuous social isolation starting in adolescence can increase adult BLA excitability (Rau et al., 2015). Whether adolescent stress can have persistent effects on BLA firing, and if so, whether there are sex- and exposure-age dependencies, are unknown. In humans, prepubertal and

postpubertal maltreatments have been differentially associated with adult amygdala response to threatening stimuli (Zhu et al., 2019). Therefore, we hypothesize that developmental stress can differentially affect adult BLA firing depending on stress exposure age and sex.

To test this, we recorded from putative BLA pyramidal neurons both 1-2 weeks (short-term effect) and approximately >5 weeks (long-term effect) after stress. BLA pyramidal neurons were identified based on previously reported electrophysiological criteria (Zhang & Rosenkranz, 2012; Zhu & Grace, 2021) (Figure 4A and B). For the short-term PreP-S effect, a significant group median difference was detected (data non-normally distributed, Kruskal–Wallis test, $H=13.33$, $p<0.01$), and Dunn's multiple-comparison tests revealed a sex-selective increase in PreP-S:Males ($p<0.01$) (Figure 4C). This effect is persistent, as a significant group median difference was also selectively observed in PreP-S:Males at >5 weeks after stress (data non-normally distributed; Kruskal–Wallis test, $H= 24.69$, $p<0.0001$; Dunn's test, PreP-S:Males, $p<0.0001$) (Figure 4D). In contrast, no stress-related effect was observed in the short-term response to PostP-S. For long-term PostP-S effects, although significant group median differences were observed (Kruskal–Wallis test, $H=13.64$, $p<0.01$), post hoc Dunn's analysis did not reveal any stress-related difference. Instead, only between-sex group differences were found in PostP-S:Males vs. Naïve:Females ($p<0.05$) and PostP-S:Males vs. PostP-S:Females ($p<0.05$) comparisons.

Altogether, this dataset indicates that while PreP-S can chronically activate the BLA specifically in males, PostP-S failed to affect BLA firing in either sex. Therefore, such early emergent BLA hyperactivity might be selectively detrimental to males.

2.2.4 Sex- and exposure age-dependent stress effects on mPFC-BLA inhibitory control

The dorsomedial PFC exerts "top-down" control of stress-induced BLA activation (Hariri et al., 2003; Radley et al., 2006; Rosenkranz & Grace, 2001, 2002; W.-H. Zhang et al., 2021). Electrophysiologially, the modulatory actions of PFC on BLA neuronal firing can be studied by spike plasticity recordings. Specifically, we have demonstrated previously that for PFC-evoked BLA pyramidal neuron extracellular activity, high-frequency electric stimulation (HFS) in the prelimbic PFC (plPFC) can lead to spike long-term depression (LTD) (Uliana et al., 2021). Consistently, such inhibitory mPFC-BLA regulation has been demonstrated by plPFC chemogenetic activation (Wei et al., 2017) and is attributed to a feedforward inhibition mechanism driven by BLA interneurons (Rosenkranz & Grace, 2002). Functionally, this PFC-BLA control is thought to be adaptive to cope with the immediate stress-induced BLA hyperactivity (Uliana et al., 2021), a putative mechanism mediating cognitive regulation of emotion (Selleck et al., 2018). Notably, this PFC Inhibitory modulation over BLA neurons is prone to severe stress (Uliana et al., 2021; Wei et al., 2017) and remains immature during adolescence (PD39) (Selleck et al., 2018; Zhang & Rosenkranz, 2016). These previous findings predict that PFC-BLA inhibitory regulation may have heightened stress vulnerability during adolescence that are age- and sex-dependently regulated (Ferrara et al., 2021). Considering all of these factors, we next evaluated whether the longitudinal impact of PreP-S and PostP-S stress in this pathway correlates with the observed changes in BLA single-unit activity.

The impact of plPFC HFS on BLA pyramidal neuron evoked spiking was assessed <3 weeks or >6 weeks after stress. HFS-induced spike plasticity recording was conducted based on our previously published protocols (Belujon et al., 2014; Gill & Grace, 2013; Uliana et al., 2021). We did not observe any difference in baseline evoked-firing properties (Figure 5A and B; Also see

SI Appendix Methods; Table S2). For the short-term PreP-S effect (tested at PD37-51), in the time course response a two-way RM ANOVA in males indicated significant effects of PreP-S [$F(1,13)=7.283$, $p<0.05$] and PreP-S and time interaction [$F(7,91)=2.269$, $p<0.05$]. Bonferroni's post hoc analyses indicated significant spike depression at 5 ($p<0.01$) and 10 minutes ($p<0.05$) post-HFS, whereas these effects were absent in PreP-S:Females (Figure 5C). Notably, the negative main effect of time suggested an overall immature circuit response to HFS at this age, consistent with our previous finding (Uliana et al., 2021). Accordingly, in the mean post-HFS responses, all groups displayed minimal (<20%) HFS-induced spike probability alteration with no significant group differences (Figure 5D). Notably, this male-specific increase in HFS-induced spike depression was reminiscent of an adult-like response, and we tentatively concluded this to be a precocious maturation of plasticity.

For the long-term PreP-S effects, in the time course response we found significant effects of stress [$F(1,9)=28.42$, $p<0.001$], time [$F(7,63)=2.574$, $p<0.05$] and interaction [$F(7,63)=5.674$, $p<0.0001$] in males, with significant LTD deficits at 10-30 minutes post-HFS. Similar LTD deficits were observed in PreP-S:Females, in which an impaired spike depression was observed at 15-30 minutes post-HFS [interaction: $F(7,91)=4.773$, $p<0.001$); Figure 5E]. Consistently, significant long-term PreP-S effects were observed in the mean spike response in both sexes [PreP-S: $F(1,22)=32.47$, $p<0.0001$)] (Figure 5F).

With respect to PostP-S effects, in males, LTD deficits in the time course response were observed at both <3 weeks [interaction: $F(7,77)=2.663$, $p<0.05$; 25 and 30 minutes Post-HFS, $p<0.05$; Figure 5G] and >6 weeks [interaction: $F(7,91)=4.296$, $p<0.001$; 10–30 minutes Post-HFS, $p<0.05$; Figure 5I]. These effects were completely absent in females at both testing ages (Figure 5G and I). Consistently, in the mean spike response, while there is only a statistical trend for a

short-term effect [interaction: $F(1,27)=3.698$, $P=0.0651$; Figure 5H] , after 6 weeks post-stress, only PostP-S:Males showed robust PFC-BLA spike LTD deficits [PostP-S: $F(1,23)=9.589$, $p<0.01$; PostP-S:Males>Naïve:Males, $p<0.05$; Figure 5J].

In conclusion, these findings suggest distinct stress vulnerability at the level of the ilPFC-BLA inhibitory control circuit. Whereas females are only vulnerable to the long-term effects of PreP-S, males display more pronounced vulnerability to both stress paradigms. In addition, shortly after the PreP-S (PD37-51), males displayed an accelerated ilPFC-BLA inhibitory control maturation. Considering that at a similar age (PD37-44) PreP-S:Males also show increased BLA firing rate, we speculate that this plasticity modulation might represent a concomitant adaptive response of the ilPFC to control BLA hyperactivity, albeit insufficient to eventually limit the BLA hyperactivity. Overall, these plasticity recording data correspond strongly with male-selective BLA firing activation.

2.2.5 Age- and sex-dependent stress vulnerability of parvalbumin interneurons in the BLA and the vHipp

The observed increase in BLA and vHipp activities can be driven by structural and functional impairments of PVIs. During adolescence, a critical maturational event for corticolimbic PVIs is the aggregation of extracellular matrix structures, namely perineuronal nets (PNNs), which is proposed to enhance GABAergic inhibition and support PVI fast-spiking ability (Lensjø, Lepperød, et al., 2017). Converging evidence indicates that developmental stress can induce a broad range of adult PVI cellular alterations, including decreased PV and PNN expression and their co-localization (Perlman et al., 2021). Given that PVIs are important in regulating pyramidal neuron firing rate (Woodruff & Sah, 2007), impairments to PVIs could lead to the

observed pyramidal neuron disinhibition. To explore this structural basis, we next analyzed the longitudinal impact of stress on PVIs, emphasizing their co-expression of PNNs.

PVI impairments were longitudinally assessed by immunohistochemistry and fluorescent microscopy in the basal nucleus of the BLA (Figure 6A and B). Substantial PreP-S-induced PVI impairments were found mostly in males rather than in females (Figure 6C-D). Thus, at PD75 PreP-S:Males displayed reduced numbers of PV+ (multiple Welch t-test; $t(8.863)=4.349$, $p<0.01$), PNN+ [$t(8.913)=2.555$, $p<0.05$], and co-labeled cells [$t(5.634)=2.934$, $p<0.05$]. Reduced PV/PNN co-labeling was also detected at PD41, suggesting a persistent PVI impairment. These effects were absent in females. Instead, PreP-S:Females only displayed transient reductions of PNN+ [$t(7.309)=2.819$, $p<0.01$] and PV/PNN co-labeled cells [$t(9.997)=2.495$, $p<0.05$] at PD31 (i.e., 1-day after stress). Notably, these effects were exposure age-dependent, as PostP-S failed to change these markers in either sex (Figure 6E-F).

We next explored stress-induced PVI impairments in the vHipp (Figure 7A-B). In males, PreP-S reduced PV+ [$t(9.120)=4.939$, $p<0.001$] and PV/PNN co-labelled cells [$t(5.832)=3.773$, $p<0.01$] only at PD95. In contrast, PV+ and PNN+ cell counts in PreP-S:Females were largely unaffected, except for a transient decrease of PV+ cell count at PD41 [$t(9.561)=2.291$, $p<0.05$] (Figure 7C-D). In contrast, a reversed sex dependence was found in PostP-S animals. Thus, after PostP-S only females at PD95 displayed significant reductions of PV+ [$t(9.573)=6.918$, $p<0.001$] and PV/PNN co-labeled cells [$t(10.00)=3.845$, $p<0.01$] (Figure 7E-F).

In sum, we found BLA and vHipp PVIs to be sex- and age-dependently disrupted by adolescent stress. While in the vHipp PVI impairments are strongly correlated with sex-dependent heightened pyramidal neuron activity (Figure 3), in the BLA the stress-induced persistent PVI impairments appeared to be male-dominant.

2.3 DISCUSSION

2.3.1 Summary of findings

This is the first electrophysiological study to systematically assess sex- and exposure age-dependent differences of adolescent stress on the VTA DA system and its afferent regulation. We found PD21-30 and PD41-50 to be distinct stress sensitive windows, which are sex-dependent. Whereas PreP-S selectively increased adult DA neuron population activity in males, in females hyperdopaminergic states were observed only after PostP-S. Both stress paradigms activated the medial aspects of the VTA, a region that projects predominantly to the reward- and affect-related ventral striatum (Lammel et al., 2008), without affecting phasic firing parameters. The PreP-S effect on DA neuron firing accompanied male-selective adult anxiety and recognition memory deficits. The male-selective responses in EPM anxiety-like behaviors are broadly consistent with several previous reports with neonatal or juvenile stress (Barna et al., 2003; Brydges, Jin, et al., 2014; Prusator & Greenwood-Van Meerveld, 2015; Slotten et al., 2006), and the observed male-selective cognitive deficits are consistent with the emerging findings that early life stress biases males toward adult cognitive deficits (Bangasser et al., 2018). The biological basis for these behavioral effects is presumably complex and is hence worth future investigations. Notably, this abnormal DA system activation correlated with sex-selective and age-dependent vHipp hyperactivity. Physiological alterations in the BLA were largely male-specific, characterized by PreP-S-induced increase in BLA pyramidal neuron firing rates. In contrast, PostP-S failed to induce equivalent BLA deficits in both sexes. Furthermore, stress-induced plPFC-BLA inhibitory control deficits were also found to affect predominantly males. Thus, while PreP-S produced a transient precocious maturation in PFC-BLA circuit control, rats from both sexes displayed PreP-

S-induced spike plasticity deficits in adulthood. In contrast, PostP-S produced a male-selective LTD deficit without affecting females. Lastly, corresponding age- and sex differences were also found in PVI impairments. Thus, in the vHipp PreP-S produced delayed PVI impairments at PD75 only in males, whereas PostP-S was found to only affect female vHipp PVI at this age. In the BLA, whereas PreP-S produced male-selective persistent PVI impairments, PostP-S did not produce comparative changes in either sex. Altogether, our dataset complements our previous reports and indicates that adolescence contains several temporally distinct windows of vulnerability, during which stress exposure can dynamically produce sex-dependent physiological alterations that are putatively relevant to schizophrenia pathophysiology.

2.3.2 Selection of stress paradigm and age groups

Prolonged rodent adolescence (i.e., PD21-60) can be divided into substages (Green et al., 2016). We grouped adolescent animals based on chronological age and defined stress procedures defining PD21-30 and PD41-50 as "prepubertal" and "postpubertal stress", respectively. We did not individually measure or control pubertal onset, as techniques that reliably measure puberty onset (e.g., vaginal lavage or molecular puberty assays) are intrusive and stressful (Sharp et al., 2003) and can therefore confound our analyses. Nevertheless, these operational definitions are consistent with our previous publication (Zimmerman et al., 2013), and the designation of PD21-30 as "prepuberty" is line with multiple other reports (Brydges, Wood, et al., 2014; Tsoory & Richter-Levin, 2006; Ueno et al., 2018). We confidently predict female PD41-50 to be postpubertal due to early female pubertal onset at around PD36 (McCormick et al., 2017). In males, although PD41-50 may overlap slightly with pubertal onset (defined by preputial separation (Korenbrot et al., 1977); ~PD41), the majority of this period is still postpubertal, therefore justifying our

designation of stress groups. Importantly, PD41-50 is temporally distant from PD21-30. Therefore, we believe for our purpose to investigate exposure age-dependent effects, these windows are sufficient. PD21-30 and PD41-50 in rodents approximate late childhood and adolescence in humans (Eiland & Romeo, 2013; Sheth et al., 2017; Watt et al., 2017), which are postulated to be sensitive periods for stress-induced risks for later life psychopathologies that involve a dysfunctional DA system (e.g., schizophrenia (Alameda et al., 2016; Croft et al., 2019)) (Carr et al., 2013). These windows have been seldom explored for electrophysiological stress impact. Furthermore, we included these windows to purposefully parallel our recent studies using the same stress procedure during PD31-40 separately in males and females (Gomes & Grace, 2017; Gomes et al., 2020; Klinger et al., 2019). This allowed us to generalize conclusions within a broader context.

Notably, sensitive periods are defined by region-specific and stress-induced outcome measures (Hodes & Epperson, 2019; Teicher et al., 2006). In this context, we focus this study primarily on the stress-induced electrophysiological states of the DA system and its afferent regulators (i.e., the BLA and the vHipp). We used 10-day FS+RS combined stress as we reported previously (Gomes & Grace, 2017). This stress paradigm's duration is suitable for being placed within substages of rodent adolescence, allowing us to infer age and developmental stage specificity. Moreover, current literature on long-term adolescent stress impact on VTA DA neuron activity has been almost exclusively conducted in social stress models (Douma & de Kloet, 2020; Watt et al., 2017), despite in humans childhood adversity exposure with no substantial social element has also been strongly associated with risks for DA-related psychopathologies (Morgan & Gayer-Anderson, 2016) . Common adversities are often repeated in humans and involve

multiple forms that confer added risks for later life. Thus, considering all these factors, we chose to study a non-social stress paradigm that is heterotypic.

2.3.3 Stress-induced DA system activation: relevance to previous studies

Our DA recording data showed that stress during chronologically discrete, sex-dependent adolescent sensitive periods induced long-term DA neuron tonic activation in adults without affecting phasic DA firing (Figure 1D-E and Figure 2D-E). Spontaneous tonic DA neuron firing is a prerequisite for functional DA release (Grace, 2016). Thus, this study confirmed the vast microdialysis literature on stress-induced increase in DA release in VTA target regions [reviewed in (Douma & de Kloet, 2020; Holly et al., 2015)]. Interestingly, although the exact responsive windows shifted between sexes, overall adolescent stress induced a relatively uniform long-term DA neuron activation. Our findings on the chronicity of this effect and the engagement of tonic DA activity are novel because, although studies using chronic social defeat demonstrates DA neuron phasic activation can last 28 days (Cao et al., 2010; Friedman et al., 2014), few other works utilized long post-stress delay and/or assessment of multiple DA neuron firing states. Overall, the present data indicate that adolescence is perhaps a unique window for stress to induce enduring DA system tonic activation, a circuit basis strongly implicated in schizophrenia (Grace, 2016).

2.3.4 Relevance to schizophrenia

Correlating with VTA DA hyperactivity, PreP-S males and PostP-S females exhibited vHipp hyperactivity and PVI impairments as adults. Collectively, these results are consistent with an established neurodevelopmental model of schizophrenia risks, i.e., the MAM model (Gomes et

al., 2019b; Modinos et al., 2015), PD31-40 peripubertal stress model (Gomes et al., 2020), as well as schizophrenia clinical observations (Modinos et al., 2015). Specifically, human imaging studies show elevated presynaptic striatal DA functions in schizophrenia patients (Howes & Nour, 2016), which implicates an increased number of active DA terminals, consistent with the observed increased DA neuron spontaneous firing. The increased vHipp and BLA firing are consistent with the increased cerebral perfusion in homologous regions of schizophrenia patients (Benes, 2010; Lieberman et al., 2018b). Thus, although the exact sensitive period timing differs between sexes, adolescent stress as a whole uniformly recapitulates neurophysiological disruptions observed in schizophrenia. Intriguingly, we observed previously that in both sexes, once animals enter adulthood, i.e., PD65-74, they show relative resilience to the long-term stress impacts on persistent changes in DA neuron firing (Gomes et al., 2020; Klinger et al., 2019). Thus, the current findings add to our previous reports, which together indicate that adult DA neuron activity states are dynamically modulated by stress history and are highly vulnerable in sex-selective and age-dependent adolescent sensitive periods. Interestingly, in the present study we also observed PD21-30 male rats to be vulnerable to the long-term effects of singular FS on DA neuron activity (Appendix A; Figure S2), a vulnerable phenotype mimicking early PFC-lesioned rats (Gomes & Grace, 2017). This indicates that prepubertal males may have a not yet developmental PFC, which contributes to their specific vulnerability to broader stressor types.

2.3.5 Potential mechanisms of age-dependence

Several mechanisms may underlie the observed age dependence of stress. We postulate stress-induced vHipp activity alterations to be a driving factor for DA hyperactivity. Corresponding to adult hyperdopaminergic states, PreP-S males and PostP-S females exhibited

vHipp hyperactivity. The vHipp is a well-established afferent regulator of DA neuron tonic activity, acting via a well-established vSub-NAc-VP polysynaptic circuit (Grace, 2016). Thus, the observed age-dependent effects in vHipp pyramidal neuron firing could be an upstream mechanism leading to distinct vulnerability of the VTA DA system. The cellular mechanisms of vHipp hyperactivity are likely multifaceted, potentially involving a complex interplay between genetic factors and stress-mediating molecules (Chen et al., 2006; McEwen et al., 2016). Although the exact molecular mediators are not directly assessed in this study, we posit that age and sex-selective vHipp PVI impairments may mediate the vHipp/VTA pathophysiology (Gomes et al., 2019b). In the vHipp, PVIs are a potent source of inhibition and are stress-sensitive (Perlman et al., 2021). Importantly, PV knockdown directly upregulates vHipp pyramidal neuron activity and VTA DA neuron population activity (Stephanie M. Perez et al., 2019), similar to the effects observed here. Thus, the stress-induced vHipp physiological alterations are potentially secondary to PVI impairments.

The developmental trajectories of vHipp PVIs could potentially explain the observed sensitive period timing. Developmental stress can impair PVIs in part via activating oxidative stress-related processes (Jiang et al., 2013; Rossetti et al., 2018; Zaletel et al., 2016). During early adolescence, PV expression is immature (Caballero et al., 2013) and the anti-oxidative (thereby neuroprotective) PNNs are not fully developed (Lensjø, Christensen, et al., 2017; Yamada & Jinno, 2013). Thus, vHipp PVIs might be particularly vulnerable to early adolescent stress, as demonstrated by our stress paradigm during PD21-30 (this study) or PD31-40 (Gomes et al., 2020) and other works (e.g., (Deng et al., 2019)). The present male data showed that only PreP-S was sufficient to reduce adult PV, PNN, and co-labeled cell counts, whereas PostP-S failed to elicit similar histological alterations (Figure 7). PVIs lacking PNNs are incapable of fast spiking (Lensjø,

Lepperød, et al., 2017), and direct enzymatic dissolving of vHipp PNNs was found to both activate the vHipp and the downstream VTA DA output (Shah & Lodge, 2013). These convergent findings suggest that PreP-S might impair PVIs by disrupting PNN maturation, leading to vHipp disinhibition and VTA DA neuron activation. Notably, this line of evidence has been almost exclusively established in males. Preliminary evidence suggests that female PV and PNNs might develop under differential trajectories (Drzewiecki et al., 2020; Griffiths et al., 2019; Wu et al., 2014; N. Zhang et al., 2021) and hence exhibit distinct stress vulnerability (Guadagno et al., 2020), albeit these studies were conducted in other regions. Whether this proposed model readily applies to PostP-S females is unclear. Nonetheless, our data indicated PostP-S females at PD95 showed consistent PV/PNN pathology compared with males (Figure 7). Thus, it is possible that rather than a continuous increase in PV/PNN expression as observed in males (Caballero et al., 2013), female PVIs might develop following a more dynamic trajectory, contributing to selective vulnerability observed in postpuberty.

2.3.6 Potential involvement of the BLA

Chronic stress activates the BLA (Belujon & Grace, 2015; McEwen et al., 2016). Under normal conditions, BLA pyramidal neurons are potently inhibited by local PVIs, exhibiting low spontaneous firing rates (Muller et al., 2006; Rosenkranz & Grace, 1999; Woodruff & Sah, 2007). This activity state could be disrupted by PVI impairments. Importantly, the BLA sends dense glutamatergic projections to the vHipp (Pikkarainen et al., 1999), and pharmacological BLA disinhibition (e.g., via picrotoxin infusion) can disrupt schizophrenia-related hippocampal GABAergic neurotransmission (Benes, 2010), including reduced PV expression (Berretta et al., 2004). Thus, early BLA GABAergic deficits might drive hippocampal PVI pathology and VTA

hyperactivity in schizophrenia (Grace, 2016). In our male BLA recordings, high spontaneous firing emerged within 1-2 weeks after PreP-S (i.e., PD37-45; Figure 4C), which seemed to precede the adult emergence of vHipp PVI impairments (PD75; Figure 6C). Thus, these male observations lend partial support to the abovementioned model of schizophrenia risk (Berretta et al., 2004; Berretta et al., 2001).The BLA projects predominantly to Hipp pyramidal neurons but also innervates PVIs. . Therefore, whether the observed BLA activation directly confers excitotoxicity to PVIs is worth future investigations using projection-specific approaches. Since our data found almost concurrent BLA PVIs impairments (reduced PV/PNN co-labelling at PD41; Figure 6C) and BLA hyperactivity (PD37-45; Figure 4C), it is plausible that an early-onset and long-lasting BLA PVI disruption drives abnormal BLA firing which leads to sequential impairments in vHipp PV networks. Alternatively, a direct long-lasting PreP-S-induced increase in BLA pyramidal neuron excitability is also possible, which would be consistent with previous findings with continuous social isolation that starts in adolescence (Rau et al., 2015).

We also tested whether adolescent stress disrupts the functional control of plPFC on BLA spiking in an age- and sex-dependent manner. Previous studies indicate mPFC inhibitory control over BLA pyramidal neuron firing is immature during adolescence (Selleck et al., 2018). In our data, within 3 weeks after PreP-S (i.e., PD37-51), HFS in males could already induce an adult-like PFC-BLA spike LTD, whereas naïve rats at this young age displayed an immature spike response profile (Figure 4C and D). This male-selective PreP-S-induced facilitation of LTD reflects a precocious maturation, which seems to emerge as an adaptive process to ameliorate BLA hyperactivity. Nevertheless, this early change does not seem to effectively limit the observed BLA hyperactivity. Interestingly, PreP-S females did not trigger this adaptive process, which is expected because PreP-S females also did not display BLA hyperactivity. In adulthood, while both naïve

animals achieved mature PFC-BLA LTD as expected, PreP-S animals uniformly displayed LTD deficits. These adult deficits suggest that long after PreP-S, the PFC is still incapable of gating BLA activity, consistent with the observed long-lasting BLA hyperactivity in males (Figure 4C). Intriguingly, despite PFC-BLA control being disrupted (Figure 4C), adult PreP-S females did not display either BLA hyperactivity or PVI deficits. Thus, it appears that PFC-BLA dysfunctional connectivity alone might only represent the inability of PFC to regulate excessive BLA firing rather than a direct cause. On the other hand, we observed a male-selective PostP-S effect on PFC-BLA control within 3 weeks (PD57-70; i.e., early adulthood) and after 6 weeks after stress, with no effects observed in females. Collectively, these results indicate male-dominant vulnerability to stress-induced corticoamygdalar circuits regardless of stress exposure age. The behavioral implications of these sex differences in PFC-BLA inhibitory control response to stress remained to be more thoroughly determined, which putatively pertains to the processing of fear stimuli (Uliana et al., 2021).

2.3.7 Potential mediators of sex differences

Why the female DA system is protected in early adolescence but vulnerable in late adolescence is unclear. The observed PD21-30 female resilience is consistent with our previous PD31-40 results (Klinger et al., 2019), which points to late adolescence representing a sudden emergence of DA system stress vulnerability. Interesting, the PostP-S effect in females only correlated with vHipp structural and functional (i.e., PVI) deficits without a preceding BLA dysfunction like that observed in males. Therefore, it could be that in females PostP-S may directly act on vHipp, potentially via altering corticosterone signaling. In this context, despite the overall limited research in females, several previous studies using similar age groups support this

hypothesis. At PD28, female rats display a more mature profile of corticosterone response to stress, characterized by a rapid return of serum hormone level to baseline (Romeo, 2010). Prolonged corticosterone activation is hypothesized to pathologically activate PVIs through the glucocorticoid receptor (GR)-dependent non-genomic mechanisms (Hu et al., 2010). Therefore, when exposed to PreP-S, it is conceivable that females might be selectively protected from this effect on PVIs. Such corticosterone regulation reaches adult capacity in males at PD31-40 (Foilb et al., 2011), presumably explaining the male-selective PD21-30 vHipp vulnerability and PD41-50 resilience; a mechanism in parallel to the gradual maturation of PV/PNN states. In a similar vein, the prominent postpubertal female vulnerability could be attributable to female-selective long-term modulation of stress hormone signaling. Supporting this hypothesis, combined chronic restraint and social stress at PD35-47 was found to sex-selectively increase adult female CA1 presynaptic terminals onto pyramidal neurons (Hyer et al., 2021), which could act as a structural basis for increased hippocampal neuronal firing. Moreover, repeated restraint stress at PD30-52 selectively increases basal corticosterone levels in female adults (Barha et al., 2011). Furthermore, PD31-41 chronic mild stress was found to selectively upregulate vHipp stress-hormone related receptors in females, such as the mineralocorticoid receptor (MR) in the vSub (Raineki et al., 2018). Collectively, these convergent findings on the long-lasting, female-specific, and primarily postpubertal stress effects on stress hormone signaling appear to accumulate in the vHipp to lead to pyramidal neuron hyperexcitability (Maggio & Segal, 2009), which would be consistent with the present findings in females.

2.3.8 Conclusions

We examined age- and sex-dependent sensitive periods for adolescent stress and its propensity to upregulate adult VTA DA neuron tonic activity. While males are vulnerable to stress during the early, prepubertal period of adolescence, females are more vulnerable at a later stage, specifically in postpuberty. During these sensitive periods defined by adult DA system electrophysiological responses, stress exposure elicits concurrent vHipp pyramidal neuron pathophysiology and PVI impairments, which together with the observed DA hyperactivity collectively recapitulate schizophrenia-related circuit-level disruptions. Despite these sex-convergent activating effects on VTA and vHipp neuronal firing, BLA activity, PFC-BLA functional connectivity, and markers of BLA PVIs are modulated primarily in PreP-S males. Whereas in females, these constructs were largely unaffected by both stress paradigms. Altogether, these findings are consistent with the emerging clinical evidence that childhood and adolescence may represent sensitive periods for stress to specifically increase psychosis risks, and further pinpoint vHipp and VTA DA system hyperactivities as potential neurobiological mediators. Individuals at clinical high risks for schizophrenia tend to more likely to experience trauma in childhood and early adolescence (before age 12 years) (Loewy et al., 2019), a period roughly corresponding to the prepubertal time point of this study. Thus, the observed male-selective PreP-S effects might explain the well-known male-biased risks for severe schizophrenia symptoms and earlier psychosis onset (Aleman et al., 2003; Susana Ochoa et al., 2012). Although relatively protected for psychosis-related DA hyperactivity by early stress, females are vulnerable to stress post-pubertally (this study) and in adulthood (Klinger et al., 2019), which would be consistent with the human observation that adult females are at increased susceptibility to affect-related psychopathologies (Rubinow & Schmidt, 2019). Thus, these findings can have strong implications

for the etiology and pathophysiology of stress-related developmental disorders, with a particular emphasis on schizophrenia. Beyond this, the discovered sex-specific stress vulnerability might provide a framework for understanding other sex-biased, DA-related psychopathologies (Andersen, 2019; Bale & Epperson, 2015; Hodes & Epperson, 2019).

2.4 MATERIALS AND METHODS

Timed pregnant Sprague-Dawley rats were obtained at gestational day 15. Male and female pups were born to our facility at PD0 and weaned at PD21, at which the animals were randomly assigned to naïve, PreP-S, and PostP-S conditions. PreP-S and PostP-S rats were exposed to a compound 10-day stress paradigm consisting of daily FS and three sessions of one-hour RS as previously described (Gomes & Grace, 2017; Gomes et al., 2020; Klinger et al., 2019). In parallel to our previous work (Gomes & Grace, 2017; Gomes et al., 2020), a series of behavioral assays and in vivo electrophysiology experiments were performed in adulthood in anesthetized animals to determine age- and sex-dependent long-term stress-responses in VTA DA neuron and vHipp pyramidal neuron activities. Moreover, short-term (1-3 week after stress) and long-term (>5-6 weeks) effects of PreP-S on BLA neuron activity and plasticity in medial PFC-mediated BLA spike control were determined. Another set of animals was used for immunohistochemistry and fluorescent microscopy to determine cellular stress response in PVIs, particularly the co-localization with PNNs. A total of six experiments were conducted in this study. All experimental protocols were performed according to National Institutes of Health Guideline for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh. Experimental details are provided in **Appendix A.**

2.5 FIGURES

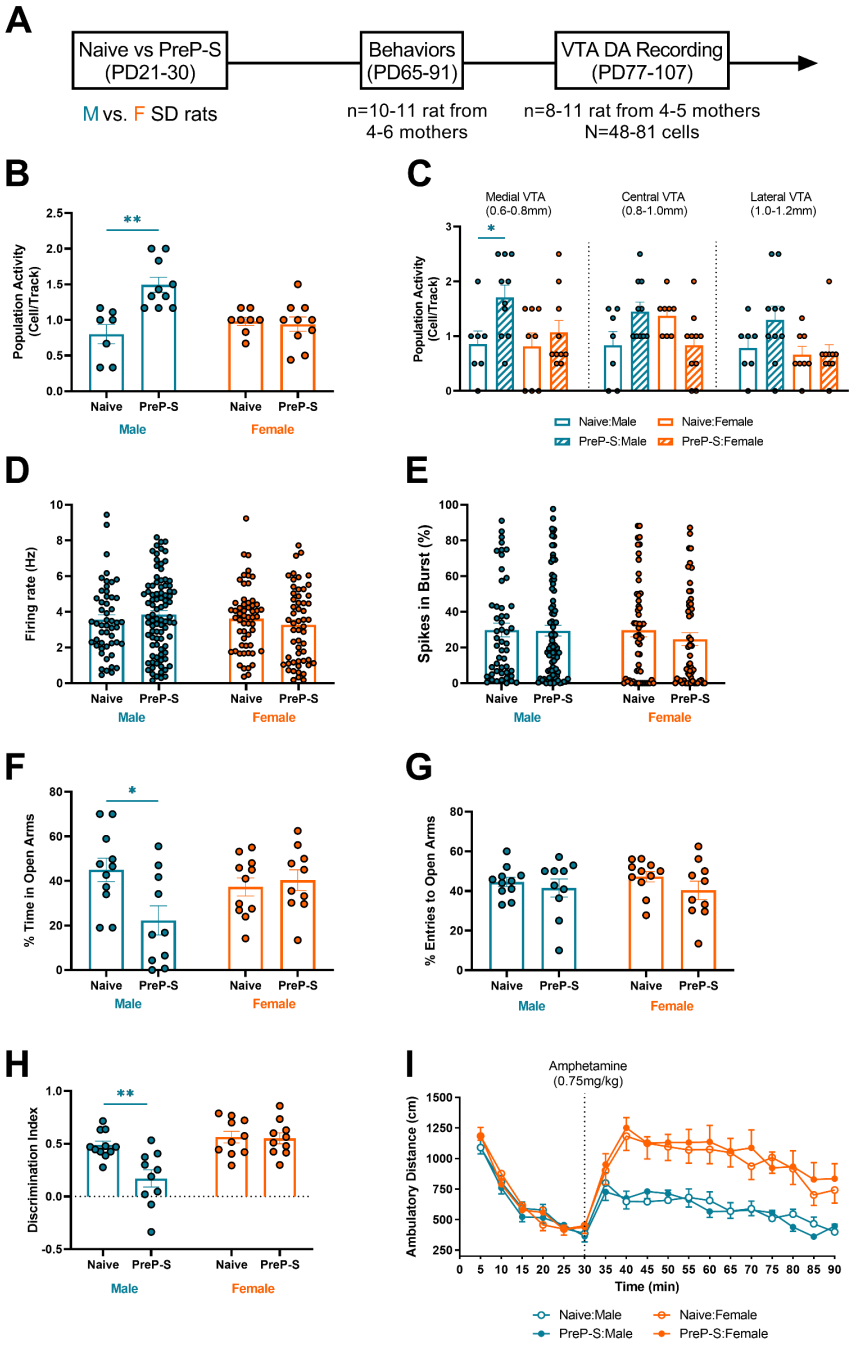

Figure 1. Effects of prepubertal stress (PreP-S) on adult ventral tegmental area (VTA) dopamine (DA) neuron activity and behaviors in males vs. females.

(A) Experimental timeline. Male (*blue*) and female (*orange*) rats were stressed during a prepubertal period (PD21-30), and when they reached adulthood (PD65-71) evaluated by elevated plus-maze (EPM), novel object recognition (NOR), and amphetamine-induced hyperlocomotion (AIH) tests. After a week of recovery, rats were subsequently tested for DA neuron activity via in vivo single-unit electrophysiology. **(B)** PreP-S produced a persistent increase in DA neuron population activity in males ($p<0.01$) but not in females. **(C)** The male-specific effect of PreP-S was confined to the medial part of the VTA. No differences were found in the phasic firing properties of the DA neurons, including **(D)** firing rate and **(E)** bursting activity. **(F)** In addition to DA dysfunction, concomitant anxiety-like behaviors were observed in male PreP-S rats, indexed by less time spent in the open arms. In contrast, females displayed resilience to PreP-S in this measure. **(G)** No significant difference was found in the percentage of open entries. **(H)** PreP-S:Male rats also displayed a reduced discrimination index that reflects memory/cognitive impairments, an effect absent in PreP-S females. **(I)** In the AIH test, although females showed significantly greater AIH than males in the post-amphetamine-injection (0.75mg/kg; i.p.) locomotor activity ($p<0.0001$), post hoc Tukey's tests did not detect any significant differences between stress vs. naïve groups in each sex. This indicates no effects of PreP-S on adult locomotor sensitivity to amphetamine.

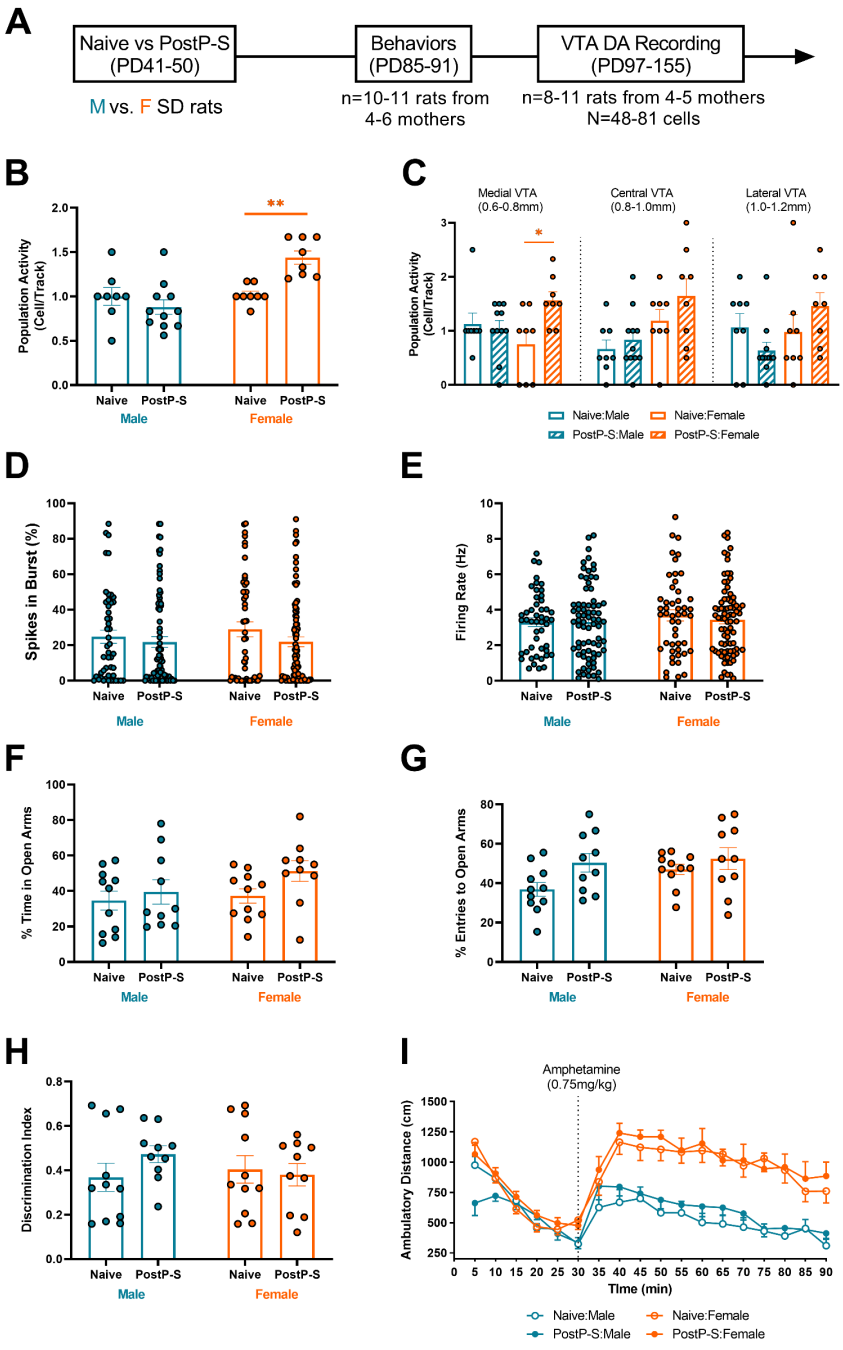

Figure 2. Effects of post-pubertal stress (PostP-S) on adult VTA DA neuron activity and behaviors in males vs. females.

(A) Experimental timeline. Male (*blue*) and female (*orange*) rats were stressed during postpuberty (PD41-50). At PD85-91, rats were evaluated by EPM, NOR, and AIH tests. After a week of recovery, rats were subsequently recorded for DA neuron activity via in vivo extracellular electrophysiology. **(B)** PostP-S produced a persistent increase

in DA neuron population activity in females ($p<0.01$) but failed to change that in males. **(C)** Female-specific PostP-S-induced DA population activity increase was confined to the medial part of the VTA. No differences were found in the phasic firing properties of the DA neurons, including **(D)** firing rate and **(E)** bursting activity. **(F-H)** No behavioral difference was found in EPM and NOR tests. **(I)** Despite significant main effects of time and conditions in the post-amphetamine (0.75mg/kg; i.p.) locomotor activity in the AIH test, no within-sex PostP-S effect was found in the post hoc analysis.

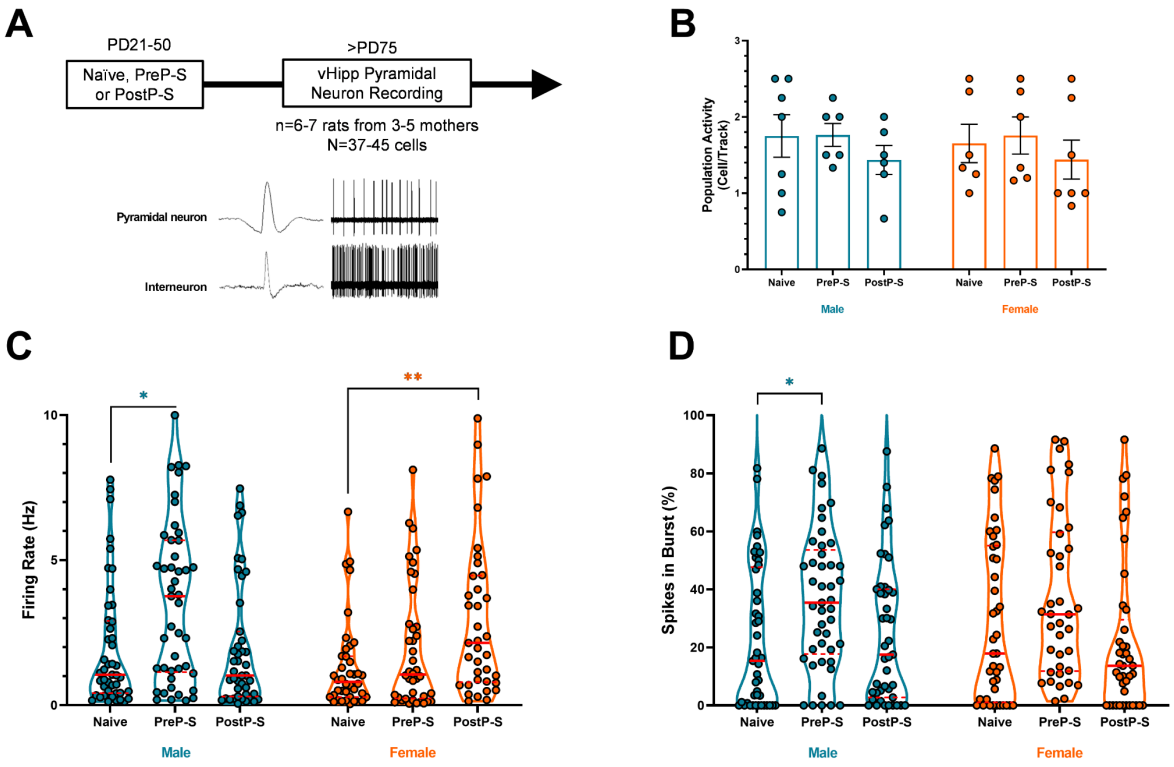

Figure 3. Sex-selective and exposure age-dependent effects of PreP-S vs. PreP-S on adult ventral hippocampus (vHipp) pyramidal neuron activity.

(A) Experimental timeline, representative waveform, 10-sec sample firing of vHipp neuronal recordings. vHipp pyramidal neurons were identified based on low firing rate (<10Hz) and long spike duration (>2.2ms). **(B)** No change was observed in the number of vHipp putative pyramidal neurons detected per electrode track. **(C)** Male rats showed a selective increase in PreP-S-induced vHipp pyramidal neuron firing rate whereas females showed a selective increase in PostP-S-induced firing rate. **(D)** A male-selective increase in the percent of vHipp spikes occurring in bursts (interspike interval <80ms). Violin plots were provided (here and in subsequent figures) to indicate datasets that contain non-normally distributed data. For these datasets, Kruskal–Wallis analysis of group medians followed by Dunn's multiple comparison test was used. Data are presented as median (solid red line) and quartiles (dashed red line). *p < 0.05; **p < 0.01. *Blue* and *Orange* dots denote males and females, respectively.

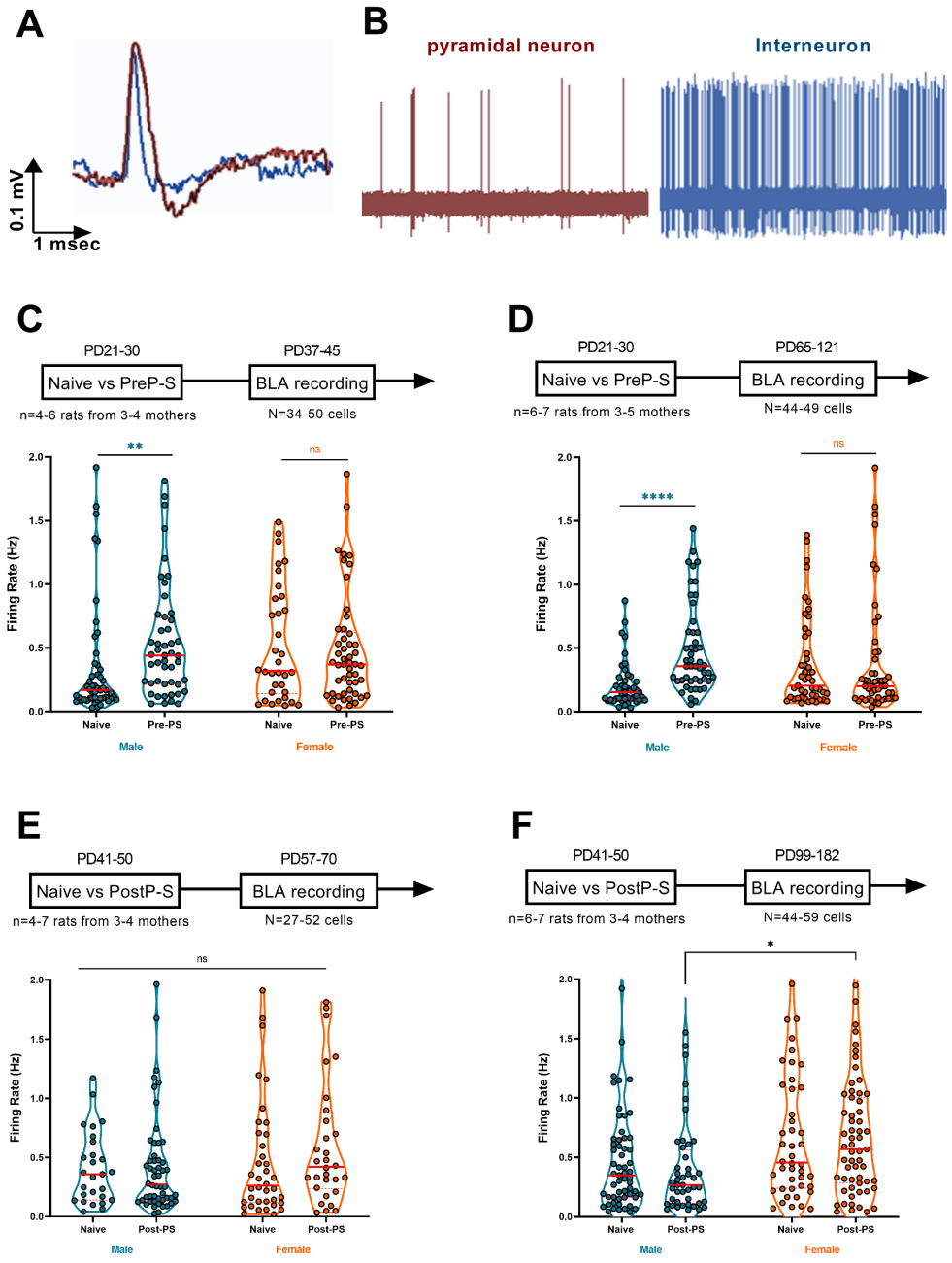

Figure 4. Sex differences in amygdala neuron firing rate following stress.

(A) and (B) Representative spike waveforms and 10-second spontaneous activity of basolateral amygdala (BLA) neurons. BLA pyramidal neurons were defined by spike duration >2.2ms and mean firing rate <2Hz. **(C)** PreP-S-induced BLA pyramidal neuron hyperactivity (i.e., increased firing rate), measured 1-2 weeks post-stress, was observed only in males, whereas females showed resilience to these short-term effects. **(D)** Male-specific, PreP-S-

induced BLA hyperactivity persisted into adulthood; no effect was observed in adult females. **(E)** No effect of sex or PostP-S was found in the 1-2 week responses. **(F)** No within-sex PostP-S effect was found in the 5-6 week response, although females showed higher stress activation compared to males. Firing data were analyzed by Kruskal-Wallis test followed by Dunn's post hoc multiple comparisons. Data are presented as median (solid red line) and interquartile range (dashed red line). **$p < 0.01$; ****$p < 0.0001$.

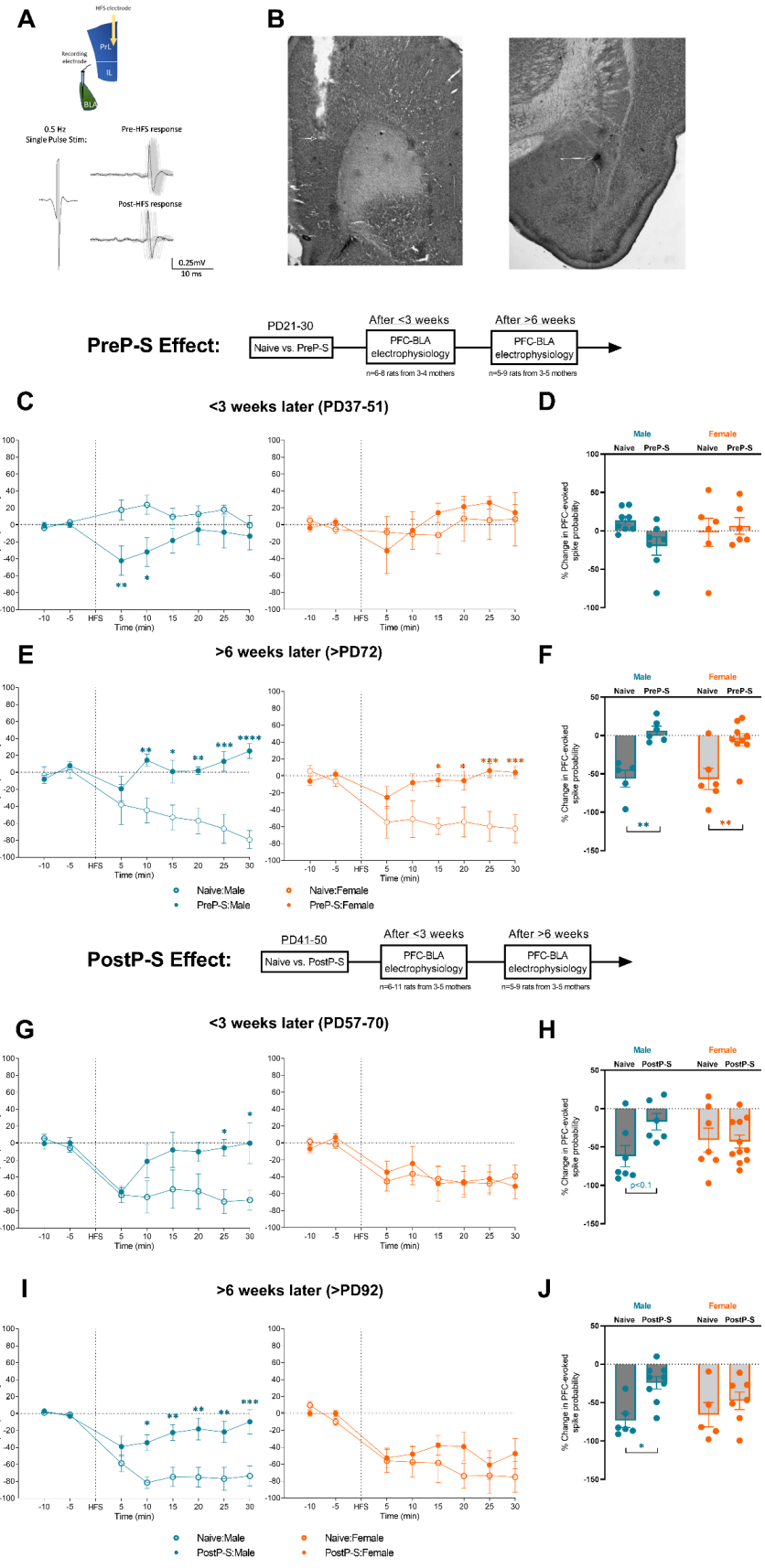
A
HFS electrode
Recording electrode
PrL
IL
BLA
0.5 Hz
Single Pulse Stim:
Pre-HFS response
Post-HFS response
0.25mV
10 ms
B
PreP-S Effect:
PD21-30
Naive vs. PreP-S
After <3 weeks
PFC-BLA electrophysiology
n=6-8 rats from 3-4 mothers
After >6 weeks
PFC-BLA electrophysiology
n=5-9 rats from 3-5 mothers
C
<3 weeks later (PD37-51)
D
E
>6 weeks later (>PD72)
F
Naive:Male
PreP-S:Male
Naive:Female
PreP-S:Female
PostP-S Effect:
PD41-50
Naive vs. PostP-S
After <3 weeks
PFC-BLA electrophysiology
n=6-11 rats from 3-5 mothers
After >6 weeks
PFC-BLA electrophysiology
n=5-9 rats from 3-5 mothers
G
<3 weeks later (PD57-70)
H
p<0.1
I
>6 weeks later (>PD92)
J
Naive:Male
PostP-S:Male
Naive:Female
PostP-S:Female
% Change in PFC-evoked spike probability
Time (min)
HFS
Male
Female
Naive
PreP-S
PostP-S

Figure 5. Sex-specific effects of stress on PFC-BLA inhibitory control.

(A, Top) A diagram illustrating recording paradigm. A stimulating electrode and a recording electrode were implanted in the prelimbic prefrontal cortex (plPFC) and the BLA, respectively. BLA pyramidal neurons responsive to repeated plPFC single-pulse stimulation (0.5 Hz; 0.1-1.5 mA; 0.25ms duration) were searched and recorded for 10 minutes to obtain baseline measures (spike probability maintained at ~50%). High-frequency stimulation (HFS; 20 Hz; 10s, suprathreshold) was given at the end of the baseline recording. Spike probability response to HFS was recorded for an additional 30 minutes (Post-HFS). **(A, Bottom)** BLA pyramidal neurons typically respond to plPFC HFS with a long-term depression (LTD) of spikes, i.e., exhibiting fewer action potential responses to PFC stimuli after HFS. **(B)** Representative photomicrographs of plPFC stimulating electrode and BLA recording electrode placement. **(C)** In <3 weeks after stress, PreP-S induced a male-specific precocious form of PFC-BLA spike LTD in the first 10 minutes of post-HFS recordings (left), whereas in females PreP-S did not induce an effect (right) (time-course data). **(D)** No short-term effect of PreP-S was found across the test interval in the mean Post-HFS spike probability change. **(E)** In >6 weeks after PreP-S, stressed rats (solid circles) of both sexes failed to show HFS-induced LTD (time course data). **(F)** PreP-S induced impaired mean LTD averaged across test intervals in both sexes. **(G)** In <3 weeks post-stress, PostP-S induced a male-specific LTD impairment at 25-30 minutes post-HFS. **(H)** When averaged across the entire Post-HFS testing period, there was only a trend towards LTD impairment in males. **(I)** In >6 weeks post-stress, PostP-S induced a robust LTD deficit in the time course response only in males. **(J)** In >6 weeks post-stress, averaging across the entire test interval showed significant LTD impairments only in PostP-S males. Time-course data were analyzed by repeated measure two-way ANOVA with Bonferroni tests at each time point. Mean post-HFS response was analyzed by two-way ANOVA with Tukey's post hoc test. *$p<0.05$; **$p<0.01$.

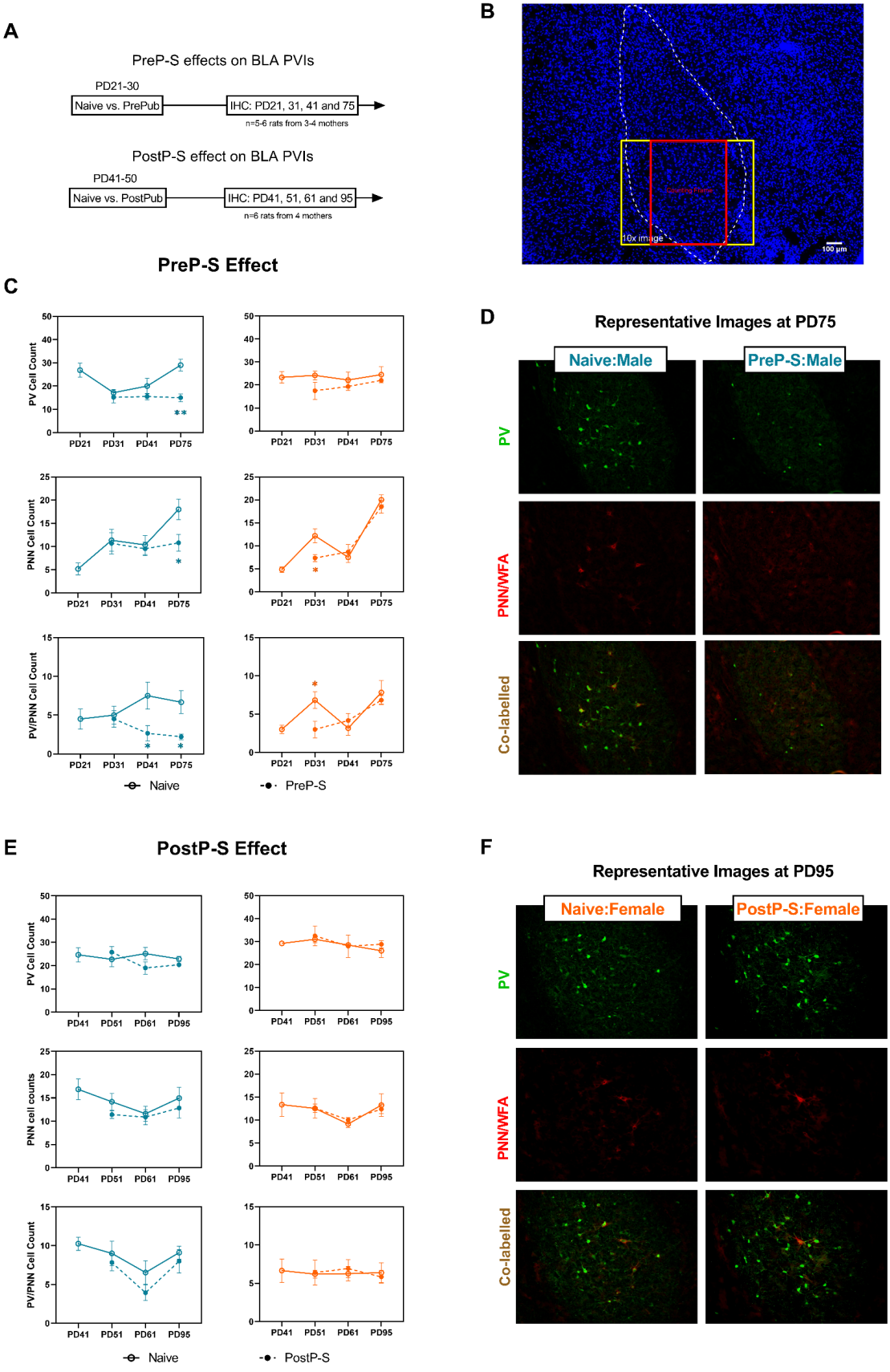
A
PreP-S effects on BLA PVIs
PD21-30
Naive vs. PrePub
IHC: PD21, 31, 41 and 75
n=5-6 rats from 3-4 mothers
PostP-S effect on BLA PVIs
PD41-50
Naive vs. PostPub
IHC: PD41, 51, 61 and 95
n=6 rats from 4 mothers
B
10x image
100 µm
PreP-S Effect
C
PV Cell Count
PNN Cell Count
PV/PNN Cell Count
PD21 PD31 PD41 PD75
Naive
PreP-S
D
Representative Images at PD75
Naive:Male
PreP-S:Male
PV
PNN/WFA
Co-labelled
E
PostP-S Effect
PNN cell counts
PD41 PD51 PD61 PD95
Naive
PostP-S
F
Representative Images at PD95
Naive:Female
PostP-S:Female

Figure 6. Sex differences in the longitudinal impact of PreP-S and PostP-S on BLA parvalbumin (PV) interneurons.

(A) After stress exposure, immunohistochemistry and fluorescent microscopy were performed in the BLA at various post-stress time points. Specifically, the BLA was sampled before the stress paradigms (in naïve rats) and subsequently at 1, 10, 45 days after stress termination. **(B)** 4x image with DAPI staining showing BLA anatomical borders and the counting frame. Cell counts of PV+, perineuronal-net+ (PNN+, labelled by WFA) neurons, and their co-labelling were measured in a 550 x 690μm counting frame on 10x images (909 × 692μm). **(C)** PreP-S-related changes were detected primarily in males, including delayed reductions of PV+ and PNN+ cell counts only at PD75 and chronically reduced PV+/PNN+ co-labeled cell counts at PD41 and PD75. In the female BLA, PreP-S resulted in immediate and transient reductions of PNN+ and PV+/PNN+ co-labeled cells only at PD31 (i.e., one day after stress), suggesting potential recovery at later time points. **(D)** Representative 10x images from PreP-S:Males at PD75. **(E)** PostP-S did not impair BLA PV interneurons in either sex. **(F)** Representative images from PostP-S:Females at PD95. Data are presented as mean ± SEM. Unpaired t-test with Welch correction was conducted at each post-stress time point. *$p<0.05$, **$p<0.01$, indicating stress-related changes.

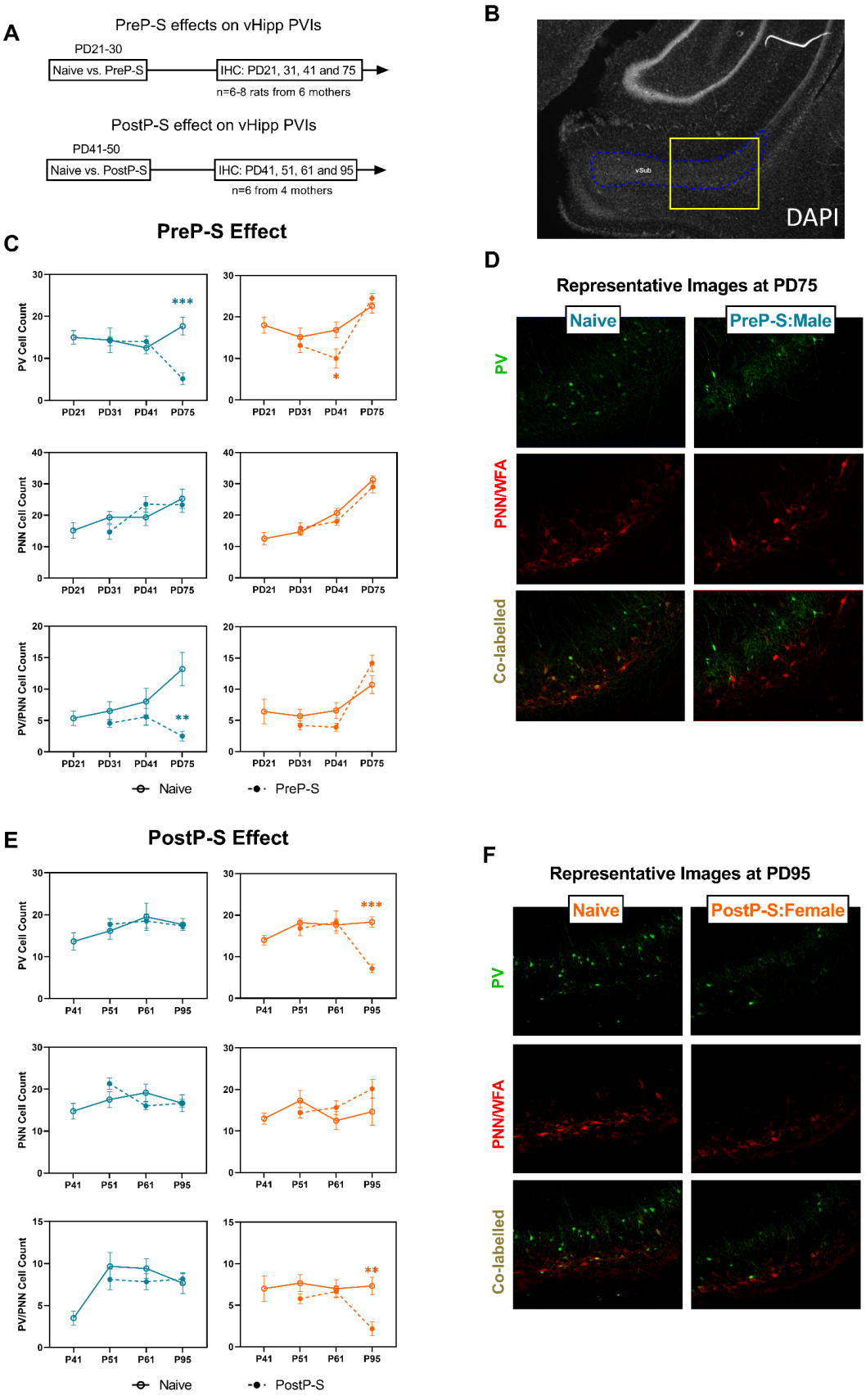
A
PreP-S effects on vHipp PVIs
PD21-30
Naive vs. PreP-S
IHC: PD21, 31, 41 and 75
n=6-8 rats from 6 mothers
PostP-S effect on vHipp PVIs
PD41-50
Naive vs. PostP-S
IHC: PD41, 51, 61 and 95
n=6 from 4 mothers
B
vSub
DAPI
C
PreP-S Effect
PV Cell Count
PNN Cell Count
PV/PNN Cell Count
PD21
PD31
PD41
PD75
Naive
PreP-S
D
Representative Images at PD75
Naive
PreP-S:Male
PV
PNN/WFA
Co-labelled
E
PostP-S Effect
P41
P51
P61
P95
Naive
PostP-S
F
Representative Images at PD95
Naive
PostP-S:Female
PV
PNN/WFA
Co-labelled

Figure 7. Sex differences in the longitudinal impact of stress on vHipp PV interneurons.

(A) vHipp was sampled at different time points after PreP-S and PostP-S to examine potential stress-induced PV interneuron (PVI) impairments. (B) A 4x image with DAPI staining showing the relative location of the 10x imaging site targeting the ventral subiculum. (C) PreP-S induced male-dominant PVI impairments in the vHipp. PreP-S effect in males is delayed, as stress-related reductions of PV and PV/PNN co-labeled cell counts were only observed at PD75 (i.e., 45 days after stress). Female vHipp responded to stress with a minor PVI deficit, characterized by a PV reduction at PD41 (i.e., 10 days after stress) but did not persist into PD75. (D) Representative images showing PreP-S effect on PVIs measured at PD75. (E) In contrast to PreP-S, PostP-S induced female-selective PVI impairments. Specifically, in PostP-S females, stress-related reductions of PV and PV/PNN co-labeled cell count were only observed at PD95 (i.e., 45 days after stress), whereas in males, PostP-S did not induce any change in any marker. Data are presented as mean ± SEM. Unpaired t-test with Welch correction was conducted at each post-stress time point. ∗ ∗p<0.01; ∗∗∗p<0.001, indicating stress-related changes.

3.0 PREPUBERTAL ENVIRONMENTAL ENRICHMENT PREVENTS DOPAMINE DYSREGULATION AND HIPPOCAMPAL HYPERACTIVITY IN MAM SCHIZOPHRENIA MODEL RATS

Chapter 3 is a modified version of:

Zhu, X., & Grace, A. A. (2021). Prepubertal Environmental Enrichment Prevents Dopamine Dysregulation and Hippocampal Hyperactivity in MAM Schizophrenia Model Rats. *Biological Psychiatry*, 89(3), 298–307. https://doi.org/10.1016/j.biopsych.2020.09.023

(Supplementary figures mentioned in this chapter are on the journal's website: https://ars.els-cdn.com/content/image/1-s2.0-S0006322320319533-mmc1.pdf)

3.1 INTRODUCTION

Schizophrenia (SCZ) has long been proposed to be a neurodevelopmental disorder (Murray & Lewis, 1988; Weinberger, 1987), and its etiology involves genetic predisposition (Owen & O'Donovan, 2017) and environmental factors (van Os et al., 2010), which collectively interfere with brain development (McCutcheon et al., 2020; Rapoport et al., 2012; Van Os et al., 2008). As a core feature of SCZ, psychosis typically manifests relatively late in the clinical course, often preceded by an extended prodromal stage in adolescence (Millan et al., 2016; Wood et al., 2011). Several meta-analyses have concluded that the risk of transition to psychosis can be reduced by active intervention during the prodromal phase, including antipsychotic medication, nutritional support, cognitive behavioral therapy, psychoeducation, and exercise (de Koning et al., 2009;

Fusar-Poli et al., 2012; M. J. Millan et al., 2016; Stafford et al., 2013), although not all have proven effective upon replication. In addition to the plausible preventative efficacy against positive symptoms, recent studies also suggest that early intervention may also reduce the risks for the emergence of other symptom domains (Sommer et al., 2016).

Whereas clinical evidence suggests that both early-life pharmacological and environmental interventions are potentially effective in preventing SCZ, the former is relatively disadvantageous due to ethical limitations, economical infeasibility, and potential side effects given that most individuals will never transition to psychosis (Nithianantharajah & Hannan, 2006; Sommer et al., 2016). Early exposure to environmental enrichment (EE) is a form of behavioral intervention that is broadly beneficial to a wide range of neuropsychiatric conditions, including SCZ (Kentner et al., 2016; Kentner et al., 2019; McFarlane et al., 2015; van Praag et al., 2000). For example, Raine et al. reported that a 2-year environmental intervention at age 3-5 might protect against behavioral manifestation of SCZ in early adulthood (Raine et al., 2003). In terms of preclinical research, several studies suggested that early EE can prevent selective behavioral abnormalities relevant, but not specific, to SCZ, such as locomotor hyperactivity, social cognition, and sensorimotor gating in SCZ models involving drug treatment (Akillioglu et al., 2012; Murueta-Goyena et al., 2020; Nozari et al., 2015), genetic manipulation (Burrows et al., 2015; C. E. McOmish et al., 2008), and lesion (Lee et al., 2012). However, key preclinical evidence supporting the preventative efficacy of EE is still lacking, because beyond its beneficial effects on SCZ-relevant behavioral endpoints, whether EE can prevent other functional deficits of SCZ is largely unknown. A recent study attempted to address this knowledge gap by testing EE in methylazoxymethanol (MAM) GD17 model (Lodge, 2013) of SCZ, in which Bator et al. (Bator et al., 2018) found that 7-day juvenile exposure to EE not only prevented SCZ-related behavioral deficits, but also the decrease

in the expression of glutamate decarboxylase 67. Although this recent study extended the current scope of EE research by indicating EE's efficacy against GABAergic pathologies implicated in the pathogenesis of SCZ (Nakazawa et al., 2012), several key questions remain unanswered. In particular, whether EE can prevent dopamine (DA) dysfunction and hippocampal hyperactivity, core features of the pathophysiology of SCZ (McCutcheon et al., 2019), is still unknown (Howes et al., 2004).

Using the MAM model, the main goal of this study is to understand the long-term electrophysiological impacts of prepubertal EE on the regulation of the DA system of adult animals. Given that hippocampal hyperactivity and the associated DA dysregulation are robust features of SCZ (Lodge & Grace, 2011), we also examined the impact of EE on neuronal firing in the ventral hippocampus (vHipp), an upstream regulator of the midbrain DA system (Floresco et al., 2001; Floresco et al., 2003). Given the high comorbidity between anxiety and SCZ (Achim et al., 2011) and its implication in the pathogenesis and pathophysiology (Benes, 2010; Devylder et al., 2013; Johnstone et al., 2005; Owens et al., 2005), we also determined whether prepubertal EE can ameliorate anxiety and the hyperactivity in the basolateral amygdala (BLA) in adult MAM rats (Du & Grace, 2016).

3.2 MATERIALS AND METHODS

Animals. Timed pregnant Sprague–Dawley rats (Envigo) were obtained at gestational day (GD) 14. At GD17, pregnant rats were injected with 0.9% saline or MAM (20mg/kg, i.p.; MRI Global). Animals were housed in a temperature- (22°C) and humidity-controlled (47%) environment (12-hr light/dark cycle; lights on at 7 am) with *ad libitum* access to food and water. To avoid litter effects, individual experimental groups were formed by animals from at least 3 litters (range: 3-6) and counterbalanced across all experiments. Experiments were conducted according to the guidelines established by the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

Experimental design. At postnatal day (PD) 21, male offspring prenatally exposed to saline (SAL) or MAM were randomly assigned into a regular housing environment (RE) throughout the study or an enriched environment (EE) for 20 days until PD40. EE rats were returned to RE on PD41, and stayed in RE until the end of experiments. At PD65-71, rats were tested for performance in the elevated plus maze (EPM, PD65-66) and amphetamine-induced hyperlocomotion (AIH, PD69-71). Following a week of recovery (>PD77), animals were randomly assigned into *in vivo* single-unit recording experiments (Figure 8). Separate cohorts of rats were also enriched during adulthood (PD65-84), juvenility (PD21-30), and adolescence (PD31-40) to assess possible age-dependence of EE effects.

Environmental conditions. Animals in RE were pair- or triple-housed in typical rodent cages (L38cm×W26cm×H18cm). The EE paradigm was modified from previously established protocols (Fischer et al., 2007; Ma et al., 2016). Briefly, rats were group-housed in five large plastic tubs (L93cm×W53.3cm×H49.5cm) containing objects including toys and tunnels of different

shapes, running wheels, chewing materials, and plastic ladders attached to a metal platform. The enrichment boxes also contained increased nesting materials and an increased amount of beddings, which were changed twice a week. The orientation and the color of the objects were altered three times a week.

Behavioral experiments. Experiments were conducted during the dark cycle (7:00pm – 7:00am).

Elevated plus maze (EPM). Animals were first habituated to the testing room for 90 minutes. Rats were introduced to the central area facing an open arm, and their movements were recorded for 5 min. Time spent in open arms and the number of open arm entries were measured to index anxiety-like behaviors.

Amphetamine-induced hyperlocomotion. Locomotor activity was assessed in open-field chambers (Coulbourn Instruments) with ambulatory movement in the x-y plane recorded for 30 minutes. Rats were next injected with d-amphetamine sulfate (0.75 mg/kg, i.p.; Sigma), followed by the recording of locomotion for 60 minutes. Data were computed in 5-min bins for time-course analysis, and the total distance traveled post-amphetamine was calculated.

***In vivo* electrophysiology.** Rats were anesthetized with chloral hydrate (400 mg/kg, i.p.; Sigma) and mounted on a stereotaxic frame (Kopf; Tujunga, CA). See Supplement for details.

Glass electrodes were lowered through six to nine vertical tracks in a predetermined pattern within VTA (A/P: -5.4mm from bregma, M/L: ±0.6mm, and D/V: 6.5-9.0mm from brain surface (Gomes & Grace, 2017; Gomes et al., 2019a)). Spontaneously active DA neurons were identified based on well-established criteria (Figure S1A-B; Online) (Ungless & Grace, 2012).

Spontaneously active neurons were recorded in the vHipp by four to six tracks (A/P: -5.5 to -5.9mm, M/L: ±4.6-4.8mm from Bregma, D/V: -5.5 to -8.5mm from brain surface). Putative

pyramidal neurons were identified based on published criteria of firing rate <2 Hz (Perez & Lodge, 2013; Ranck Jr, 1973; Van Der Meer & Redish, 2011), which was also validated in this study. Fast-spiking vHipp interneurons were defined by average firing rate >4 Hz (Van Der Meer & Redish, 2011) and spike duration <1.0ms, from peak to valley. For BLA recording, single-unit activities were recorded by four to six vertical tracks (A/P: -3.0 to -3.4 mm, M/L: ±4.6-4.8 mm from Bregma, D/V: −6.0mm to −8.5 mm from brain surface). Putative projection neurons were identified based on previously published criteria (see Supplement).

Statistical analysis. All results are presented as mean ± SEM, and statistical calculations were performed using GraphPad Prism 8. Data were tested for normal distribution (Kolmogorov–Smirnov normality test) and subsequently analyzed with two-way ANOVA with treatment (SAL or MAM) and environment (RE or EE) as main factors, or two-way repeated measure ANOVA (in AIH experiment) with the developmental condition (SAL:RE, SAL:EE, MAM:RE, or MAM:EE) as a main factor and time/bin as a repeated measure factor. Tukey's *post hoc* test was used when a significant main effect or interaction was detected. Differences were considered significant at $p<0.05$.

3.3 RESULTS

3.3.1 Prepubertal EE prevented the electrophysiological and behavioral phenotypes of DA dysregulation in adult MAM rats.

Consistent with previous reports (Du & Grace, 2013; Lodge & Grace, 2007), SAL:RE (*n*=8, 62 neurons) rats displayed an average of 1.0±0.1 spontaneously active DA neurons per electrode track (Figure 9A). A two-way ANOVA revealed a significant main effect of EE [$F_{environment}(1,29)=12.91$, $p<0.01$] and a significant interaction between treatment and environment [$F_{interaction}(1,29)=6.913$, $p<0.05$]. Tukey's *post hoc* tests revealed that MAM:RE group (*n*=9, 94 neurons) showed greater population activity (1.4±0.1 cells/track, $p<0.05$). Compared to MAM:RE group, MAM:EE group (*n*=8 rats, 47 neurons) showed significantly lower population activity (0.8±0.1 cells/track; $p<0.001$). Furthermore, population activity in MAM:EE *vs* SAL:RE groups were not significantly different ($p>0.05$). Prepubertal EE did not have significant effects in SAL animals, as SAL:EE group (*n*=8, 52 neurons) showed an average of 0.9±0.1 cells/track, which was not significantly different from SAL:RE group ($p>0.05$). SAL:RE rats displayed an average firing rate of 3.5±0.3 Hz, with 26.7±3.5% spikes fired in bursts, consistent with previous reports (Du & Grace, 2013; Lodge & Grace, 2007). The firing rate (3.5±0.3, 3.4±0.2, and 3.1±0.3 Hz) and %SIB (21.1±3.0, 26.1±2.6, and 20.2±3.7%, in SAL:EE, MAM:RE, and MAM-EE groups, respectively) did not differ significantly (Figure S1C-D, $p>0.05$; two-way ANOVA). Further analysis of population activity throughout the mediolateral VTA divisions revealed that the increased DA population activity in MAM:RE rats was confined to the medial and the lateral VTA (Figure 9B), consistent with our previous report (Lodge & Grace, 2012). We found the EE was effective in reducing MAM-induced DA hyperactivity across all subregions (MAM:EE vs. MAM:RE, $p<0.01$

in medial VTA; $p<0.05$ in central and lateral VTA; *Tukey's post hoc* tests following two-way ANOVA).

Locomotor response to amphetamine is heightened in adult MAM rats (Du & Grace, 2013; Flagstad et al., 2004; Lodge & Grace, 2007; Moore et al., 2006). Consistently, MAM:RE (n=12) group showed significantly higher levels of locomotor activity in response to amphetamine administration (0.75 mg/kg; i.p.) compared to SAL:RE group (n=13) [Figure 9C; $p<0.01$ at 40- and 45-min, $p<0.05$ at 60-min; Tukey's *post hoc* test following repeated measures two-way ANOVA on post-amphetamine movement; interaction of developmental condition*time: $F(1,44)=17.46$, $p<0.001$]. In contrast, MAM:EE rats (n=13) showed a significantly lower level of amphetamine-stimulated locomotion compared with MAM:RE rats ($p<0.001$ at 35-50 and 65-70 min; $p<0.01$ at 55-60 min), and were not significantly different from SAL-RE rats ($p>0.05$ at all post-amphetamine timepoints). Furthermore, prepubertal EE in SAL rats did not affect amphetamine-stimulated locomotion (SAL:RE vs SAL:EE rats, n=8, $p>0.05$ at all post-amphetamine timepoints). The total movement post-amphetamine administration revealed a similar result (Figure 9D), as two-way ANOVA indicated a significant interaction between prenatal MAM treatment and prepubertal environment [$F_{interaction}(1,44)=17.46$, $p<0.001$]. MAM:RE rats showed a significantly higher total movement compared with SAL:RE ($p<0.01$) and MAM:EE rats ($p<0.001$).

To examine the age-dependence of EE, separate sets of MAM rats were enriched during PD21-30 or PD31-40 (Figure 10). Similar to the 20-day EE paradigm, 10-day EE paradigms were found to be effective in normalizing the electrophysiological phenotypes of DA hyperresponsivity (Figure 10A), although no effect of 10-day prepubertal EE paradigms was observed in AIH or EPM (Figure S2B-C). In contrast, in adult rats the 20-day enrichment paradigm (Figure 10B) did

not impact DA population activity. Based on these results, subsequent experiments on BLA and vHipp activities were only conducted with animals exposed to 20-day prepubertal EE.

3.3.2 Prepubertal EE prevented vHipp hyperactivity in adult MAM rats.

An increase in vHipp activity is proposed to underlie the DA system hyperresponsivity in SCZ and animal models (Modinos et al., 2015). We therefore performed recordings from identified pyramidal and putative fast-spiking interneurons in the vHipp (Figure 11A). In total, 50 neurons/5 rats in the vHipp of SAL:RE group were recorded (Figure 11B), which were divided into two populations each with a normal distribution (Kolmogorov-Smirnov test of normality, $p>0.1$) based on previously reported firing rate cut-off of 2 Hz (Perez & Lodge, 2013). A significant difference in the mean firing rate in the pyramidal vs. non-pyramidal neurons was detected (Figure 11B; $t=12.26$, Welch's correction, $df=23.61$, $p<0.001$), confirming the applicability of this identification criterion.

No changes in the number of spontaneously active pyramidal neurons detected per track across groups were observed (Figure 11C). Consistent with previous data (Lodge & Grace, 2007; Perez & Lodge, 2013), vHipp pyramidal neurons in SAL:RE (28 cells/5 rats) group displayed a mean firing rate of 0.62±0.08 Hz (Figure 11D). A two-way ANOVA revealed a significant effect of MAM [$F_{treatment}(1,125)=8.675$, $p<0.01$], enrichment [$F_{environment}(1,125)=9.717$, $p<0.01$], and their interaction [$F_{interaction}(1,125)=6.396$, $p<0.05$]. Tukey's *post hoc* tests revealed that MAM:RE group (28 cells/6 rats) displayed significantly higher firing rates (1.13±0.11 Hz; $p<0.01$, vs. SAL:RE), which were prevented by prepubertal exposure to EE (MAM:EE, 48 cells/8 rats; 0.60±0.07 Hz; $p<0.001$, vs. MAM:EE). Furthermore, in SAL rats, we did not observe any change associated with EE (SAL:EE, 25 cells/4 rats; $p>0.05$, vs. SAL:RE).

Of the identified non-pyramidal cells (i.e. firing rate >2 Hz), we further separated neurons at relatively higher firing rate (>4 Hz) and with shorter spike duration (<1.0ms, from peak to valley) (Figure 11E). These operationally defined non-pyramidal neurons putatively represent fast-spiking neurons (Csicsvari et al., 1999; Van Der Meer & Redish, 2011). A two-way ANOVA revealed a significant effect of enrichment [$F_{environment}(1,54)=5.50$, $p<0.05$]. Tukey's *post hoc* tests revealed that MAM:EE group (19 cells/7 rats) displayed a significantly higher firing rate (7.97±0.68 Hz), compared to MAM:RE (13 cells/5 rats; 5.93±0.50 Hz; $p<0.05$), SAL:RE (15 cells/4 rats; 5.60±0.32 Hz; $p<0.01$), and SAL:EE (11 cells/3 rats; 5.72±0.32 Hz; $p<0.05$) groups.

3.3.3 Prepubertal EE did not prevent anxiety-like behaviors in EPM and BLA hyperactivity in adult MAM rats.

Heightened anxiety and stress sensitivity are proposed to contribute to the onset of DA dysregulation in MAM rats (Du & Grace, 2016; Gomes et al., 2019b). Confirming previous findings (Du & Grace, 2013, 2016), MAM:RE (n=9) rats display higher level of anxiety-like behaviors in EPM, indexed by decreased time spent in open arms [Figure 12A; $F_{treatment}(1,42)=12.84$, $p<0.001$; two-way ANOVA] and decreased percent entries into open arms [Figure 12B; $F_{treatment}(1,42)=11.85$, $p<0.01$; two-way ANOVA]. *Post hoc* Tukey's tests revealed that MAM:RE rats spent less time in open arms ($p<0.05$) and had lower percent entries into open arms ($p<0.05$), compared to SAL:RE (n=11) rats. Prepubertal EE did not rescue anxiety-like behaviors in MAM rats [open arm time: Figure 12A; $F_{environment}(1,42) = 5.251$, $p< 0.05$; Tukey's test, MAM:RE vs. MAM:EE (n=16), $p=0.577$ or percent open arm entries [Figure 12B; $F_{environment}(1,42)=0.1856$, $p=0.669$]. Overall locomotion, indexed by total arm entries, was not different among groups [Figure 12C; $F_{interaction}(1, 42)=0.3923$, $p=0.53$]. To assess the effect of EE

on anxiety-like behaviors during prepuberty, in a separate group of rats we measured the EPM responses at PD43-44 (Figure S3A). While we observed a main effect of MAM in both open arm time [Figure S3B, $F_{treatment}(1,16)=5.576$, $p<0.05$] and percent open arm entries [Figure S3C, $F_{treatment}(1,16)=5.745$, $p<0.05$], these measures were not different between MAM:RE vs. MAM:EE group in *post hoc* tests, suggesting EE's inability to rescue MAM-induced anxiety starts early in development.

We recorded from putative projection neurons in the BLA, a key region involved in the regulation of fear and anxiety-like behaviors (Romeo & McEWEN, 2006). Projection neurons were identified based on previously published criteria (Du & Grace, 2016; Rosenkranz & Grace, 1999): (1) bi- or triphasic waveforms, (2) long spike duration (>2 ms), and (3) slow firing rate (<1 Hz) (Figure 12D). No changes in the number of spontaneously active neurons in each track were observed across groups (Figure 12E). For firing rate (Figure 12F), confirming previous results (Rosenkranz & Grace, 1999), the average firing rate of the recorded putative projection neurons was very low (SAL:RE, n=45 cells/6 rats, 0.21±0.03 Hz). A two-way ANOVA revealed a significant main effect of MAM [$F_{treatment}(1,124)=6.220$, $p<0.05$], but only a trend toward significance for enrichment [$F_{environment}(1,124)=3.504$, $p=0.0636$]. Tukey's *post hoc* analysis revealed that, compared to SAL:RE and SAL:EE (20 cells/4 rats, 0.1849±0.03 Hz) groups, MAM:RE group (36 cells/5 rats) displayed significantly higher BLA projection neuron firing (0.34±0.04 Hz, $p<0.05$), which was not significantly different from that of MAM:EE rats (28 cells/5 rats, 0.23±0.03 Hz, $p=0.19$), consistent with the behavioral measures in the EPM. Altogether these data suggest prepubertal EE is not effective in preventing anxiety in terms of EPM or BLA activity in adult MAM rats.

3.4 DISCUSSION

In this study, we examined prepubertal EE for the prevention of psychosis-related dopamine dysregulation in an animal model. Rearing MAM offspring in an enriched environment prepubertally prevented the emergence of DA system hyperresponsivity and vHipp hyperactivity, without affecting anxiety-like responses and the firing of BLA projection neurons. Altogether, these results indicate that early EE might be effective in reducing psychosis-related electrophysiological changes predisposed by early-life risk factors.

We used the MAM GD17 model (Lodge, 2013), in which a single injection of a neurospecific, short-acting mitotoxin (Cattabeni & Di Luca, 1997) during late gestation selectively disrupts neurodevelopment (Moore et al., 2006; Penschuck et al., 2006), resulting in phenotypes in the offspring consistent with SCZ (Jones et al., 2011; Modinos et al., 2015). This model is effective in screening preventative strategies due to its ability to recapitulate certain prodromal aspects of SCZ, specifically increased stress susceptibility, anxiety-like response, and hippocampal pathology during prepuberty (Du & Grace, 2013, 2016; Gill & Grace, 2014; Zimmerman et al., 2013), before the manifestation of DA-related behavioral abnormalities in adults (Moore et al., 2006).

Previous research on EE effects in SCZ-relevant models tends to focus on behavioral phenotypes, including sensorimotor gating deficits, social interaction impairment, hyperactivity, and memory deficits (Bator et al., 2018; Ishihama et al., 2010; Caitlin E McOmish et al., 2008; Melik et al., 2014). To our knowledge, the present study represents the first examination of whether EE can protect against psychosis-related dopamine dysregulation, and hence provides novel insight for early intervention. We showed that prepubertal EE is sufficient to prevent the vHipp-driven DA hyperactivity across VTA subregions of adult MAM rats. Noteworthy, the ability of

prepubertal EE to prevent DA hyperresponsivity in the lateral VTA (Figure 9B) is strongly consistent with the DA dysfunction in human SCZ, which is most prominent in this region and its target (i.e. associative striatum) (McCutcheon et al., 2018).

DA hyperresponsivity in SCZ likely originates in its afferent regulators (Grace, 2016), such as the limbic hippocampus which can potently regulate DA system responsivity via a polysynaptic, disinhibitory circuit (Floresco et al., 2003; Grace et al., 2007). Thus, aberrant activity in vHipp will induce DA hyperresponsivity through ventral pallidum mediated disinhibition (Lodge & Grace, 2007). Consistent with this model, anterior hippocampal hyperactivity is reported in SCZ patients (Heckers, 2001; Medoff et al., 2001), which may in turn drive the DA dysfunction (McCutcheon et al., 2019) that underlies psychosis (Silbersweig et al., 1995). Moreover, studies of at-risk groups posited a pathogenic role for hippocampal dysregulation in psychotic conversion (Lieberman et al., 2018a; Provenzano et al., 2020). Importantly, hippocampal parvalbumin (PV) interneuron deficits have been implicated in the pathophysiology of SCZ (Eyles et al., 2002; Konradi et al., 2011; Torrey et al., 2005; Zhang & Reynolds, 2002). Closely recapitulating this clinical feature, MAM rats display similar abnormalities in the vHipp (a functional equivalent of anterior hippocampus in primates (Fanselow & Dong, 2010; Grace, 2012)), which leads to VTA DA hyperactivity (Lodge et al., 2009; Lodge & Grace, 2007; Moore et al., 2006). Altogether, these findings suggest that the hyperdopaminergic state in SCZ might be a consequence of excessive hippocampal activity, driven by the loss of PV or PV interneurons (Gomes et al., 2019b; Nakazawa et al., 2012).

We found prepubertal EE prevented pyramidal neuron hyperactivity in the vHipp of MAM rats (Figure 11), as well as the DA hyper-responsivity in the VTA (Figure 9). These results are consistent with previous reports using pharmacological (Lodge & Grace, 2007), genetic (Perez et

al., 2019), and stem-cell-based (Perez & Lodge, 2013) approaches to modulate vHipp activity and hence to reduce DA hyperactivity. Previous research also indicated that EE attenuates the decrease of the PV interneurons in the hippocampus of MAM rats (Hernan et al., 2018), which could be the structural basis underlying the observed functional prevention. During prepuberty, vHipp interneurons undergo significant development and maturation, characterized by an increase in PV expression and enhanced wrapping of the perineuronal nets (PNNs) (Caballero et al., 2013; Gomes et al., 2019a). PNNs have diverse functions (Wen et al., 2018b), and the protection of PV neurons against cellular damage and oxidative stress is likely relevant to this study. Post-mortem studies have linked PNN loss to the pathogenesis of SCZ (Bitanihirwe & Woo, 2014). Given the preclinical evidence that early EE can increase PNN expression (Carstens et al., 2016; O'Connor et al., 2019), the observed prevention of DA dysregulation might be mediated by positive modulation of PNNs in the vHipp, thus enhancing the resilience of the PV interneurons to increased oxidative stress known to be present in MAM rats (Steullet et al., 2017). Protection of PV interneurons in the MAM vHipp would enhance local inhibition of pyramidal neurons, consistent with the present data in vHipp recording (Figure 11D, E). In contrast, EE in adulthood (PD65-84) was unable to modulate abnormal DA activity in MAM rats (Figure 10B). Since the PV loss in MAM rats emerges early (Gill & Grace, 2014), this failure of adult EE to prevent DA dysregulation suggests that the enrichment paradigm is indeed a preventive rather than therapeutic approach, addressing a need for future research to focus on the translation of EE by identifying the optimal window to apply this early intervention (Millan et al., 2016; Sommer et al., 2016). Furthermore, given the important sex differences in SCZ (Mendrek & Mancini-Marïe, 2016) and the sexually dimorphic behavioral effects of EE (Lin et al., 2011; Simpson & Kelly, 2011), it is likely that female MAM rats will show significant developmental stage-specific changes that differ

from males particularly with respect to the impact of stress (Klinger et al., 2019). Further studies are required to investigate if the findings described here in males would be observed in females as well.

During prepuberty, MAM rats display increased stress susceptibility, heightened anxiety-like responses, decreased adaptability to stress, and increased BLA firing (Du & Grace, 2013; Zimmerman et al., 2013). Furthermore, treating anxiety in MAM rats with diazepam during prepuberty prevents the adult DA dysregulation (Du & Grace, 2013). These findings and the epidemiologic evidence on the pathogenic role of stress (Ruud Van Winkel et al., 2008; Walker et al., 2008) suggest that abnormal stress vulnerability during critical developmental stages, such as adolescence (Paus et al., 2008; L. P. Spear, 2000), may lead to later-onset of SCZ-related pathophysiology (Gomes et al., 2019b). Previous studies suggest that EE can mitigate the negative behavioral effects of stress by enhancing resilience and stress adaptability (Lehmann & Herkenham, 2011; Schloesser et al., 2010; Southwick et al., 2005). Furthermore, previous studies have also found that EE can mitigate anxiety and the associated maladaptive structural and molecular plasticity in the BLA, examined shortly after EE (Ashokan et al., 2016; Novaes et al., 2018). However, whether EE can chronically modulate BLA activity is unknown. Intriguingly, PD21-40 EE in MAM rats was not sufficient to prevent anxiety-like responses in the EPM and hyperactivity in identified BLA projection neurons (Figure 12A-C and E). These data point to dissociable behavioral and neurophysiological benefits of early EE in the MAM model. Speculatively, these observed negative results in EPM and BLA-related measurements could be related to the anxiogenic effect of enrichment loss (i.e. returning to RE on PD41), which would be consistent with a previous study reporting a rapid loss of the effect of EE on anxiety in open field test when animals return to home cages (Nader et al., 2012). This explanation would also be

supported by the EPM data measured at PD43-44 (Figure S3), during which we found that EE did not rescue anxiety-like behavior even shortly (i.e. 3-4 days) after the termination of the paradigm. Alternatively, these data also suggest possible sensitive periods for EE to produce long-lasting behavioral and/or neurophysiological benefits, which may partially explain the differential effects of 10-day EE starting PD21 or 31 (Figure 10A and S2). A recent study reported that pre-weaning (PD2-21) enrichment can positively modulate anxiety-related behaviors, spine density, and brain-derived neurotrophic factor in the BLA (Hegde et al., 2020). Thus, the full beneficial effects of developmental EE on adult MAM-related phenotypes is possibly achieved via a sensitive-period-like, sequential mechanism, with prepubertal enrichment selectively targeting vHipp-related pathophysiology and DA dysfunction. Although many effective enrichment paradigms incorporate an early post-weaning phase, the exact outcomes can vary dramatically depending on EE procedures, with onset, duration, and continuity of EE being critical variables (Simpson & Kelly, 2011).

The generalization of rodent enrichment protocols to humans is challenging, as modifications of rodent housing are not directly comparable to treatments in humans (Ball et al., 2019). Thus, one should carefully consider control groups when interpreting the EE effects in animals. The RE cages here are similar to a typical rodent housing environment, characterized by reduced and unvarying environmental stimuli. This could be construed as relatively impoverished mainly for a lack of cognitive stimulation, an element provided by most EE cages (Simpson & Kelly, 2011). One interpretation of the present study could be that the observed EE effects against SCZ-relevant changes might be generalizable selectively to a population raised in an impoverished environment, such as individuals with low socioeconomic status (SES), a known risk factor for SCZ (Agerbo et al., 2015; Werner et al., 2007). Lack of cognitive stimulation is a critical mediator

of the low SES effects, which can act synergistically with other prenatal factors to negatively affect neurodevelopment (Hackman et al., 2010). According, while the effect of MAM has been largely attributed to the *in utero* neurodevelopmental disruption (i.e. the "MAM-phenotypes" (Lodge, 2013)), current data and the emerging evidence (Gomes et al., 2019b) raised the possibility that the adult SCZ-relevant phenotypes of MAM rats might also arise from the impoverished postnatal environment. Whether early EE can specifically counteract the influence of direct neurodevelopmental disruption and/or the impoverished environment in MAM rats warrants future studies.

In summary, the present study supports prepubertal environmental enrichment as a useful preventative approach against the pathophysiological development of SCZ. Although prepubertal EE did not fully prevent abnormal pathophysiology in the adult (such as anxiety-like response and BLA hyperactivity), our results indicate that prepubertal EE is sufficient to prevent DA dysregulation and vHipp hyperactivity in the MAM model.

3.5 FIGURES

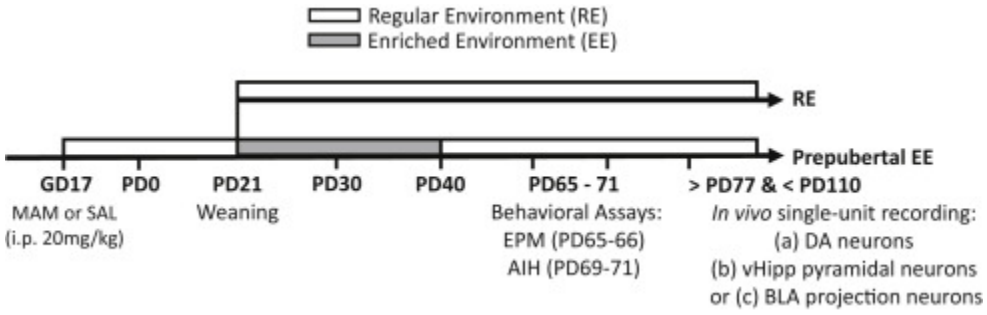

Figure 8. Schematic depiction of the postnatal environmental enrichment protocol for rats treated prenatally with either SAL or MAM at gestational day 17 (GD17).

Animals were weaned at PD21 followed by rearing in RE or EE for 20-days. Behavioral assays were performed in PD65-71, and rats were then randomly assigned into three recording experiments.

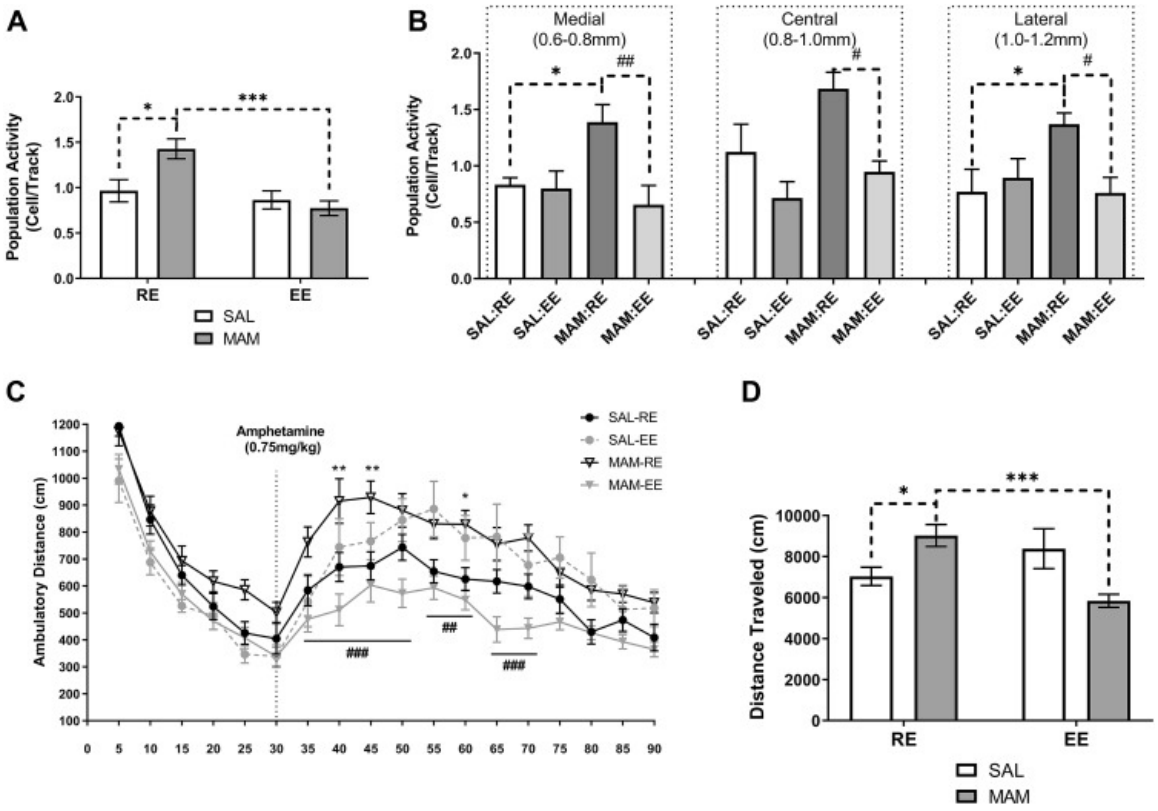

Figure 9. Prepubertal environmental enrichment prevented dopamine hyperactivity in adult MAM rats.

(A) MAM:RE rats displayed an increased number of spontaneously active VTA DA neurons comparing to SAL:RE rats, and prepubertal (PD21-40) exposure to EE prevented the heightened population activity DA neurons (n=8-9). (B) In MAM:RE, the increased in the number of spontaneously active DA neurons was confined to medial and lateral VTA, which were normalized by exposure to EE. (C) The behavioral manifestation of DA hyperresponsivity was measured by AIH, and MAM:RE rats had an augmented locomotor response to amphetamine (0.75 mg/kg; i.p. injection indicated by the dashed line), resulting in (D) increased total distance traveled after amphetamine injection. These changes were prevented by prepubertal EE. (n=8-14). Data are presented as mean ± SEM. *p or #p<0.05; **p or ##p<0.01; ***p or ###p<0.001; * indicated MAM:RE vs. SAL:RE; # indicates MAM:RE vs. MAM:EE

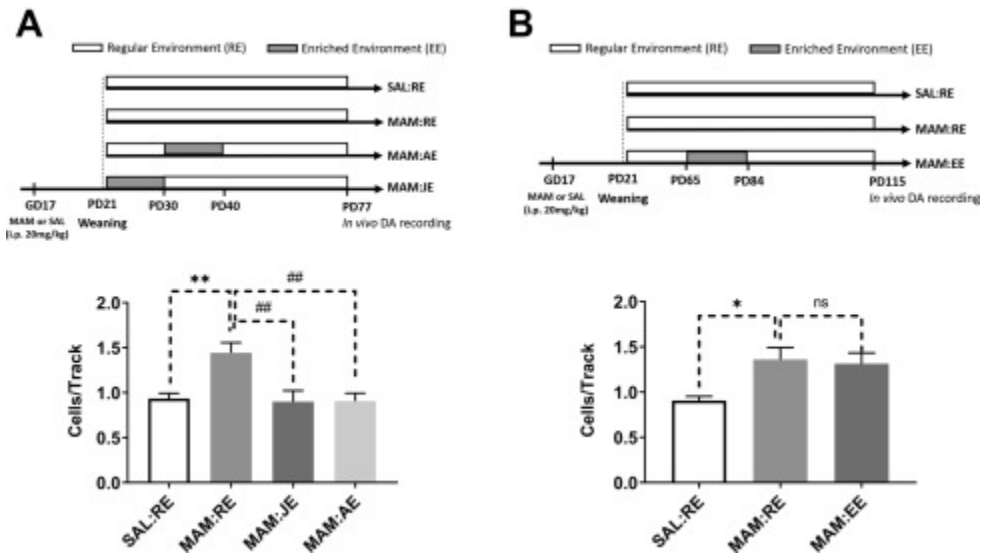

Figure 10. The effects of 10-day prepubertal and 20-day adult environmental enrichment on DA hyperactivity in MAM rats.

(A, top) A separate cohort of rats (n=10) was exposed to early EE during juvenility (JE, PD21-30) and adolescence (AE, PD31-40). (A, bottom) VTA DA neurons population activity was significantly affected by developmental conditions (one-way ANOVA, $F(3,36)=7.110$, $p<0.001$), such that DA hyperactivity induced by prenatal MAM treatment (Tukey's *post hoc* test, MAM:RE vs. SAL:RE, $p<0.01$) was prevented by both JE ($p<0.01$) and AE ($p<0.01$). (B, top) To validate the age-dependent effect of EE, a separate cohort of rats (n=4-6) was enriched during adulthood (PD65-84). (B, bottom) A main effect was detected for developmental conditions [$F(2,12)=5.203$, $p<0.05$], and MAM:RE rats displayed increased population activity (Tukey's *post hoc* test, $p<0.05$), which was not prevented by adult EE ($p>0.05$, MAM:RE vs. MAM:EE). Data are presented as mean ± SEM. *$p<0.05$; **p or ##$p<0.01$; ns: not significant ($p>0.05$). * indicated MAM:RE vs. SAL:RE; # indicates effects of enrichment groups.

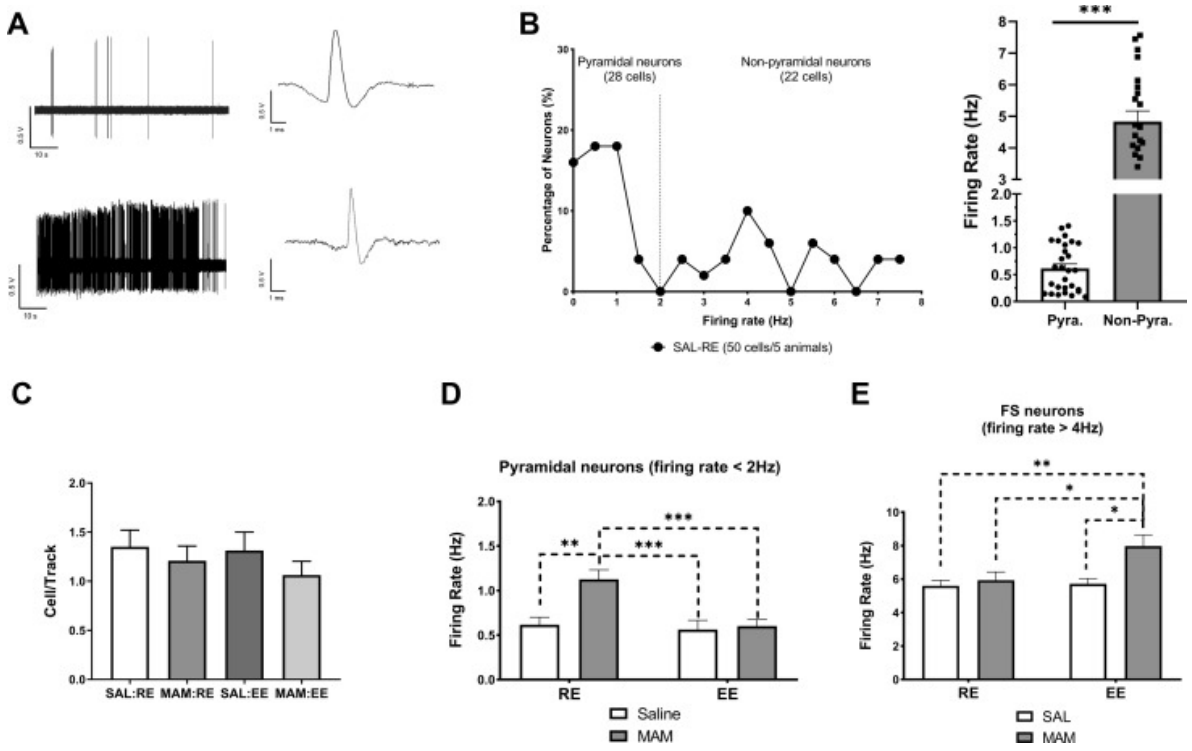

Figure 11. Prepubertal environmental enrichment prevented hyperactivity in vHipp pyramidal neurons.

(A) 1-min segments of spontaneous activity and representative waveform of a putative pyramidal neuron (top) and a putative fast-spiking neuron (bottom) in the vHipp. (B) Neuronal firing rate distribution of neurons detected in SAL:RE rats supports the presence of two populations of vHipp neurons putatively following bimodal distribution that can be separated into two normal distributions (with a 2Hz-cutoff). (C) No change was found in the number of spontaneously active pyramidal neurons per track was detected across groups (n = 4-8 rats). (D) MAM:RE rats displayed increased firing rates of pyramidal neurons in the vHipp, which was prevented by prepubertal EE (25-48 cells/4-8 rats). (E) Of the fast-spiking (firing rate > 4 Hz) non-pyramidal neurons (n=11-19 cells/3-7 rats), a main effect of EE was detected (two-way ANOVA, $F(1,54)=5.500$, $p<0.05$), and MAM:EE rats displayed increased firing rate in fast-spiking cells (Tukey's *post hoc* test). Data are presented as mean ± SEM. *$p<0.05$; **$p<0.01$; ***$p<0.001$. pyra.: putative pyramidal neurons; FS: fast-spiking neurons.

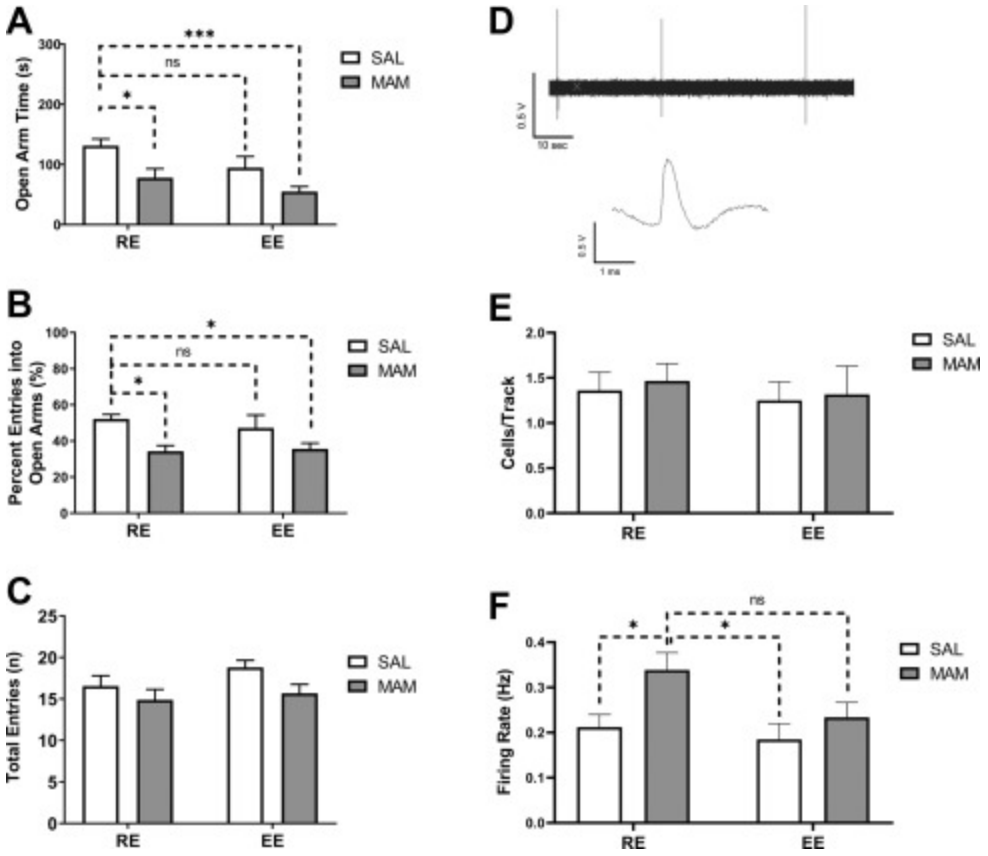

Figure 12. Prepubertal environmental enrichment did not prevent anxiety-like responses in the elevated plus maze or BLA hyperactivity in adult MAM rats.

(A-C) Adult MAM:RE rats, compared to SAL:RE rats, exhibited (A) less time spent in open arms, (B) lower percent of entries into open arms, but (C) no difference in the total number of entries, consistent with increased anxiety. Prepubertal EE did not prevent these changes in MAM rats. (n = 9-16 rats). (D-F) the effect of prepubertal EE on BLA neuronal firing. (D) Representative recording of 1-min spontaneous activity of identified putative BLA projection neurons and its waveform. (E) No change was found in the number of spontaneously active projection neurons detected per electrode track. (F) The hyperactivity of BLA neurons in MAM:RE rats was not prevented by prepubertal exposure to EE (n = 20-45/4-6 rats). Data are presented as mean ± SEM. *p<0.05; ***p<0.001; ns: not significant.

4.0 THALAMIC RETICULAR NUCLEUS IMPAIRMENTS AND ABNORMAL PREFRONTAL CONTROL OF DOPAMINE SYSTEM IN A DEVELOPMENTAL MODEL OF SCHIZOPHRENIA: PREVENTION BY N-ACETYLCYSTEINE

Chapter 4 is a modified version of:

Zhu, X., Cabungcal, J. H., Cuenod, M., Uliana, D. L., Do, K. Q., & Grace, A. A. (2021). Thalamic reticular nucleus impairments and abnormal prefrontal control of dopamine system in a developmental model of schizophrenia: prevention by N-acetylcysteine. *Molecular Psychiatry*, 10.1038/s41380-021-01198-8. https://doi.org/10.1038/s41380-021-01198-8

(Supplementary figures mentioned in this chapter are on the journal's website: https://static-content.springer.com/esm/art%3A10.1038%2Fs41380-021-01198-8/MediaObjects/41380_2021_1198_MOESM1_ESM.docx)

4.1 INTRODUCTION

Developmental interneuron deficits have been linked to the pathophysiology of schizophrenia (Marín, 2012). Specifically, the fast-spiking, parvalbumin (PV) interneurons and aberrant PV neural circuits are posited to underlie circuit dysfunction in schizophrenia (Steullet et al., 2017). Because of their widespread distribution and functional importance in high-frequency neural synchronization, disturbances in PV networks can induce dramatic functional impairments (Gonzalez-Burgos et al., 2015), manifesting as diverse attributes of schizophrenia

symptomatology (Nakazawa et al., 2012). Therefore, understanding the mechanisms driving abnormalities in the PV network is critical to the development of novel therapeutics.

Oxidative stress is a candidate mechanism underlying PV disruption in schizophrenia (Perkins et al., 2020). PV neurons are fast-spiking with heightened metabolic rates and elevated mitochondrial functions (Kann et al., 2014), resulting in increased vulnerability to oxidative stress (Do et al., 2009). Clinical evidence suggests a strong association between redox dysregulation and schizophrenia. For example, antioxidant deficits and accumulation of oxidative stress have been observed in schizophrenia patients (Emiliani et al., 2014; Flatow et al., 2013), including the most abundant endogenous non-protein antioxidant, glutathione (GSH) (Kulak et al., 2013). Such deficits may arise from a genetic origin, as gene polymorphisms relevant to GSH synthesis are reported in schizophrenia patients (Gysin et al., 2007). Moreover, oxidative stress-induced impairments are found in animal models carrying genetic and environmental risks for schizophrenia (Steullet et al., 2017), and permanent or transitory disruptions to endogenous antioxidant defense (e.g., GSH) can recapitulate selective endophenotypes relevant to schizophrenia (Cabungcal et al., 2007; Kulak et al., 2012). Lastly, the GSH precursor, N-acetylcysteine (NAC), shows efficacy in individuals with early-phase schizophrenia (Berk et al., 2008; Conus et al., 2018). Given the heterogeneity in schizophrenia etiology (Millan et al., 2016), these findings suggest that diverse risk factors of schizophrenia may converge onto deficits in redox pathways to disrupt PV circuits, ultimately leading to the development of psychosis (Steullet et al., 2017).

Many studies of oxidative PV impairments focused on cortical structures (Perkins et al., 2020), whereas the vulnerability of subcortical PV neurons is less clear. Specifically, the vulnerability of thalamic PV neurons to oxidative stress is underexplored, although thalamus-

related abnormalities are reported in schizophrenia (Steullet, 2019). Among thalamic nuclei, the fast-spiking PV neurons are almost exclusively located in the thalamic reticular nucleus (TRN) (Csillik et al., 2005; Lein et al., 2007), and are vulnerable to oxidative stress (J. H. Cabungcal et al., 2019; Steullet et al., 2018). Anatomically, the TRN receives collaterals from both thalamocortical and corticothalamic projections, enabling this region to exert strong feedforward inhibition of thalamic relay neurons and hence gating corticothalamic information flow (Crabtree, 2018). This organizational scheme was first characterized in sensory processing but applies to other functional modalities (Crabtree, 2018). Given its complex interconnections, TRN deficits can cause network-level dysfunctions and behavioral abnormalities relevant to neurodevelopmental disorders (Krol et al., 2018), including schizophrenia (Ferrarelli & Tononi, 2011; Pratt & Morris, 2015; You et al., 2021). Indeed, 19 risk genes are robustly expressed in the TRN of schizophrenia patients (Richard et al., 2017). In animal models, NMDA antagonists can induce metabolic malfunction and lesions to the TRN (Cochran et al., 2003; Sharp et al., 2001; Tomitaka et al., 2000), which are posited to precipitate psychosis-like phenotypes (Ferrarelli & Tononi, 2011). A recent study (Steullet et al., 2018) provided the first direct evidence of morphological abnormalities in the TRN of schizophrenia patients; i.e., decreased PV expression and associated extracellular matrix (i.e., perineuronal nets; PNNs) deficits. Such TRN alterations were proposed to be induced by oxidative stress, as transgenic mice with compromised antioxidant defense (i.e., *Gclm* knockout mice (Steullet et al., 2010)) exhibited similar TRN pathology and abnormal TRN activity (Steullet et al., 2018). Consistently, *Gclm* knockout mice exhibit increased susceptibility to oxidative stress, and oxidative damage to TRN PV neurons preceded that in other regions (J. H. Cabungcal et al., 2019). Whether oxidative stress-induced TRN pathology

functionally contributes to core schizophrenia pathophysiology, especially dopamine dysregulation, is unclear.

The midbrain dopamine system is regulated by complex afferent inputs (Grace, 2016). In schizophrenia, the primary deficits are thought to be in the afferent regulation of dopamine neurons, rather than in dopamine neurons themselves (Grace, 2012). The hippocampus (Lieberman et al., 2018b) and the prefrontal cortex (PFC) (Lewis et al., 2012), both of which are capable of regulating dopamine neuron activity in the ventral tegmental area (VTA), have emerged as potential sites of dopamine dysregulation in schizophrenia. We have demonstrated that pharmacological manipulation of the ilPFC can bidirectionally regulate VTA dopamine neuron population activity (i.e., number of active DA neurons) (Patton et al., 2013). Whereas activation of the ilPFC decreased dopamine neuron activity dependent on the amygdala, inactivation of the ilPFC increased dopamine population activity via the vHipp (Patton et al., 2013). However, unlike the mPFC-BLA pathways, there are no direct mPFC-vHipp projections, and thus the ilPFC input to vHipp must go through a thalamic relay (Vertes, 2004), which we determined to be the reuniens of the midline thalamus (RE). Specifically, we demonstrated that the anterior TRN (aTRN) is under afferent control by the infralimbic PFC (ilPFC) to inhibit RE activity (Zimmerman & Grace, 2018). Moreover, changes in RE output are sufficient to bidirectionally regulate ventral hippocampus (vHipp) activity, impacting VTA dopamine neuron firing (Zimmerman & Grace, 2016) via a well-established pathway comprising the vHipp, the nucleus accumbens (NAc), and the ventral pallidum (VP) (Grace, 2016). These findings implicate the TRN and RE as novel regions involved in the control of the dopamine system. Therefore, the newly discovered TRN deficits in schizophrenia (Steullet et al., 2018) may directly contribute to dopamine abnormalities purported to underlie psychosis (Modinos et al., 2015). This was tested using a

neurodevelopmental model of schizophrenia risk (i.e., methylazoxymethanol acetate (MAM) E17 model (Modinos et al., 2015) to examine whether oxidative stress and the associated PV/PNN deficits are present in the TRN, and whether this leads to abnormal ilPFC control of dopamine neurons. Moreover, since redox dysregulation is a putative prophylactic target of schizophrenia (Sawa & Seidman, 2014), we tested whether treating early oxidative damage can avert schizophrenia-relevant histological and neurophysiological phenotypes of the MAM model. Furthermore, to assess the direct involvement of oxidative stress-associated PV/PNN damage in dopamine dysfunction, we enzymatically digested PNNs in the aTRN of normal rats and investigated whether this targeted manipulation would cause similar neurophysiological alterations as observed in MAM rats.

4.2 MATERIALS AND METHODS

Animals. Experiments were performed on adult male offspring (aged 75-125 days) of rats injected gestationally with 0.9% saline (SAL) or methylazoxymethanol acetate (20mg/kg, i.p.; MRI Global), based on prior studies showing significant susceptibility differences between male and female MAM offspring (Moore et al., 2006; S. M. Perez et al., 2019). To avoid litter effects, individual experimental groups were comprised of animals from at least 4 independent litters (range: 4-6) from 2-3 independent cohorts. No more than two pups from a single litter were used in each experimental group, and all the experimental groups within an experiment were counterbalanced. Experiments were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh. See *Supplementary Information* for details on animal preparation and histological confirmation of recording and infusion sites.

NAC treatment. Daily freshly made solution (900 mg/L) of NAC (A7250, Sigma-Aldrich, USA), an antioxidant and a precursor of GSH, was provided as drinking water (Vehicle, Veh) to lactating mothers and their pups from postnatal day (P) 11-25. Previous rodent work has indicated that NAC orally consumed at similar doses is transmitted to pups via breast milk to achieve antioxidative and protective effects on PV neurons (Cabungcal et al., 2014; das Neves Duarte et al., 2012). Animals were weaned at P25 and thereafter received normal drinking water until euthanasia.

Immunohistology. Perfusion, tissue preparation, immunohistochemistry, confocal microscopy, and analyses were similar to previous reports with minor modifications (Cabungcal, Steullet, Kraftsik, et al., 2013; Steullet et al., 2018). See *Supplementary Information* for details.

Electrophysiology. Single-unit extracellular recordings of VTA dopamine neurons were performed on rats anesthetized with chloral hydrate (Sigma-Aldrich; 400mg/kg, i.p.), as previously

described (Zimmerman & Grace, 2016). Briefly, glass microelectrodes were filled with 2M nacl containing 2% Chicago Sky Blue (impedance 7 to 15 MΩ *in situ*) and lowered through the VTA (beginning at AP: −5.4 mm, ML: +0.6 mm, DV: −6.5 to −9 mm) via 4-6 vertical tracks (each separated by 0.2 mm) in a predetermined pattern. Dopamine neurons were identified by well-established criteria (Ungless & Grace, 2012) and recorded for at least 90 seconds. Population activity (i.e., average number of spontaneously active neurons recorded each track), average firing rate, and the average percentage of spikes in burst were analyzed. See *Supplementary Information* for details.

Acute chondroitinase treatment and confirmation of PNN degradation. Following chloral hydrate-induced anesthesia, and at least one hour before the extracellular recordings, a subset of rats was infused bilaterally with 0.5µl chondroitinase ABC from Proteus Vulgaris (chabc, 0.05U/µl), or Dulbecco's PBS (dpbs), into the anterior TRN (A/P: −1.5, M/L: ±2.5, D/V: −5.5 mm). This treatment was designed to acutely digest pnns and was based on chabc's rapid action *in vitro* at a significantly lower concentration (Balmer, 2016; Klein et al., 2018). The time course of PNN degradation within the time frame of a recording experiment (i.e. 4-5 hours) was also characterized in this study. See Supplementary Information for details.

Intra-ilpfc and -TRN microinjection. Immediately before VTA recordings, tetrodotoxin (TTX; 1 M, 0.5 µl) or dpbs vehicle was infused into the ilpfc at the following coordinates (mm): AP: +2.7; ML: +0.6; DV: −3.9. This microinfusion protocol has been validated previously, and the spread was limited to the ilpfc (Moreines et al., 2017). See *Supplementary Information* for details of cannula-based microinfusion.

Statistical analysis. Sample sizes were determined based on similar previous studies (Cabungcal et al., 2014; Zimmerman & Grace, 2018). Group data were tested for normal

distribution by the Shapiro-Wilk test. If passed, group data were analyzed by two-way ANOVA, with treatment (SAL or MAM) and TTX infusion (Veh or TTX) as main factors, followed by Tukey's *post hoc* test when a significant effect was detected. In the electrophysiological experiments in a within-subject design, group data were analyzed with two-way repeated measure ANOVA with developmental (SAL:H_2O, SAL:NAC, MAM:H_2O, or MAM:NAC) or TRN treatment (PBS vs. Chabc) condition as a main factor and TTX infusion (pre-TTX vs. Post-TTX) as a repeated measure, followed by Bonferroni *post hoc* test. If data failed to pass the normality test, a Kruskal–Wallis one-way ANOVA on Ranks, followed by Dunn's *post hoc* analysis, was applied. Statistics were calculated using Prism8 (graphpad Software). Post-hoc Dunnett's t-tests were performed to compare the mean number of PV cells, Wisteria floribunda agglutinin (WFA; a PNN maker)/ PV cells, and the overall 8-oxo-dg immunolabeling between the groups. These statistics were performed using JMP 12 (SAS Institute Inc., USA). All data are represented as the mean ±SD or SEM. Differences were considered significant at $p<0.05$.

4.3 RESULTS

4.3.1 Increased oxidative stress and reduced PV and WFA/PNNs in the TRN of adult MAM rats was prevented by early antioxidant treatment

To assess TRN oxidative stress in MAM rats, mitochondrial DNA oxidation was labeled using 8-oxo-7, 8-dihydro-20-deoxyguanosine (8-oxo-dG) and quantified (Cabungcal et al., 2014). Additionally, subcellular nitration of proteins and free tyrosine residues, as another evidence of oxidative stress, was confirmed using 3-Nitrotyrosine (3-NT) immunolabeling. Dunnett's *post hoc*

analysis revealed an increased level of oxidative stress labeling by ~350% with 8-oxo-DG and ~320% with 3-NT in the anterior segment of the TRN in adult MAM:H_2O rats compared to SAL:H_2O rats (8-oxo-dG: Figure 13A, B; D=0.87, p<0.0001, and 3-NT: Figure 13E,F; D=1.96, p<0.0001). Since PV neurons are vulnerable to oxidative stress (Cabungcal, Steullet, Morishita, et al., 2013), the expression of PV in the TRN was assessed. The number of PV neurons and PV intensity significantly decreased by 31% and 460%, respectively, in MAM:H_2O group compared to SAL:H_2O group (Figure 13A, C; D=241.6, p<0.0001 and Figure 13E,G; D=5.86, p<0.0001), revealing prominent impairments to the PV circuitry in MAM rats. PNNs, labeled by WFA, are maturational markers of PV neurons and are protective against oxidative stress (Cabungcal, Steullet, Morishita, et al., 2013). Thus, to further determine if the observed oxidative stress affects the maturation and resilience of PV circuitry, the extent of PV neurons associated with PNNs and PNN (WFA) labeling intensity were assessed. Compared to SAL:H_2O rats, a significantly lower number of PV/PNN neuronal colocalizations (Figure 13A, D; D=185, p<0.0001) and lower PNN intensity (Figure 13E and H; D=2.2, p<0.001) were found, suggesting a relatively immature state of PV circuitry in MAM rats with increased vulnerability to oxidative stress.

Accumulation of oxidative damage occurs over an extended period (J. H. Cabungcal et al., 2019), which is potentially preventable by early interventions that restore redox balance, such as NAC supplementation (Cabungcal et al., 2014). To test whether limiting developmental oxidative stress can prevent TRN abnormalities of MAM rats, we administered NAC during P11-25 and assessed the integrity of TRN PV circuitry in adult MAM rats. MAM:NAC rats exhibited decreased oxidative stress labeling compared to MAM:H_2O rats (8-oxo-dG: Figure 13A, B; D=1.08, p<0.0001 and 3-NT: Figure 13E, F; D=1.95, p<0.0001). Furthermore, NAC treatment prevented the decreased PV neuron number (Figure 13A, C; D=231.9, p<0.0001), PV intensity

(Figure 13E, G; D=1.95, p<0.0001), decreased number of PV/PNN co-labeled cells (Figure 13A, D; D=197.8, p<0.0001) and PNN intensity (Figure 13E, H; D=3.07, p<0.0001), which was not found in SAL:NAC rats compared to SAL:H_2O rats. Collectively, these data indicate that early NAC treatment was able to prevent circuit impairments to both PV and PV/PNN neurons in the TRN of MAM rats.

4.3.2 Inverse effects of ilPFC inactivation on VTA dopamine neurons in MAM rats

The medial PFC is a key regulator of dopamine activity (Patton et al., 2013). Specifically, the ilPFC controls VTA dopamine activity via a thalamic relay under the feedforward inhibitory control from the TRN (Zimmerman & Grace, 2016). Considering the extensive oxidative damage to TRN PV neurons, we determined whether such morphological deficits could functionally affect the ability of the ilPFC to modulate dopamine activity. ilPFC inactivation specifically upregulates dopamine neuron firing in a manner dependent on the vHipp and the thalamic relay involving the TRN (Patton et al., 2013; Zimmerman & Grace, 2016; Zimmerman & Grace, 2018), and is therefore the focus of this study. Following pharmacological inactivation of the ilPFC by TTX, *in vivo* extracellular recordings were performed on identified VTA dopamine neurons, displaying well-established physiological characteristics such as irregular firing and long spike duration (Figure 14A) (Ungless & Grace, 2012). For population activity (i.e., number of neurons firing spontaneously; Figure 14B), a two-way ANOVA revealed a significant interaction [F(1, 34)=21.08, p<0.001]. SAL:Veh group (n=12 rats/78 cells) displayed 0.79±0.08 spontaneously active dopamine neurons per track. In contrast, SAL:TTX group (n=7 rats/60 neurons) had significantly increased VTA dopamine neuron population activity (1.30±0.17 cells/track) compared to SAL:Veh group (Tukey's *post hoc* test, p<0.05), confirming previous results that

ilPFC inactivation upregulates population activity (Moreines et al., 2017; Patton et al., 2013; Zimmerman & Grace, 2016). The MAM:Veh group (n=10 rats/98 neurons) displayed significantly higher dopamine population activity (1.36±0.13 cells/track) compared to SAL:Veh group (Figure 14B, $p<0.01$) as reported previously (Lodge & Grace, 2007). MAM:TTX rats (n=10 rats/69 cells) exhibited significantly decreased population activity (0.82±0.11 cells/track) compared to MAM:Veh rats ($p<0.01$). Altogether, these results revealed opposite effects of ilPFC inactivation on dopamine activity between SAL and MAM rats, suggesting abnormal prefrontal control of dopamine neuron tonic activity in the MAM offspring.

No significant effect was detected in either firing rate or burst firing (Figure 14C and D). These results are consistent with previous reports that ilPFC inactivation primarily affects dopamine neuron tonic firing, with only limited effects on phasic firing (Moreines et al., 2017; Patton et al., 2013; Zimmerman & Grace, 2016).

4.3.3 Early antioxidant treatment prevented the increased baseline activity and the abnormal prefrontal modulation of dopamine neurons in MAM rats

Since TRN PV deficits in MAM rats can be prevented by early NAC treatment (Figure 13B-D, F-G), we tested whether the dopamine dysfunction in MAM rats can also be prevented. Using a within-subject design, we performed *in vivo* extracellular recordings from dopamine neurons before and after TTX-induced ilPFC inactivation. For population activity (Figure 15A), a two-way repeated measure ANOVA revealed a significant main effect of TTX infusion [$F(1, 24)=14.34$, $p<0.001$] and a significant interaction [$F(3, 24)=10.46$, $p<0.001$]. For baseline dopamine population activity (i.e., "pre-TTX" groups), Bonferroni *post hoc* analysis showed that MAM:H_2O group (n=6 rats/55 neurons) exhibited increased dopamine population activity

(1.70±0.20 cells/track) compared to SAL:H_2O controls (n=6 rats/38 neurons; 0.86±0.17; $p<0.05$). Juvenile NAC treatment significantly lowered baseline dopamine population activity in MAM rats, and MAM:NAC group (n=10 rats/48 neurons; 0.84±0.15 cells/track) exhibited lower dopamine population activity compared to MAM:H_2O group ($p<0.01$). No significant difference in baseline population activity was detected between SAL:H_2O and SAL:NAC (6 rats/25 cells; 0.87±0.10 cells/track; $p>0.05$) groups. For the effect of ilPFC infusion (i.e., "post-TTX" groups), in SAL:H_2O group (post-TTX: 6 rats/50 neuron) we observed increased population activity (1.53±0.29 cells/track; $p<0.01$), which is comparable to previous results (Figure 14B). In contrast, in MAM:H_2O group (post-TTX: 6 rats/33 cells), ilPFC inactivation decreased dopamine population activity (1.17±0.17 cells/track; $p<0.01$), confirming the abnormal prefrontal control observed in Figure 14B. Notably, this effect was prevented in MAM:NAC group (post-TTX: n=10 rats/66 cells), in which MAM:NAC rats displayed increased dopamine population activity in response to TTX infusion (post-TTX: 1.24±0.19 cells/track; $p<0.05$). SAL:NAC group (post-TTX: 6 rats/48 cells) similar to that observed in the SAL:H_2O group, in which TTX infusion increased dopamine population activity (1.60±0.12 cells/track; $p<0.001$).

Firing rate and burst firing of dopamine neurons were also analyzed (Figure 15C and D). For firing rate (Figure 15C), no significant effect among groups was detected, which was consistent with previous results showing inactivation of ilPFC alone selectively affected tonic firing without affecting the average firing rate of dopamine neurons (Patton et al., 2013). There was a significant difference in burst firing among groups [Figure 15D; Kruskal-Wallis H test, $H=16.90$, $p<0.05$]. Dunn's *post hoc* analysis revealed significantly reduced post-TTX burst firing of dopamine neurons in MAM:H_2O ($p<0.01$) and MAM:NAC ($p<0.05$) groups.

4.3.4 ChABC-induced PNN digestion in the TRN of normal rats recapitulated the MAM-like electrophysiological phenotypes.

To further elucidate the functional implications of TRN abnormalities in MAM rats, we acutely degraded PNNs using ChABC in the TRN of normal rats and recorded the response of VTA dopamine neurons. Specifically, in rats injected bilaterally with ChABC or PBS control for one hour, we recorded dopamine neurons before and after TTX-induced ilPFC inactivation (Figure 16A-C). A two-way repeated measure ANOVA revealed a significant interaction in dopamine neuron population activity [$F(1, 11) = 127.6$, $p<0.0001$]. Comparable to previous findings and similar to SAL controls in this study (Figure 16A and 14A), PBS controls show baseline population activity of 1.01±0.17 cell/track (n=6 rats), which is significantly increased after TTX-induced ilPFC inactivation (1.88±0.15 cells/track; $p<0.0001$). In contrast, in ChABC-treated rats, the baseline population activity is significantly increased compared to PBS controls (1.59±0.10 cells/track, n=7 rats; $p<0.01$), resembling MAM rats. After ilPFC inactivation, ChABC-treated rats showed decreased population activity of 0.80±0.09 cells/track ($p<0.0001$, vs. ChABC:Pre), which is significantly lower compared to the post-TTX recording in PBS controls (Figure 16A).

To verify the extent of PNN degradation, immediately after the recording TRN brain sections were collected and processed for immunohistochemistry (Figure 16D). We found decreased mean TRN WFA intensity in ChABC-treated (80.44±11.69 a.u., n=7) versus control animals (137.7±12.17 a.u., n=6; $t_{(11)}=3.369$; $p<0.01$), whereas the TRN PV intensity was not different between these groups (76.47±5.88 vs. 82.18±4.79 a.u.; $p>0.05$). This result confirmed the TRN PNN degradation in recorded animals, indicating that ChABC is capable of effectively degrading PNNs within the typical time frame of VTA recording experiments (~5 hours). To further elucidate the temporal dynamics of PNN degradation, we performed unilateral intra-TRN

ChABC injection and compared that with the PBS-treated side on the same coronal sections (n=2-3 rats; N=2-4 sections/rat) throughout post-infusion time points (Figure 16E). Consistent with in vitro studies(Klein et al., 2018), PNN degradation was observable one hour after the ChABC treatment (Figure 16F), and the WFA signal was reduced to 51.6±6.5%, which is significantly lower compared to the control PBS injection sides (paired t-test, $p<0.0001$) (Figure 16G). Moreover, the reduction in WFA intensity was stable throughout the recording period, as significant PNN degradation was still observed at 2- and 4-hour post-infusion. Collectively, these results demonstrate that direct adult perturbation to TRN PNNs is sufficient to elevate baseline activity and disrupt infralimbic prefrontal control of VTA dopamine neurons, reminiscent of the dopamine dysregulation of MAM rats.

4.4 DISCUSSION

We found increased oxidative damage in the TRN, along with decreased PV immunoreactive cell count and fewer PV cells associated with PNNs in the MAM developmental disruption model of schizophrenia. Such TRN deficits were accompanied by elevated dopamine population activity and abnormal prefrontal control of dopamine neurons. Targeted digestion of TRN PNNs in normal rats recapitulated these neurophysiological abnormalities. All of these TRN morphological deficits and dopamine neurophysiological dysfunctions in MAM rats were prevented by early (P11-25) antioxidant treatment.

Several studies on redox dysregulation in schizophrenia focused on the PFC and the hippocampus, providing consistent findings of increased oxidative damage and decreased capacity of the redox system in this disorder (Perkins et al., 2020). Emerging evidence, however, suggested that oxidative stress in schizophrenia can affect subcortical regions, particularly the TRN (Steullet, 2019). Noteworthy, in young mice with genetically induced redox dysregulation, oxidative impairments to PV circuits tend to occur earlier in subcortical regions (e.g., at P20 in the TRN and P40 in the amygdala) compared to the cortex and the hippocampus, raising the possibility that early perturbation to TRN integrity might affect the development of other regions, eventually leading to brain-wide deficits (J. H. Cabungcal et al., 2019). These recent breakthroughs inspired this study.

The MAM model is based on *in utero* disruption of neural development by the mitotoxin (Lodge, 2013), and adult MAM-exposed offspring recapitulate histological, neurophysiological, and behavioral deficits analogous to several clinical features observed in schizophrenia, particularly those consistent with circuit disruption (Modinos et al., 2015; Moore et al., 2006). Previous research of redox dysregulation in the MAM model is limited. To date, only two studies

examined the oxidative impairments in MAM rats, both reporting increased oxidative-stress markers and substantial PV damage in the PFC (Do et al., 2015; Steullet et al., 2017). Complementing these studies, we now demonstrate oxidative impairments in the TRN of adult MAM rats. Together, current evidence indicates putative widespread oxidative pathology in PV circuits in MAM rats, encompassing cortical and subcortical regions.

The increased oxidative stress in MAM rats may relate to GSH disruption. In schizophrenia patients, several magnetic resonance spectroscopy (MRS) studies indicated brain-wide GSH reduction, including the PFC, the anterior cingulate cortex, and the striatum (Das et al., 2019; Do et al., 2000; Kumar et al., 2018; Nucifora et al., 2017; Reyes-Madrigal et al., 2019). A recent MRS study further revealed a thalamic-selective GSH reduction in first-episode psychosis patients (Wang et al., 2019), linking regional GSH dysregulation to schizophrenia pathogenesis. In MAM rats, gestational exposure to MAM is known to reduce brain GSH level, leading to progressive neuronal death in GABAergic interneurons (Fonnum & Lock, 2004). Thus, an early GSH dysregulation in the TRN of MAM rats may contribute to the observed oxidative damage to PV neurons. Noteworthy, vulnerability to early stress substantially mediates MAM-induced pathology (Gomes et al., 2019b). Since exposure to environmental stressors impairs redox processes at cellular and molecular levels (Möller et al., 2011; Schiavone et al., 2015), the oxidative damage in MAM rats might exacerbate their heightened susceptibility to a negative environment (Zimmerman et al., 2013). Thus, future studies should elucidate possible interactions between deficits in the GSH system and excessive environmentally induced oxidative stress in MAM rats.

To test whether early antioxidant prevents later development of oxidative deficits, MAM rats were treated with a GSH precursor, NAC, during the juvenile period (P11 – 25). This NAC treatment regimen was based on numerous studies on early insults to the redox system, all of which

demonstrated that oral NAC treatment was especially effective against oxidative pathology when given during a preweaning period (Cabungcal et al., 2014; Cabungcal, Steullet, Kraftsik, et al., 2013; das Neves Duarte et al., 2012; Otte et al., 2011; Phensy et al., 2017). Such efficacy of early treatment might be related to maturational changes of GSH inhibitory feedback control (Meister, 1995). The present treatment was also designed to parallel TRN PV development and account for their early onset of susceptibility to oxidative stress. Specifically, TRN PV expression in rodents is detectable at P0 and continues to increase until approximately P30 (Majak et al., 1998; Mitrofanis, 1992). Moreover, PV neurons manifest vulnerability to oxidative stress as early as P20 (J. H. Cabungcal et al., 2019). Thus, a preweaning period (i.e., P11-25) was selected to account for these developmental hallmarks. Notably, both the increased oxidative stress markers and the morphological deficits in TRN PV circuits in MAM rats were prevented by juvenile NAC treatment (Figure 13). These findings highlight early oxidative stress as a promising prophylactic target for the pathological development of schizophrenia. The timeline of treatment also suggests that the pathological sequelae of oxidative stress in the TRN of adult MAM rats, and perhaps in schizophrenia patients (Steullet et al., 2018), might have a developmental origin in childhood and/or adolescence.

The TRN contains predominantly inhibitory PV neurons, estimated to account for 50-90% of the total neuron population (Hou et al., 2016; Steullet et al., 2018; Zikopoulos & Barbas, 2006). In principle, the TRN is the major inhibitory system for corticothalamic circuits, providing strong feedforward inhibition to thalamic relay nuclei (Halassa & Acsády, 2016). The TRN is topographically organized, and the aTRN receives monosynaptic projections from the ilPFC (Cornwall et al., 1990) and in turn innervates the RE (Kolmac & Mitrofanis, 1997), forming parallel ilPFC-TRN-RE and ilPFC-RE pathways (McKenna & Vertes, 2004; Varela et al., 2014).

To our knowledge, there are no specific data relevant to Guillery and Sherman's distinction between "driver" and "modulator" input in ilPFC-RE pathways. However, as the RE receives dense ilPFC projections from layer V, presumably ilPFC projections are driving inputs to the RE (Sherman & Guillery, 2013). We recently demonstrated that the ilPFC acts through parallel pathways to dynamically regulate RE neuron activity (Zimmerman & Grace, 2018), which by itself is sufficient to affect both the baseline and the ilPFC control of VTA dopamine neuron activity (Zimmerman & Grace, 2016). While the exact circuit mechanism warrants a more comprehensive future study, we speculate that the significant aTRN PV/PNN impairments in MAM rats (Figure 13) might impair TRN inhibitory output to the RE, and thereby disrupt prefrontal-hippocampal interaction to affect afferent control of dopamine neurons (Figure 17). Specifically, in control animals with an intact TRN, the ilPFC-RE circuit is proposed to control downstream dopamine neurons primarily via the indirect pathway (Zimmerman & Grace, 2016), allowing TRN inhibitory neurons to overcome direct excitation from the ilPFC (Figure 17A). At a system level, such organization would enable the ilPFC to provide tonic inhibition to the ventral subiculum (vSub) of the vHipp, therefore preventing hippocampal hyperactivation (Grace, 2016). This dominance of the ilPFC-TRN-RE indirect pathway would also be consistent with the findings that the primary action of ilPFC NMDA stimulation on RE is inhibitory (Zimmerman & Grace, 2016). Furthermore, potent inhibitory TRN pathways appeared to be common in corticothalamic communication (Paz et al., 2011), allowing powerful feedforward TRN inhibition to overwhelm the direct yet weaker corticothalamic projections (Crandall et al., 2015). The biological basis of such circuit dominance has been attributed to stronger synaptic connections formed in the TRN (Warren et al., 1994), possibly related to abundant TRN PNN expression known to enhance the excitability of fast-spiking interneurons (Balmer, 2016). Consequently, in SAL rats with an intact

TRN ilPFC inactivation would primarily attenuate TRN-mediated feedforward inhibition, and therefore disinhibit the RE-vSub pathway, leading to hippocampal hyperactivity and disinhibition of midbrain dopamine neuron via a well-characterized pathway involving vSub, NAc, and VP (Figure 17C) (Grace, 2016). In contrast, in MAM rats with substantial TRN PV decrease, TRN-mediated feedforward inhibition would be compromised, causing the direct ilPFC-RE glutamatergic projections to predominate (Figure 17B). Such circuit imbalance, when combined with hippocampal inhibitory PV neuron impairments (Lodge et al., 2009), could contribute to hippocampal hyperactivity and thereby dopamine neuron hyperresponsivity in MAM rats (Lodge & Grace, 2007), consistent with functional impairments in the medial temporal lobe in schizophrenia (Modinos et al., 2015). A compromised TRN would also be consistent with the emerging finding of PFC/thalamus dysconnectivity in schizophrenia (Woodward & Heckers, 2016) In addition to dopamine baseline firing, TRN defects could also impact prefrontal control of dopamine activity. In MAM rats, due to the lack of TRN-mediated feedforward inhibition, ilPFC inactivation would act predominantly upon the direct, glutamatergic ilPFC-RE projection, leading to decreased activity of the RE-vSub pathway and subsequently a decreased VTA dopamine output (Figure 14B, 17D), which is opposite to the PFC regulation of dopamine neurons in SAL controls. Unexpectedly, we also observed a small decreased burst firing in MAM rats responding to ilPFC inactivation (Figure 15D). This effect could be due to multiple alternate pathways through which the ilPFC can impact the dopamine phasic firing, which may include amygdala, a region that also shows oxidative stress-related alterations in pathological states such as schizophrenia (Pantazopoulos et al., 2010).

Since NAC treatment prevented TRN PV/PNN pathology (Figure 13), we examined whether it can also prevent dopamine dysregulation in MAM rats (Figure 15). We found that both

the baseline hyperdopaminergic activity and the abnormal prefrontal control of dopamine neurons in MAM rats were prevented by juvenile NAC treatment (Figure 15A). Together with the morphological findings, these data indicate clear prophylactic effects of NAC on TRN PV neuron impairments and dopamine dysfunction. Furthermore, this prevention also provides insights into the pathophysiology of schizophrenia. The primary action of NAC is to increase and restore GSH levels in the nervous system (das Neves Duarte et al., 2012). Since brain GSH level is stringently regulated (Meister, 1995), NAC treatment is posited to be effective only in conditions with significantly altered redox balance (Aldini et al., 2018) and is largely ineffective in subjects with intact redox systems (das Neves Duarte et al., 2012; Reyes-Madrigal et al., 2019). Given this selective action, current findings with NAC treatment support the hypothesis that regional redox dysregulation might mediate the pathophysiological development of schizophrenia-related endophenotypes.

While this study primarily focused on the TRN, the extent of oxidative-stress induced impairments to PV/PNNs in MAM rats likely extends beyond thalamic networks. Thus, MAM rats also display decreased levels of PNN components in the vHipp (Shah & Lodge, 2013). Therefore, to pinpoint the precise role of TRN PV/PNN abnormalities in dopamine-related pathophysiology, we acutely digested PNNs with ChABC and recorded from VTA dopamine neurons (Figure 16). We found that intra-TRN ChABC infusion resulted in a rapid and long-lasting PNN degradation (Figure 16), which is sufficient to elevate baseline population activity and reverse prefrontal control of dopamine neurons (Figure 16A), closely resembling that of MAM rats (Figure 15A). This result provided a direct mechanistic link between oxidative stress-associated PNN deficits and key schizophrenia pathophysiology. Previous electrophysiological studies reported that cortical (Balmer, 2016) and TRN (Klein et al., 2018) PV inhibitory neurons lacking PNNs were

unable to maintain high-frequency bursting, thereby diminishing the normally robust inhibition of their synaptic targets. Thus, the TRN PNN loss, as observed in schizophrenia and MAM rats, may decrease TRN inhibitory output to thalamic relay nuclei projecting to "downstream" afferent structures (e.g. the vHipp) involved in dopamine control.

Beyond thalamic abnormities, PV-associated deficits in the BLA and the vHipp were also found in MAM rats (Gomes et al., 2019b), suggesting extensive oxidative pathology. A key question is the spatio-temporal patterns of oxidative stress accumulation and the associated PV impairments, as this can potentially explain the progressive development of schizophrenia-related phenotypes in MAM rats (Moore et al., 2006). Translating to patients, as structural alterations of specific thalamic nuclei connected to the PFC were recently observed in early psychosis and chronic schizophrenia patients (Alemán-Gómez et al., 2020), such early TRN impairments might be central to a circuit-based development of the disease pathophysiology. Noteworthy, the early time course of the treatment in this study might implicate age-dependent mechanisms of NAC's efficacy, which warrants future studies to further elucidate optimal windows for prevention.

In summary, this study complements the growing knowledge of TRN-related abnormalities in schizophrenia pathophysiology. Our data indicate excessive TRN oxidative stress in adult MAM rats associated with significant impairments in PV/PNNs and neurophysiological deficits in the prefrontal control of dopamine neurons. We also found that early antioxidant treatments can prevent TRN PV/PNN deficits and dopamine dysfunction in MAM rats. In normal rats, ChABC-induced TRN PNN degradation recapitulates MAM-like dopamine dysregulation. Together, this study suggests that thalamic redox dysregulation could represent both a pathophysiological mechanism and a promising prophylactic target for schizophrenia.

4.5 FIGURES

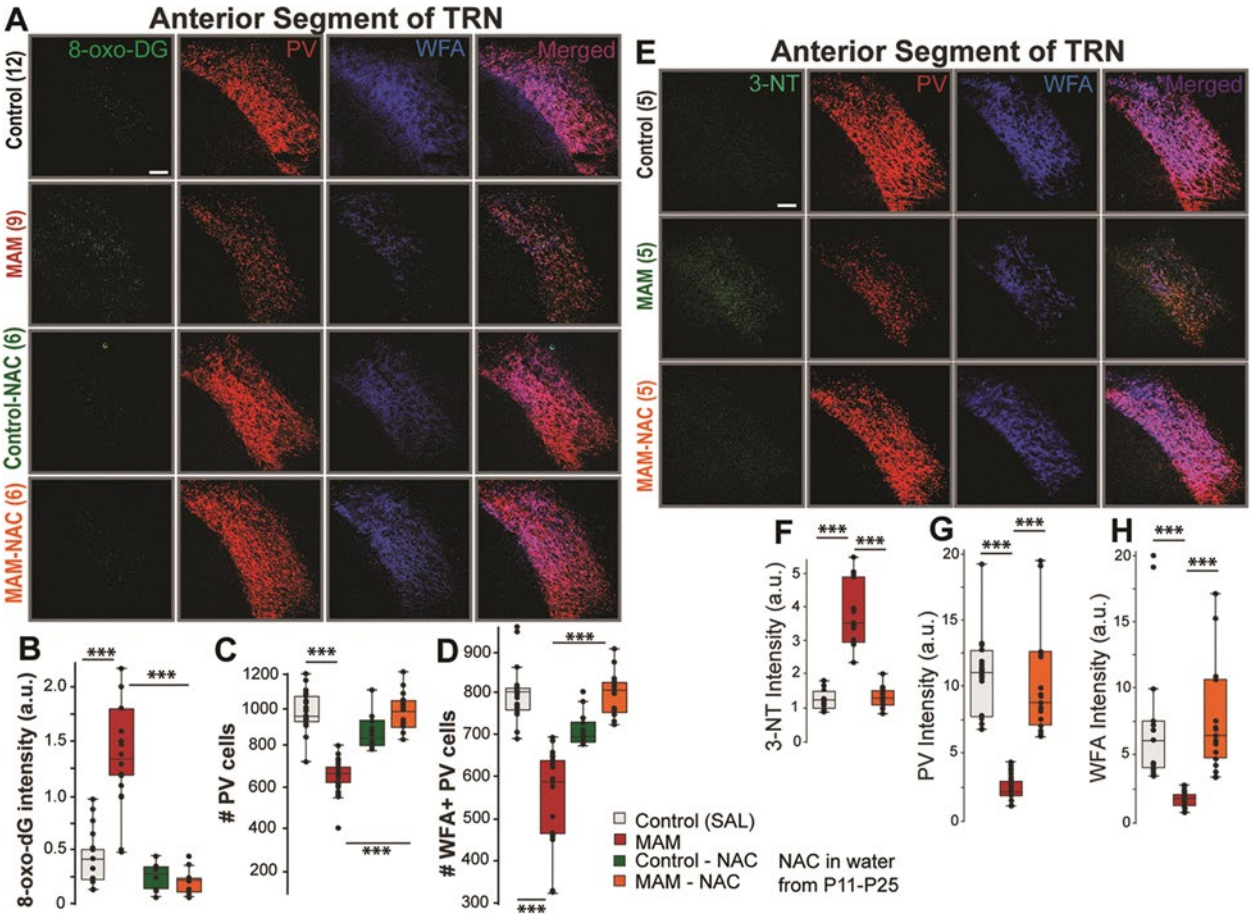

Figure 13. Oxidative stress-induced PV and PNN circuitry impairment in the anterior segment of TRN in adult MAM rats was prevented by juvenile N-acetylcysteine (NAC) treatment.

A Micrographs show labeling for 8-oxo-dG (green), PV (red), and WFA (labels PNN, blue) in the TRN of Control and MAM rats in the absence or presence of juvenile NAC treatment. Scale: 40 µm. **B** NAC prevents the increase in 8-oxo-dG labeling in MAM rats. **C** Stereological quantification reveals that NAC prevents oxidative stress-induced decrease of PV and **D** WFA + PV number in MAM rats. **E** Micrographs show labeling for another oxidative marker, 3-NT (green), PV (red), and WFA (labels PNN; blue) in the aTRN of Control and MAM rats in the absence

or presence of juvenile NAC treatment. Scale: 40 μm. **F** NAC prevents the increase in 3-NT fluorescent intensity (a.u.). **G**, **H** NAC also prevents the loss of PV and WFA labeling intensity (a.u.) in MAM rats. Scatter and box plots showing medians (horizontal line) and quartile (the bottom and top of the box indicate the first (Q1) and third (Q3) quartiles) values; the upper limit equals Q3 plus 1.5 times interquartile range (IQR), and the lower limit equals Q1 minus 1.5 times interquartile range. For each group **A**–**D**: $n = 12$ (Control), 9 (MAM), 6 (Control-NAC), and 6 (MAM-NAC), **E**–**H**: $n = 5$ (Control), 5 (MAM), and 5 (MAM-NAC) ***$p < 0.0001$ (pair-wise Dunnett tests). NAC treatment was added to drinking water from P11 to P25.

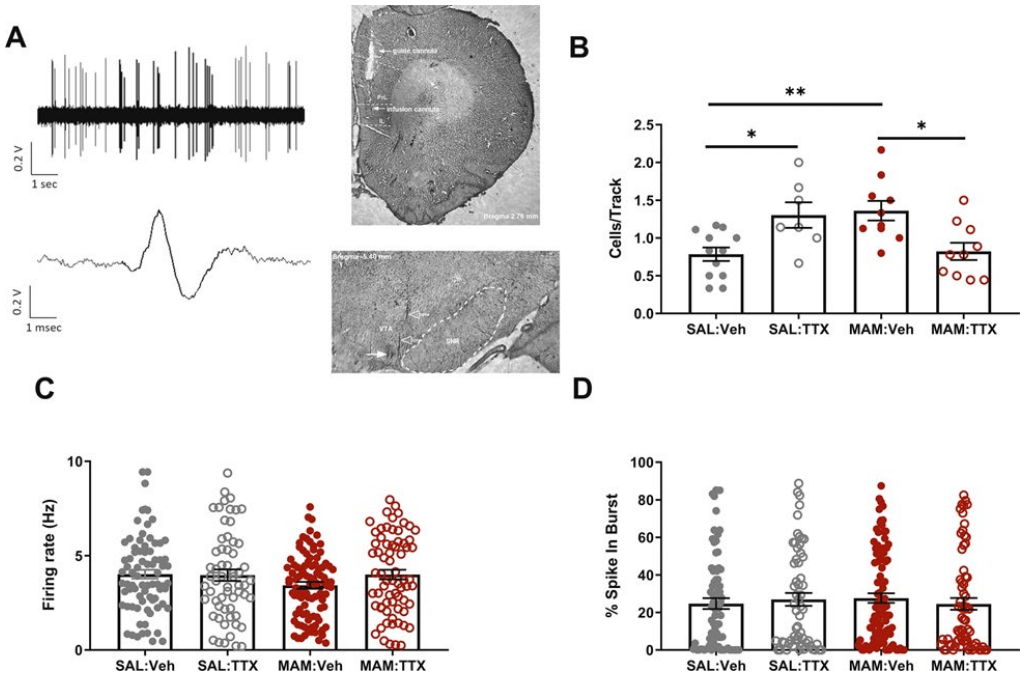

Figure 14. Population activity and ilPFC control of VTA dopamine neurons were altered in MAM rats.

A Left, representative recording of a dopamine neuron from SAL:Veh rats. Right, representative images of histological placements of infusion and recording sites in the ilPFC and the VTA (solid arrow: electrode tip; open arrow: electrode track). **B** In vehicle (Veh)-treated groups (solid circles), MAM rats (red circles) display heightened VTA dopamine population activity compared to SAL controls (gray circles). In addition, TTX-mediated ilPFC inactivation (open circles) induced opposite effects on VTA dopamine neurons in SAL vs. MAM rats. n(rat) = 7–12; n(litter) = 4–6. **C**, **D** No effect of either exposure to MAM or TTX infusion was observed on firing rate or burst firing of dopamine neurons. n(rat) = 7–12; N(cell) = 60–98. *$p < 0.05$; **$p < 0.01$; Data are presented as mean ± SEM. PrL: prelimbic PFC; IL: infralimbic PFC; SNR: substantia nigra, reticular part.

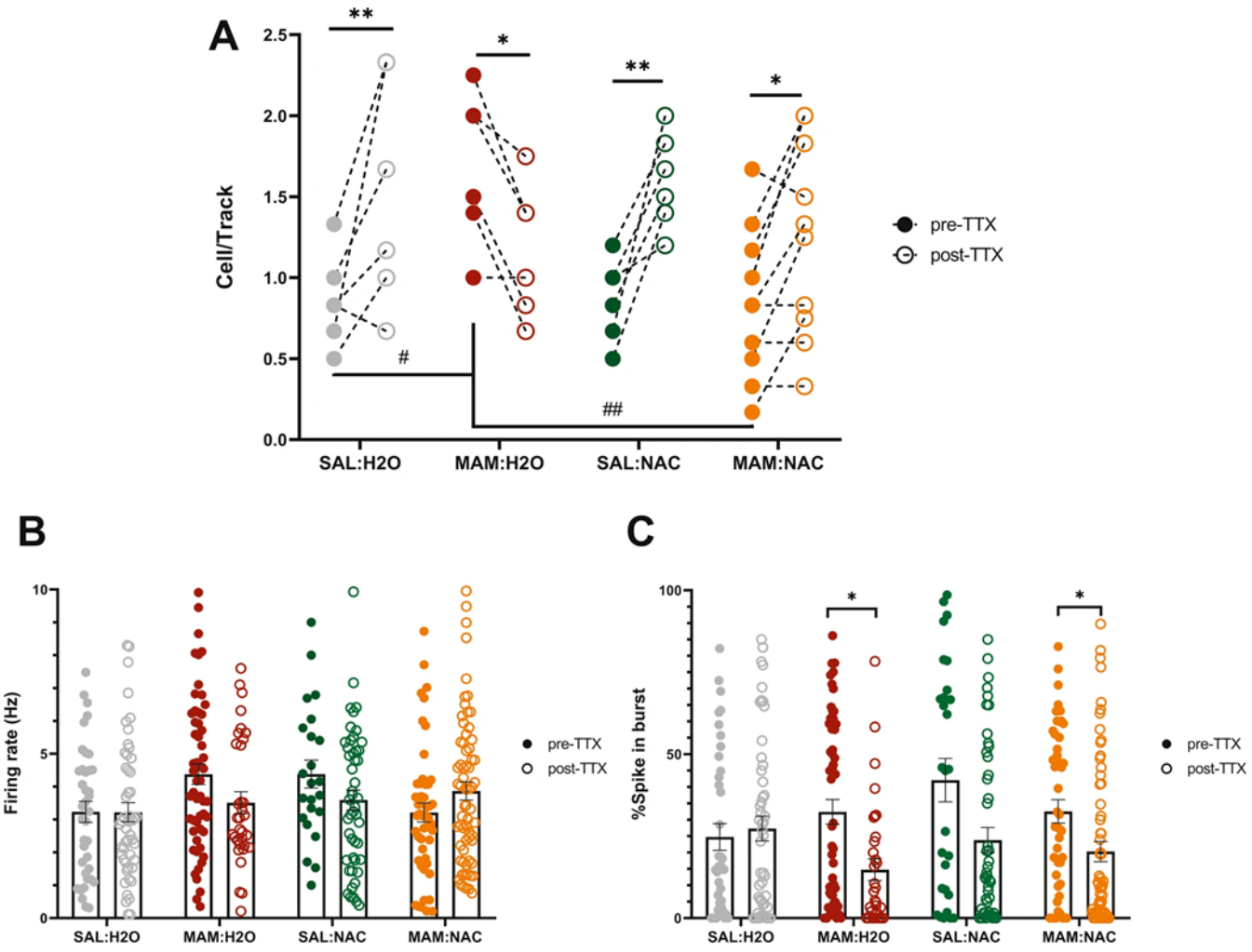

Figure 15. Enhanced baseline activity and abnormal prefrontal control of VTA dopamine neurons were prevented by P11−25 NAC oral treatment.

A Before ilPFC inactivation (i.e., solid circle; pre-TTX), MAM rats displayed heightened dopamine population activity, which was prevented by early NAC treatment. In response to ilPFC inactivation (i.e., open circle, post TTX), SAL rats displayed upregulated dopamine population activity, which is affected by early NAC treatment. In contrast, MAM:H_2O rats displayed downregulated dopamine population activity in response to ilPFC inactivation, which is reversed in MAM:NAC group. n(rat) = 6–10; n(litter) = 4–6. **B** The firing rate of dopamine neurons was not affected by any manipulation ($H = 13.45$, $p > 0.05$, Kruskal–Wallis test, Dunn's post hoc). n(rat) = 6–10; N(cell) = 25–55. **C** Burst firing of dopamine neurons significantly differed across groups ($H = 16.90$, $p < 0.05$), Dunn's post hoc analysis revealed that the percentage of cells firing in burst was significantly lower after TTX infusion in MAM:H_2O

and MAM:NAC groups. Data are presented as mean ± SEM. *p or #$p < 0.05$; **p or ##$p < 0.01$; * indicates difference related to TTX infusion; # indicates difference in baseline dopamine population activity before TTX infusion.

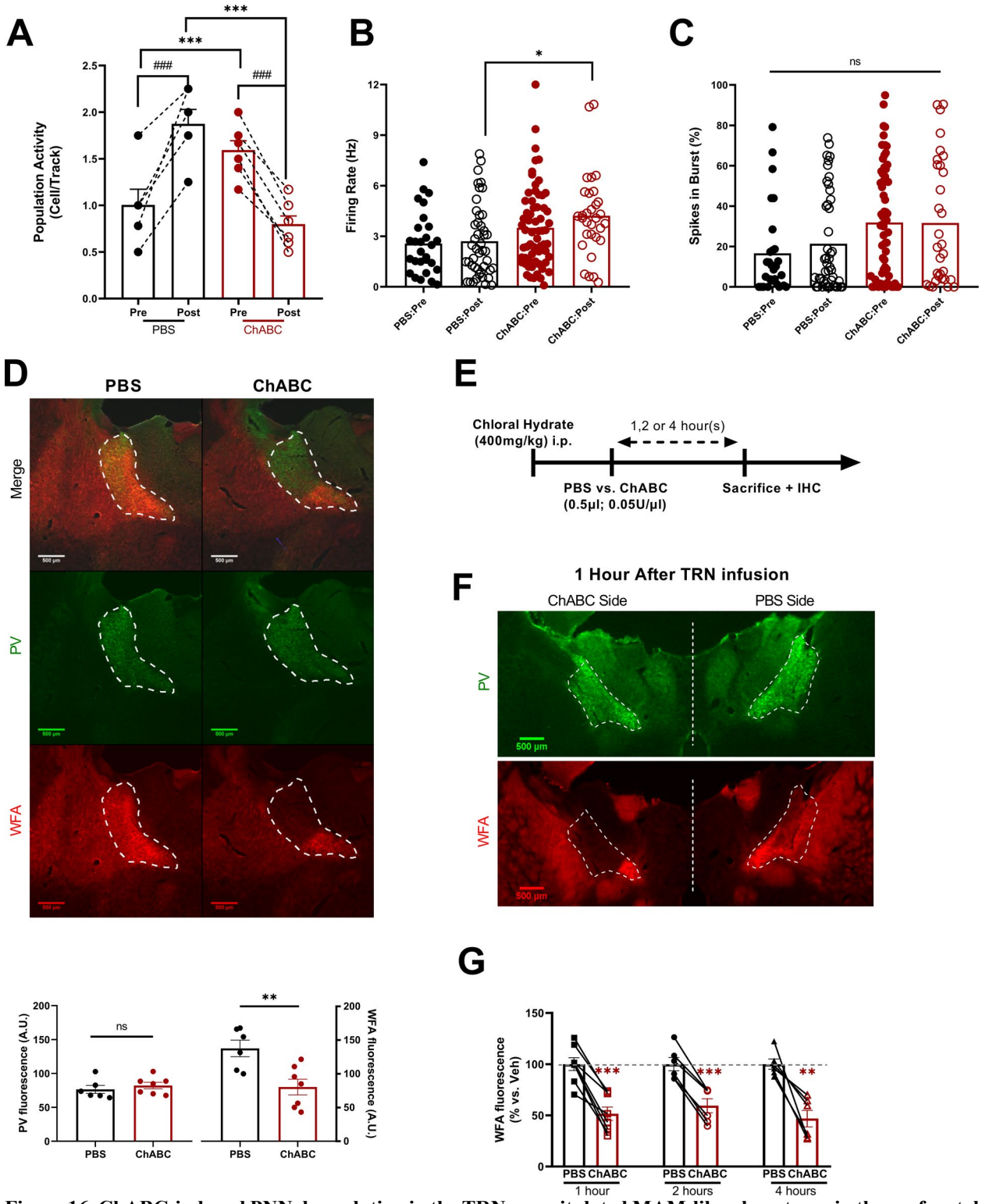

Figure 16. ChABC-induced PNN degradation in the TRN recapitulated MAM-like phenotypes in the prefrontal control of VTA dopamine neurons.

A PBS vehicle or ChABC was infused bilaterally into the aTRN. After 1 h of PNN digestion, animals were tested for VTA dopamine population activity before and after TTX-induced inactivation of the ilPFC. ChABC-treated animals displayed increased baseline dopamine population activity and an inverse response to ilPFC inactivation, resembling those observed in MAM rats. n(rat) = 6–7; n(litter) = 4. **B** After ilPFC inactivation, the dopamine neurons recorded from ChABC-pretreated rats display a slightly increased firing rate, compared to those of PBS-pretreated rats. n(rat) = 6–7; N(cell) = 25–66. **C** No change in dopamine neuron burst firing was observed. **D** (top) Immediately after the recordings, animals were euthanized for immunohistochemistry to verify PNN degradation. Note that thalamic PV is almost exclusively located to the TRN (marked by dashed lines), where the WFA staining was markedly decreased. **D** (bottom) At the end of recording experiments, the intensity of WFA immunoreactivity was significantly reduced, whereas that of parvalbumin was unaffected. **E** Design of a separate experiment characterizing WFA intensity after aTRN ChABC injection. **F** One hour after the injections, the aTRN on the ChABC-treated sides already displayed visibly decreased WFA intensity compared to the PBS-treated side, indicative of rapid PNN digestion. **G** Quantification of ChABC-induced PNN degradation. N(brain section) = 6–8; n(rat) = 2–3. Measurements were normalized to the PBS control group mean at each time point, and a paired t-test was used. *p or #$p < 0.05$; **p or ##$p < 0.01$; ***p or ###$p < 0.001$; * or # indicates significant effects of ChABC or TTX, respectively. Data are presented as mean ± SEM. PBS: 0.5 µl of Dulbecco's PBS. ChABC: chondroitinase ABC, 0.05U/µl, 0.5 µl.

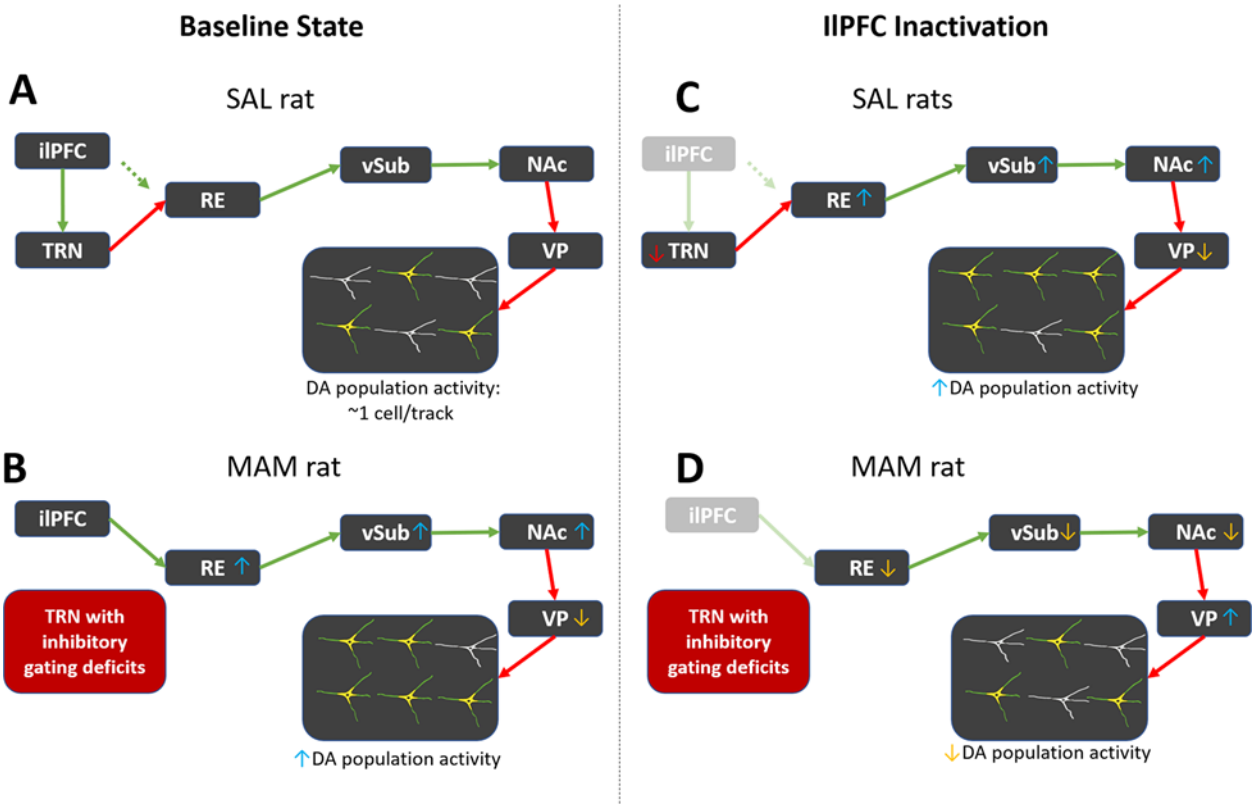

Figure 17. Schematics of the proposed pathways mediating the differential effects of ilPFC inactivation on VTA dopamine neurons in SAL vs. MAM rats.

A In SAL rats, at baseline, ilPFC output is primarily mediated by TRN-driven feedforward inhibition of the RE. This pathway maintains normal vSub activation and hence the normal dopamine population activity in the VTA (green/yellow-colored neurons indicate spontaneously active cells), through a multisynaptic pathway involving the nucleus accumbens (NAc) and the ventral pallidum (VP). **B** In MAM rats, oxidative stress-induced impairments of the TRN PV neurons inactivate TRN-mediated feedforward inhibitory gating and hence shift pathway dominance. As a result, the ilPFC output is mainly mediated by direct excitatory pathways to RE; this can contribute to the vSub hyperactivity and the consequent dopamine hyperactivity in MAM rats. **C** In SAL rats, given the predominant feedforward inhibition from the TRN, the effect of ilPFC inactivation is mainly mediated by the TRN-driven pathway, resulting in a net effect of increased vSub activity and consequently disinhibition of VTA dopamine neurons. **D** In MAM rats, due to the impairment in the TRN, ilPFC inactivation is primarily mediated by a multisynaptic excitatory pathway to vSub, potentially leading to attenuation of vSub activity and the consequent downregulation of VTA dopamine activity. Green arrow: glutamatergic projection; red arrow: GABAergic projection. Blue ↑: increase of activity; orange ↓: decrease of activity.

5.0 GENERAL DISCUSSION

5.1 SUMMARY OF FINDINGS

This dissertation reveals age- and sex-dependent adolescent stress-sensitive periods in rats to contribute to schizophrenia-like electrophysiological dysfunctions in the VTA DA system and its corticolimbic regulators. Additionally, in MAM rats, we found that prepubertal EE and early NAC treatment prevented the hyperdopaminergic states well-known to this model. Through these studies, we systematically determined the developmental trajectory of vulnerabilities to adolescent stress and provided novel proof-of-concept evidence on the possibilities of targeted early preventions for psychosis. Together, these studies elucidated distinct risk states in adolescence and generated novel insights into potential psychosis prevention.

In our previous studies, we demonstrated that in male rats, adolescent PD31-40 stress induced a distinct electrophysiological phenotype corresponding to human schizophrenia pathophysiology, namely persistently increased population activity in VTA DA neuron spontaneous firing and aberrant vHipp pyramidal neuron activity (Gomes & Grace, 2017; Gomes et al., 2020). These findings, when compared with PD65-74 adult stress outcomes, demonstrated sensitive-period effects, as adult stress only produced a temporary DA hypoactivity, consistent with models of depressions (Gomes et al., 2020). The stress-induced adult consequences were preceded by vHipp PVI impairment and were able to be reinstated by activating critical period reopening mechanisms, such as histone deacetylase inhibition (Gomes et al., 2020). Altogether, this initial study comparing adolescent and adult stress consequences established the existence of sensitive periods for stress to modulate long-term DA system function and regulations.

In Chapter 2, we extend our research scope to identify sensitive periods in substages of rat adolescence and examine their sex dependence. Interestingly, we found that while males are selectively vulnerable to PD21-30 PreP-S, females are selectively vulnerable to PD41-50 PostP-S. These age- and sex-selective stress sensitive periods were defined by the long-term stress consequences in the VTA DA system, vHipp and BLA pyramidal neuron firing, and PVI impairments in the vHipp and the BLA, all of which are robust pathophysiological or pathological features of schizophrenia. Specifically, while PreP-S in males and PostP-S in females both increased adult DA population activity and vHipp pyramidal neuron firing rate, males selectively displayed persistent BLA hyperactivity and abnormal PFC-BLA inhibitory plasticity. This study highlights the possibility that while early life adversities are generally associated with adult psychosis risks in both sexes, the underlying pathophysiological mechanisms and the level of BLA involvement might be age- and sex-dependent.

In Chapter 3 and 4, we utilized the MAM model and tested two early prophylactic approaches to prevent psychosis-related DA pathophysiology. In Chapter 3, we found that EE during multiple prepubertal windows (PD21-30, PD31-40, and PD21-40) can prevent VTA DA dysregulations, which correlated with ameliorated vHipp activity but not with changes in BLA activity or anxiety. In Chapter 4, we focused on the TRN of the thalamus, a newly discovered region containing PVI deficits in schizophrenia and a promising early target for oxidative stress vulnerability. We found that adult MAM rats recapitulated oxidative PVI impairments in the TRN as adults, a condition prevented by early life antioxidant NAC treatment from PD11-25. The TRN is a feedforward inhibitory relay region between the ilPFC and the RE, a pathway implicated in the control of VTA DA neuron firing. We found that MAM rats showed reversed ilPFC control of VTA neuron firing, a condition attributable to TRN deficits. Moreover, targeted PNN dissolvement

in the TRN by itself reversed normal rats to obtain a MAM-like dysfunctional ilPFC modulation of DA neurons. Furthermore, both the baseline VTA hyperdopaminergic activity and the altered prefrontal control in MAM rats were prevented by early antioxidant treatment from PD11-25. Altogether, these studies using MAM rats suggest EE and NAC treatment as promising approaches in psychosis prevention.

5.2 TECHNICAL CONSIDERATIONS

5.2.1 Selection of stressor

In this dissertation, we used mainly a 10-day combined stressor consisting of repetitive FS and RS as our model system. This stress paradigm was purposefully designed with several reasons. First, we chose to use chronic repeated stress, rather than single acute stress, to approximate human trauma exposure in psychosis risk association research, which tended to be chronic and cumulative (Gibson et al., 2016; Shevlin et al., 2008). Moreover, FS and RS as homotypic stressors have been widely used in early life stress research (Cohen et al., 2016; McLaughlin et al., 2014). It is known that animals typically do not habituate to FS (measured by stress hormone response) as well as to other stressors (e.g., noise and light exposure) (Bali & Jaggi, 2015). This is an advantage for our studies because our primary objective was to study long-term stress outcomes, which required the initial stress activation to be chronic and intense. Of note, we have confirmed the sufficiency of our FS protocol to elicit sustained HPA axis response (plasma corticosterone activation) and other indicators of stress responsivity (e.g., ultra sound vocalization) in our previous study (Zimmerman et al., 2013). Furthermore, in adolescent PD31-40 rats, we have found that combined FS+RS,

compared to either homotypic stressor alone, is specifically sufficient to drive adult VTA DA system hyperactivity (Gomes & Grace, 2017). Considering all these factors, we decided to use the combined stress to specifically explore age and sex-related sensitive periods mechanisms (Chapter 2).

Notably, childhood trauma, especially in the forms of interpersonal violence (e.g., bully, physical abuse, etc), contain strong social elements. Some, but not all, studies have concluded stronger risk associations between schizophrenia symptoms and "social risk factors" or "interpersonal trauma" (Stain et al., 2014; Varchmin et al., 2021), although the assignment of complex adverse childhood experience, such as minority status or migration, as "social" is often tentative and hence debatable. However, to parallel these epidemiological insights, preclinical studies have used primarily social stress in the forms of isolation and defeat to study the impact of stress on DA neuron activity, DA release, and related behaviors [reviewed in (Douma & de Kloet, 2020; Watt et al., 2017)]. Consequently, whether nonsocial stress can modulate DA system activity in the long term has been significantly understudied. In this aspect, the present dissertation work bridged the current knowledge gap by demonstrating the feasibility of using nonsocial stressors to chronically modulate DA system activity. However, future studies should ideally compare social and non-social stress in a side-by-side design to fully elucidate potential stressor-type specific mechanisms.

5.2.2 Linking rodent adolescence to human: rationale for age groups

Adolescence is generally referred to as the prolong transitional period between childhood and adulthood (Sisk & Foster, 2004). In both human and rodent literatures, there is no consensus on the exact onset and offset timing for adolescence (McCormick & Mathews, 2007), but most

studies have agreed that adolescence contains puberty or sexual maturation. In this dissertation, stress sensitive periods were determined in discrete adolescent windows spanning PD21-50. We refer to this broad period as adolescence according to several reviews (Sengupta, 2013; Sheth et al., 2017; L. Spear, 2000). All the assessed timing effects were defined by chronological age. In Chapter 3 we additionally approximated PD21-30 or PD41-50 as "prepuberty" and "postpuberty". These definitions are consistent with the terminology used in previous works (Brydges, Jin, et al., 2014; Ueno et al., 2018; Wilkin et al., 2012; Zimmerman et al., 2013). However, we only used these terms tentatively, because determining precise pubertal onset would involve intrusive approaches that interfere with our stress paradigms. Whether pubertal onset directly interacts with stress vulnerability defined based on DA-related consequences is worth a future comprehensive study.

5.2.3 Electrophysiological determination of neuronal types

Ideally, in vivo electrophysiological experiments should be conducted in a visually guided fashion to allow for simultaneous identification of cells while being recorded. However, this has not been feasible primarily for rat models and for deep structures evaluated in this study. In this dissertation, VTA DA neurons were identified based on well-established criteria on discharge rate and waveform (Grace & Bunney, 1983, 1984; Ungless & Grace, 2012). By estimate, VTA contains 70% DA neurons and 30% GABAergic interneurons, with glutamatergic neurons only comprising 2-3% (Ungless & Grace, 2012). GABAergic interneurons are more readily distinguishable from DA neurons, given their narrow waveforms and rapid firing. The misidentification rate of glutamatergic neurons as DA neurons is low due to its small percentage. We acknowledge the caveats that the identification of pyramidal neurons in the vHipp and the BLA is only putative.

Nevertheless, we kept the identification criteria consistent with several previous studies, both from our lab and other groups (see Methods and Materials in each chapter for details)

5.3 IMPLICATIONS FOR THE DEVELOPMENTAL RISK STATES FOR SCHIZOPHRENIA

Our previous study comparing adolescent and adult stress consequences indicated the existence of sensitive periods during which stress uniquely modulates ensuing VTA DA neuron activity (Gomes et al., 2020). The discovered PD31-40 stress-vulnerable window contains core features of sensitive periods derived from developmental neuroscience and learning (Gabard-Durnam & McLaughlin, 2019; Knudsen, 2004). First, stress during the PD31-40 adolescence in males produced a persistent activation of VTA DA neuron population activity, whereas the same stress produced a short-lasting inhibiting effect in adults (Gomes et al., 2020). Such discrepancy in the directionality of stress response indicates an age-specificity of experience to lead to a particular outcome, which is a recognized feature of sensitive periods (Hensch, 2018). On the other hand, PD31-40 adolescent stress induced persistent DA hyperactivity, whereas adult animals are only responsive to stress temporarily (1-2 weeks) (Gomes et al., 2020). This observation is consistent with the notion that experiences, especially the negative ones, occurring during sensitive periods tend to have more long-lasting or even permanent effects (Knudsen, 2004).

Having established the existence of sensitive periods (defined by stress-induced persistent DA system activation), in Chapter 2, we aimed to determine their developmental onset and termination, as well as potential sex differences. In males, we found similar stress response in DA neuron population activity between PD21-30 vs. PD31-40 stresses. However, once males entered

PD41-50, the long-term physiological stress responses in the VTA DA neurons terminated, although these rats still presented vulnerability to the short-term DA system activating effects. This suggested that the vulnerability for stress-induced VTA DA neuron activation was transitory, which lasted for roughly 20 days (i.e., PD21-40) and gradually attenuated in late adolescence or postpuberty (~PD50). Once males entered adulthood at PD65, adult stress at PD65-74 could no longer induce hyperactivity of the VTA DA neuron specific to adolescent stress, indicative of complete termination of plasticity. In females, the duration of stress sensitive period appeared to be shorter. Specifically, among the assessed age windows, females are only vulnerable to stress-induced DA system hyperactivity at PD41-50, with broad resilience in PD21-30, PD31-40, and in adulthood (PD65-74). In both males and females, these temporal boundaries are in broad agreement with the age limits of a sensitive period (Gabard-Durnam & McLaughlin, 2019).

The discovered windows of vulnerability provide novel insights in the pathophysiology and the etiology of schizophrenia. First, our results directly point to the existence of stress sensitive periods in adolescence, during which stress can selectively drive adult DA system tonic hyperactivity. An increased number of spontaneously active DA neurons (i.e., higher DA population activity) will set the DA system to a more responsive state, as only the spontaneously active neurons can engage in phasic firing to release synaptic DA to target regions to signal ongoing environmental stimuli. Consequently, we posit rats stressed during sensitive periods would eventually have overly responsive DA systems, which would in turn aberrantly assign salience to irrelevant stimuli and therefore contribute to psychosis via “aberrant salience” model of psychosis (Kapur, 2003). In terms of schizophrenia etiology, the present results in Chapters 2 and 3 broadly support recent human preliminary findings on sensitive periods of trauma exposure to confer greater risks of psychosis (Croft et al., 2019). Noteworthy, available human studies to

date have not yet assessed sex differences in the association strengths between trauma exposure at a set early age with adult psychosis risks. Thus, our works in Chapters 2 and 3 have provided an innovative testable hypothesis for future human research.

Our work determining stress-induced PVI impairments also provided information on the etiology of schizophrenia. Across several experiments, in adults previously stressed in putative sensitive periods we found concurrent stress-induced vHipp PVI impairment, vHipp activation, and VTA DA hyperactivity. This implies that stress-induced vHipp PVI impairment might lead to vHipp hyperactivity, which, as extensively tested by our previous studies and others, is a predominant upstream factor leading to VTA DA neuron dysfunction. Notably, the observed PVIs impairments involved reductions of both the PV+ neurons and the associated PNNs, and these cellular deficits reflect a maturational deficit. This is because during postnatal development, the expression of PNNs is an important maturational event to end neuroplasticity. The expression of PNNs expression around PVIs is known to support PVI fast spiking, stabilize existing synapses, and prevent the formation of new synaptic contacts, all of which are critical to maintain the balance of the excitatory-inhibitory circuit of a region (Wen et al., 2018a) and therefore to regulate the closure of sensitive periods of neuroplasticity (Hensch & Bilimoria, 2012). Thus, the observed findings in the vHipp PVI/PNN deficits could reflect a failure in the closure of the sensitive period, which would be consistent with an etiological model for schizophrenia (Do et al., 2015). This putatively mistimed sensitive period closure also predicts that these stressed rats would exhibit broad plasticity-related behavioral abnormalities too, which merit future investigations focusing on the behaviors.

In Chapter 3, we also examined physiological consequences of different adolescent stress on BLA neuron firing, PFC-BLA spike plasticity, and PVI PNN maturation. We found substantial

sex differences in the stress vulnerability of this region, which is different from those observed in the vHipp and the VTA. Specifically, in the BLA we found extensive male-biased stress consequences, whereas in the vHipp and the VTA it appeared that although the stress vulnerable window shift for approximately 20 days, the adult electrophysiological stress consequences were largely the same between sexes.

Stress might affect BLA firing earlier than vHipp. We predict this trajectory in electrophysiological stress responses based on numerous similar anatomical findings from other models of early life stress and humans [reviewed in (Tottenham & Sheridan, 2009)]. This prediction would also be consistent with the notion that stress-induced BLA hyperactivity and/or structural deficits are a prerequisite for subsequent Hipp synaptic dysfunctions (Kim et al., 2005; Kim et al., 2001; Patel et al., 2018; Tottenham & Sheridan, 2009). In humans, the amygdala matures earlier in females (Goddings et al., 2014; Kaczkurkin et al., 2019; Uematsu et al., 2012), but faster and more dynamically in males (Fish et al., 2020; Giedd et al., 1997). Since stress impact is predicted to be most detrimental when stressor coincide with critical development, we posit that during the human equivalent of the examined periods (i.e., late childhood - adolescence) stress might be predominantly detrimental to the BLA in males, causing PVI deficits, disinhibition, and eventually leading to BLA hyperactivity as observed in Chapter 3. Previous studies have demonstrated that direct pharmacological disinhibition of BLA is detrimental to Hipp GABAergic network, including a loss of PV. Thus, the observed vHipp PVI impairments might be partially due to an upstream BLA dysfunction. Translating to human schizophrenia, our results might suggest that males are at increased risk for childhood trauma-induced BLA hyperactivation, which might damage the limbic Hipp PVI and in turn cause VTA DA neuron dysfunctions. In our studies (Chapter 3), although sensitive-period stress in both males and females eventually cause vHipp

hyperactivity and VTA hyperdopaminergic states, the male-selective BLA stress vulnerability could be an addition risk. Since childhood adverse experience is prominent in both sexes, this male-selective risk at the BLA might explain the male-biased early prevalence, early psychosis onset, and more severe symptoms in schizophrenia (Abel et al., 2010; Mendrek & Mancini-Marïe, 2016; S. Ochoa et al., 2012). Notably, exposure to ELS is also associated with other psychiatric disorders, many of which are sex biased. Our findings in the sensitive periods of stress vulnerability in the DA system and its regulator might also account for these sex differences.

In Chapter 2, we discuss the observed stress sensitive-period effects emphasizing the HPA axis and glucocorticoid signaling, especially the potential outcomes in the PVIs. This is because the neuroendocrine effects of stress exposure are generally considered to be more long-lasting compared to the effects on the autonomic system (Joëls & Baram, 2009), which would better explain the observed long-term changes in the studied endpoints (i.e., measured at least after a week post-stress). Noteworthy, this does not necessarily exclude the possible contribution of the other stress response system (i.e., the SAM axis). Therefore, the observed age and sex-dependent effect of stress may be mediated in part by the SAM axis, which relies on peripheral signaling feedbacks to the brain to affect the function of the locus coeruleus norepinephrine (LC-NE) system (Tank & Lee Wong, 2015). LC receives monosynaptic and neuropeptidergic (i.e., corticotropin-releasing factor, CRF) inputs from the paraventricular nucleus (PVN) of the hypothalamus, as well as information from ANS via vagal nerve activation (Sara & Bouret, 2012). Compared to HPA axis activation, during each acute stress session these stress signals could operate more immediately, allowing the LC-NE system to react rapidly and adapt to stressful situations. Repeated stress can persistently increase the firing of the LC-NE neurons (Jedema et al., 2001), and this effect is especially pronounced in and perhaps specific to certain stress paradigms (Zitnik

et al., 2016). In rodents, the LC-NE system is highly sexually dimorphic at structural and molecular levels, with females exhibiting larger LC size, more numerous LC-NE neurons with more complex dendritic architectures, and more CRF receptors in LC-NE neurons with enhanced CRF signaling (Bangasser et al., 2016). Functionally, adult LC-NE neuronal firings in females are more sensitive to stress or CRF administration (characterized by hyperactivity), and this effect is proposed to be partially due to the organizational effect of estrogen surges during female puberty rather than in adulthood (Bangasser et al., 2016; Schulz et al., 2009). Estrogen also increases NE release at LC terminals via affecting presynaptic synthesis and degradation mechanisms (Bangasser et al., 2016), which when combined with female-biased stress- and/or CRF sensitivity could lead to female-specific abnormal activity in the target regions (Morris et al., 2020). Both the BLA and the vSub are densely innervated by LC-NE terminals (Oleskevich et al., 1989; Poe et al., 2020), and in both regions increased NE terminal release can increase excitability and/or neuronal output (Bacon et al., 2020; Lipski & Grace, 2013; McCall et al., 2017). Considering all these lines of evidence, it is plausible that the observed late emergence of female vulnerability to PostP-S could be partially mediated by LC-NE neurons and estrogen surges, because, as previously described, estrogen can promote terminal release of NE by modulating NE synthesis and degradation pathways (Bangasser et al., 2019).

Of note, although Chapter 2 discovered a link between severe adolescent stress exposure during sensitive periods and adult electrophysiological phenotypes strongly associated with schizophrenia pathophysiology, we are not trying to make a "schizophrenia model" *per se* nor the conclusions that severe stress in sensitive periods by itself causes psychosis. In human conditions, we speculate that stress-induced VTA DA neuron hyperactivity is an critical node in the "cumulative risk" model of schizophrenia pathogenesis by amplifying synaptic DA release in the

striatum. This underlying condition could combine with other predisposing factors and adult psychosis triggers to eventually lead to psychosis symptoms.

5.4 INSIGHTS FOR PSYCHOSIS PREVENTION

Increasing knowledge indicates that schizophrenia patients are not "doomed from the womb". In fact, there are promising ways to alter the programmed neurodevelopmental anomalies imposed by risk factors, possibly leading to prevention of psychosis/schizophrenia (Millan et al., 2016). There are different goals in interventional research in schizophrenia, ranging improving symptoms to FEP prevention in at risk individuals. Broadly, interventions could be introduced at a population level or selectively to individuals with familiar/genetic risks or displaying plausible biomarkers.

5.4.1 Timely avoiding stress in general populations

At present the most productive approach to prevent psychosis is still to avoid risk factors. In this aspect our findings in Chapter 2 and 3 extended the current knowledge by indicating that there are distinct sex- and age-dependent developmental stress vulnerable windows to drive schizophrenia pathophysiology in the VTA DA system and the Hipp. Thus, it is plausible to apply targeted programs to limit stress or improve stress resilience at the corresponding windows to prevent the onset of psychosis. Practically, these strategies can depend on publicly advocating the potential benefits of timely avoidance of stress in general populations, regardless of predisposing risk factors such as genetic liability or CHR states.

5.4.2 Applications of EE and NAC treatment in selective at-risk populations

In addition to timely avoiding stress in general population, our results from the MAM model indicated that early EE and NAC treatment might be useful for targeted interventions. Our recent studies suggest that the MAM model broadly belongs to the 'two-hit' models of schizophrenia (Bayer et al., 1999). Before their adult onset of DA hyperactivity and related behaviors, peripubertal MAM rats already display increased stress responsivity and anxiety even in the absence of experimental stressors, along with PVI impairment in corticolimbic regions (Gomes et al., 2019b). This trajectory by large parallels human schizophrenia development and is therefore useful for screening putative preventative strategies.

We found that EE during prepuberty (PD21-40) in MAM rats prevented adult vHipp and VTA DA hyperactivity, two characterizing phenotypes of the model that are mostly consistent with the pathophysiology of human schizophrenia. Translating to human, these findings suggest that EE might be particularly useful for targeting individuals at early risk states for schizophrenia predicted by in utero environmental insults (such as prenatal immune activation, obstetric complications, etc). Intriguingly, contrary to previous findings (Fox et al., 2006; Sztainberg et al., 2010), we did not observe amelioration of anxiety or BLA hyperactivity in the MAM rats. We believe that this finding does not necessarily negate the documented anxiolytic role of EE in normal rats or our own results that antianxiety treatment prevents DA hyperactivity in the MAM model (Du & Grace, 2013). This negative effect on anxiety in MAM rats could possibly reflect that there might be differential optimal durations for EE to counteract anxiety and DA system dysregulation. In humans, cognitive behavioral therapy (Mei et al., 2021) and physical exercise (Mittal et al., 2017) have been linked to the delay of psychosis conversion in CHR patients. Although these human approaches are not equivalent to rodent EE, they share similar 'enriching'

elements such as increased nonspecific cognitive stimulation and physical activity. Therefore, there has already been some face validity that EE could be usefully translated to at-risk individuals. Currently, it is challenging to directly translate EE into clinical trials or clinical settings, because what elements constitute an enriching environment is largely unknown in humans (McDonald et al., 2018). However, some recent studies have begun to answer this question by linking geographical elements of urban life with stress reactivity in the amygdala (Kühn et al., 2017) and more directly to FEP (Baumann et al., 2020). Although direct translations of EE into humans are still challenging, these studies point a promising direction and suggest that selective modifications of urban environments could counteract the compound stress effect of urbanicity, which is an epidemiologically validated risk factor for psychosis (Heinz et al., 2013).

In light of the recent mouse finding that TRN is an early risk locus upstream of PVI oxidative impairment (J.-H. Cabungcal et al., 2019) and the human conclusion that TRN PVI deficits are present in schizophrenia patients (Steullet et al., 2018), we determined the presence of oxidative impairments of TRN PVI in the MAM model and whether they are related to the DA dysregulation phenotype of MAM rats. Our findings confirmed TRN abnormalities in the MAM model, and further indicated both the DA dysfunction and the TRN PVI impairments can be prevented by early NAC treatment. This dataset could provide novel insights in preventing human schizophrenia. Oxidative stress-related system can integrate diverse genetic and environmental risk factors to act as common mediators for schizophrenia pathophysiology (Steullet et al., 2017). These findings had led to clinical trials focusing on the use of antioxidants as add-on to antipsychotics in diagnosed patients. Specifically, GSH treatment has been shown to improve symptoms, white matter integrity, and EEG mismatch negativity in schizophrenia patients (Cuenod

et al., 2021). However, these positive effects are considered limited by two recent meta-analyses, as they tend to be effective only in subgroups of patients (Yolland et al., 2020; Zheng et al., 2018).

Our findings in MAM rats suggest that NAC treatment might be selectively effective early in the trajectory of schizophrenia development. Oxidative stress is generated when the accumulation of toxic reactive chemical species exceeds the clearance capacity of antioxidant defense. When oxidative stress chronically affects a region, this can lead to permanent changes such as cell damage or cell death. Therefore, it would be advantageous to use antioxidants early to prevent PVI damage and psychosis, provided that we could reliably identify true at-risk individuals, rather than using them as adult adjunctive therapies. Alternatively, TRN deficits might only be present in a subset of patients. If true, it could be possible that early NAC treatment would only work in subtypes of schizophrenia patients with TRN deficits. Notably, severe life stress also produces oxidative stress in part via glucocorticoid signaling (Schiavone et al., 2013). As Chapters 2 and 3 showed, severe stress during sensitive periods can cause PVI impairments probably via oxidative stress-related process, which could contribute to the widespread pathophysiological changes in the DA system and its corticolimbic regulators. Thus, in a translational train of thought, it might also be useful to use NAC in early trauma victims to counteract the detrimental effects of oxidative stress on PVIs and therefore reduce the risks associated with trauma-induced psychosis. Given that genetic and environmental risk factors seem to converge onto oxidative PVI damage (Steullet et al., 2017), NAC's potential effects in reducing psychosis risks in trauma victims might be selective to individuals who have also been exposed to early predisposing risk factors (e.g., familial or genetic risks, prenatal risk factors, etc.).

Together, the findings in Chapters 4 and 5 highlight the need to translate EE and NAC into applicable human interventions. As a first step, it is important for future research to devise methods

to reliably identify the at-risk individuals who would be most responsive to EE or NAC treatment. This effort critically depends on the identification of mechanism-based biomarkers, which could involve markers oxidative stress and PVIs.

5.5 CLOSING REMARKS

Converging evidence from clinical and basic science studies suggests that schizophrenia is a disorder caused by multiple interacting factors at various stages. Central to these is stress occurring during developmental vulnerable periods such as childhood and adolescence. Early stress exposures are not equipotent in conferring psychosis risk in later life, and the present dissertation work identified sex- and age-selective adolescent windows of heighted stress vulnerability, during which sufficient stress can lead to pathological and pathophysiological changes related to schizophrenia. Therefore, there appears to be a balance, in which stress vulnerability and presence of stressors can produce an additive effect with respect to risk for schizophrenia. This dissertation also provides prospects for effective early interventions by demonstrating the feasibility of using early EE and NAC to counteract DA dysregulations in the MAM model. Altogether, by delineating developmental risk factors and testing early interventions, we hope to eventually provide a roadmap for targeted prevention for schizophrenia.

APPENDIX A SUPPLEMENTARY MATERIALS FOR CHAPTER 2

Appendix A is the supplementary information for a submitted manuscript:

Zhu, X., & Grace, A. A. (2022) Sex- and exposure age-dependent effects of adolescent stress on ventral tegmental area dopamine system and its afferent regulators. *Under Review.*

Animals. Timed pregnant Sprague-Dawley rats were obtained on gestation day 15 (Envigo). On PD0, offspring were born and left undisturbed until weaning day (PD21), at which time pups were distributed into separate cages containing 2-3 same-sex animals. Each cage was randomly assigned to naïve, prepubertal stress (PreP-S), or postpubertal stress (PostP-S) conditions. These definitions for pre- vs. post-puberty are consistent with previous studies (Green et al., 2016). We did not control for pubertal onset, but in the naïve rats of the first two experiments, we observed external signs of puberty (Hoffmann, 2018) in males and females (n=12). None of the examined animals showed puberty signs before PD31. The average age of pubertal onset is PD40.1±0.7 days in males and PD35.7±0.9 days in females. These previous studies and observations justify P21-30 and 41-50 to indicate pre- and post-puberty, respectively.

Experimental timeline. PreP-S or PostP-S rats were exposed to a 10-day stress protocol as previously reported, starting at PD21 or PD41, respectively. To avoid batch or litter effect, experimental groups were counterbalanced, and rats contributed to each group from at least three litters and two independent cohorts separated by weeks.

Stress protocol. Stress protocol in this study was the same as our previous works (Gomes & Grace, 2017; Gomes et al., 2020; Klinger et al., 2019). Briefly, over ten days, rats aged at PD21

or PD41 were exposed to daily foot-shock (FS; 25 scrambled shocks; 1.0 mA, 2 sec; inter-shock interval 60 ± 20 sec). On day 1, 2, and 10 of FS, immediately after the foot-shock rats were exposed to one hour restraint (RS) stress in Plexiglas cylindrical size-adjusted restraint tubes

In vivo extracellular electrophysiology in anesthetized rats. In vivo extracellular recordings were performed according to our previous published work (Gomes et al., 2020; Zhu & Grace, 2021). Key experimental steps are described below. Acute extracellular single-unit recordings were performed on animals under chloral hydrate anesthesia (400mg/kg; i.p.). Single barrel glass electrodes were constructed from 2 mm capillary tubes (World Precision Instruments, Sarasota, Florida) using an electrode puller (Narishige, Japan). Electrode tips were broken back under microscopic control to attain an impedance of 6–14 MΩ. Glass electrodes were filled with 2% Chicago Sky Blue dye dissolved in 2M saline and inserted vertically into target regions using hydraulic Microdrive (KOPF) to search for spontaneously active single units. Target regions were sampled by vertical electrode insertion in grid patterns, with each track separated by 0.2 mm. All single-unit recordings were recorded with open filter settings (low pass, 10 Hz; high pass, 16 kHz; Gain: 1000x). Once stable spiking was detected and isolated (signal-to-noise ratio>3:1; firing amplitude variation <15%), stable recordings were maintained for at least 60 seconds.

At the end of recording sessions, electrode placement (at the last track recorded) was marked by electrophoretic ejection of Chicago Sky Blue dye. Anesthetized rats were overdosed with chloral hydrate. The brains were extracted and fixed in 8% paraformaldehyde for at least 48 hours. Brains were then transferred to 25% sucrose solution for cryoprotection, sectioned using a cryostat (Cryostar NX50, ThermoScientific, Waltham, MA) into 60μm coronal slices, mounted on to gelatin-chromalum-coated glass slides, and stained with cresyl violet and neutral red to for the

examination of electrode placements. Only the recordings made within the anatomical border of target regions were used for analyses.

Cell identification. In each target region, single units were identified by action potential waveform, firing rate, and location (post hoc). The VTA in male adult rats (age: >PD77; weight: <500g) was sampled by 6-9 tracks in the following coordinates (mm): anteroposterior (A/P): 5.4-5.8; mediolateral (M/L): 0.6-1.0 from bregma, and dorsoventral (D/V): 6.5-9.0 from brain surface. Coordinates for adult female (weight: 200 – 300g) and adolescent rats (age: PD 37-45; weight: 100-200g) were anteriorly and medially adjust by 0.1mm and 0.2mm, respectively. DA neurons were identified by the following criteria: bi- or triphasic action potential waveform (duration>2.2ms), long spike half-width (>1.1ms), irregular or burst firing pattern, and low firing rate (<10Hz). Once identified, DA neurons were recorded for 3 minutes (1-minute minimum) when the signal-to-noise ratio exceeded 3:1. Three parameters of DA neuron firing were analyzed: average number of spontaneously active DA cells per electrode track (i.e., "population activity"), mean firing rate, and percentage of spikes in bursts, with burst initiation defined by an interspike interval of ≤80ms and burst termination defined by an interspike interval of >160 ms. This procedure allows us to reliably identify VTA DA neurons and measure both the tonic (i.e., population activity) and phasic (i.e., firing rate and bursting) activity (Ungless & Grace, 2012).

The vHipp in adult males was sampled by 6-9 tracks in the following coordinates (mm): A/P: 5.4–5.8; M/L: 4.6-5.0; D/V: 6.0-9.0. Coordinate adjustment for adult females was made similar to the DA recordings. Putative vHipp pyramidal neurons were identified based on long spike duration (>2.2 ms) and low firing rate (<10Hz), consistent with our previous study (Gomes et al., 2020). The BLA in adult males (>PD57) was sampled by 4-6 tracks at (mm): A/P: 3.0–3.2 or 3.4, M/L: 4.7-4.9, D/V: 6.0-8.5 mm. Coordinates for adult females were medially adjusted by

0.1mm. Coordinates for adolescent (<PD45) rats were (mm): A/P: 2.9-3.3, M/L: 4.4-4.6, D/V: 5.8-8.5. BLA pyramidal neurons were identified by long spike duration (>2ms) and low firing rate (<2Hz), according to previous studies.

mPFC-evoked BLA spike plasticity. mPFC-BLA spike plasticity was induced by suprathreshold high-frequency stimulation (HFS) as previously described (Uliana et al., 2021). Concentric bipolar stimulation electrodes (NEX-100X; Rhodes Medical Instruments) targeting the mPFC were lowered through a burr hole to the following coordinates in adult males: (mm) A/P:3.0, M/L: 0.5 or 0.6, D/V: 3.0. We adjusted these coordinates posteriorly and medially by 0.1mm for adult females and by 0.15 mm for adolescent rats weighing below 175g. Responsive BLA pyramidal neurons were searched under repeated single-pulse stimuli (1mA; 0.5Hz; 0.25ms pulse duration) to the mPFC. Identity of pyramidal neurons, monosynaptic responsivity, and orthodromicity was verified by the following criteria: (1) spontaneous firing rate <2Hz, (2) spike duration >2.0ms, (3) evoked spike latency <35 ms, (4) display latency jitter (>1ms) as stimulus intensity changes, consistent with our previous work (Rosenkranz & Grace, 1999; Uliana et al., 2021). Only putative pyramidal neurons were further recorded for HFS-induced spike plasticity, which consisted of 10-minutes baseline recordings followed by 30-minute Post-HFS recordings. PFC stimulus intensity was adjusted to a level for the baseline recording to evoke approximately 50% spike probability. After baseline recording, suprathreshold HFS (20 Hz; 10s) was delivered, immediately followed by 30 minutes Post-HFS recording of neuronal spike response. Cells fired 100% following each HFS stimulus were excluded for analysis, as this reflects putative antidromic activation. For outcome measures, spike probability was calculated in 5-minute blocks by dividing the total number of evoked spikes by the total number of stimuli (i.e., 150 sweeps). Spike probability at each time point was normalized to mean 10-minute baseline spike probability

(expressed as % change to baseline), which allows spike plasticity analysis of long-term potentiation (LTP) or long-term depression (LTD). Mean post-HFS % change to baseline was also calculated by averaging the six Post-HFS time-point data.

Behavioral assays. All behavioral assays were conducted in the natural dark cycle (7:00 pm – 12:00 am), and the experimental steps were performed strictly according to our previously published work (Gomes & Grace, 2017; Klinger et al., 2019; Zhu & Grace, 2021). Brief experimental details are described below.

Elevated Plus Maze (EPM). Animals were first habituated to the testing room for 90 minutes. Rats were introduced to the central area facing an open arm, and their movements were recorded for 5 minutes. Time spent in open arms and the percent of entries into open arms were measured to index anxiety-like behaviors.

Novel object recognition (NOR). The NOR test was conducted in a rectangular box (L70 cm × W40 cm × H30 cm). One day before the test session, animals were habituated to the arena for 10 minutes. On the test day, animals were submitted to 2 trials separated by 1 hour. During the first trial (acquisition trial, T1), rats were placed in the arena containing two identical objects for 5 minutes. For the second trial (retention trial, T2), one of the objects presented in T1 was replaced by an unknown (novel) object. Animals were then placed back in the arena for 5 minutes. Object exploration was defined as situations where the animal is directing its face to the object at approximately 2 cm while watching, licking, sniffing, or touching it with the forepaws while sniffing. Recognition memory was assessed using the discrimination index (discrimination index = [novel – familiar / novel + familiar]), corresponding to the difference between the time exploring the novel and the familiar object, corrected for total time exploring both objects.

Amphetamine-Induced Hyperlocomotion (AIH). Locomotor activity was assessed in open-field chambers (Coulbourn Instruments, Allentown, PA) with ambulatory movement in the x-y plane recorded for 30 minutes. Rats were next injected with D-amphetamine sulfate (0.75 mg/kg, i.p.; Sigma-Aldrich, St. Louis, MO), followed by the recording of locomotion for 60 minutes. Data were computed in 5-minute bins for time-course analysis, and the total distance traveled postamphetamine injection was calculated.

Tissue collection. On day 1, 11, 21, and 55 after the stress initiation, rats were deeply anesthetized by Fatal Plus (0.3–0.5 mL, i.p.; Vortech Pharmaceutical) and perfused transcardially with 0.1M phosphate-buffered saline (PBS) followed by 4% paraformaldehyde (PFA) in 0.1M PBS using infusion pumps. Flow rate and volume of perfusate were adjusted based on animal size. Following perfusion, brains were extracted and post-fixed in 4% PFA at four °C. Twenty-four hours later, the brains were stored in 25% sucrose until sunk, followed by sectioning (40μm) using a cryostat (CryoStar NX50, Thermo Scientific) within seven days. 6-8 coronal sections (each separated by 160 μm) targeting the BLA (A/P: -1.72 to -2.92 mm from the bregma) and the vHipp (A/P: -5.28 to -6.24 mm) were collected and stored in ethylene glycol at -20 °C until further experiments.

Immunohistochemistry (IHC). Brain sections were processed based on previously published protocols (Gomes et al., 2020). Briefly, sections were first washed three times in 0.1M phosphate buffer (PB) for 20 minutes each and then treated with 1% sodium borohydride to reduce auto-fluorescence. Sections were next washed 8 x 5 minutes with 0.1M PB. Processed sections were incubated in primary antibody mix for 48 hours at four °C, containing 1% normal goat serum (NGS), 0.3% Triton X-100, mouse anti-PV antibody (1:500, Sigma, catalog #P3088), and biotinylated Wisteria floribunda agglutinin (WFA; 1:2000 dilution, Vector Labs, catalog #B1355).

Following three times 10-minute wash in 0.01M PBS, sections were incubated for 24 hours in a secondary antibody mix, containing 1% NGS, 0.3% Triton X-100, goat anti-mouse Alexa Fluor 488 (1:500, Abcam, catalog #ab150116), and Alexa Fluor 594 conjugated to streptavidin (1:500, Life Science Technology, catalog #S32354). Lastly, sections were next washed in 0.1M PBS and processed with DAPI (1:4000 in 0.1M PB, Thermo Scientific, catalog # 62247). The finished sections were processed by tissue mounting and coverslip for fluorescence microscopy.

Image acquisition. Images were acquired using an Olympus BX51 microscope with a Hamamatsu Orca-ER camera, at a set exposure time calibrated based on expression levels of each marker of the adult naïve rats. The focus was adjusted to maximally visualize the PV somal staining. On the 4x images, target regions were identified based on DAPI staining patterns, with reference to the Rat Brain in Stereotaxic Coordinates.(Paxinos & Watson, 2006) The BLA was determined based on its "teardrop" shape under 4x magnification. Upon successful region identification, 10x images were taken at the basal nucleus of the BLA. The vHipp was identified under 4x magnification, and 10x images were taken to capture the proximal part of the vSub, with the lateral border with CA1 identified based on the change in the thickness of layer pyramidale.

Cell counting and quantification. On 10x images (size: 909 × 692 μm), a 550 x 690 μm counting frame was applied to target the basal nucleus of the BLA or the proximal vSub. Only the BLA sections between A/P levels at -2.04 to -2.40 mm and the vHipp sections between -5.40 to -5.88 mm were analyzed. Cell counting of PV, PNN, and their co-labelling was performed manually by two experimenters blinded to the group conditions as described previously (Gomes et al., 2020). Cell counting was carried out bilaterally in a balanced manner, with equal region representation from the left and right hemispheres. A mean cell count (averaged across 4-6 images) was calculated to indicate the expression of each marker in each animal.

Statistical analysis. Statistical tests were performed using Prism 9.3.1 (GraphPad, La Jolla, CA). In all electrophysiology experiments, group data were first tested for normal distribution by D'Agostino and Pearson normality test. In normally distributed datasets, groups were compared using a two-way ANOVA with stress (Naïve vs. PreP-S or PostP-S) and sex (Male vs. Female) as main factors, or time as repeated measure (RM) factor when appropriate. Tukey's or Dunnett's post hoc tests were performed following significant differences discovered by ANOVA unless otherwise specified. If the normal distribution was violated in any group, a non-parametric Kruskal-Wallis test was performed, followed by post hoc Dunn's tests to determine significant median differences in within-sex and within-stress comparisons. Given the unequal group numbers in IHC experiments, IHC data were analyzed by Welch multiple t-tests at each post-stress testing age. Results are considered significant at $p<0.05$.

Bodyweight	PreP-S					PostP-S				
	PD20 (n=24)	PD40		PD70		PD40 (n=24)	PD60		PD90	
		Naïve (n=12)	Stress (n=12)	Naïve (n=12)	Stress (n=12)		Naïve (n=12)	Stress (n=12)	Naïve (n=12)	Stress (n=12)
Male	48.60 ± 1.59	151.9 ± 2.76	142.2 ± 2.34	325 ± 3.66	335.5 ± 6.96	146.4 ± 2.4	281.9 ± 6.19	267.5 ± 2.38*	376.9 ± 6.39	389 ± 8.21
Female	47.6 ± 0.96	147 ± 2.68	139 ± 2.45	227 ± 3.22	233 ± 4.24	129.7 ± 4.62	203 ± 3.11	194 ± 4.63	262 ± 7.93	268 ± 5.99

Table S1. The impact of stress on body weight was measured 10- or 40 days after exposure.

PreP-S did not significantly alter body weight at any time. PostP-S had a transitory effect reducing body weight at PD60 in males, which did not persist to PD90. * indicates the impact of stress ($p<0.05$, unpaired t-test)

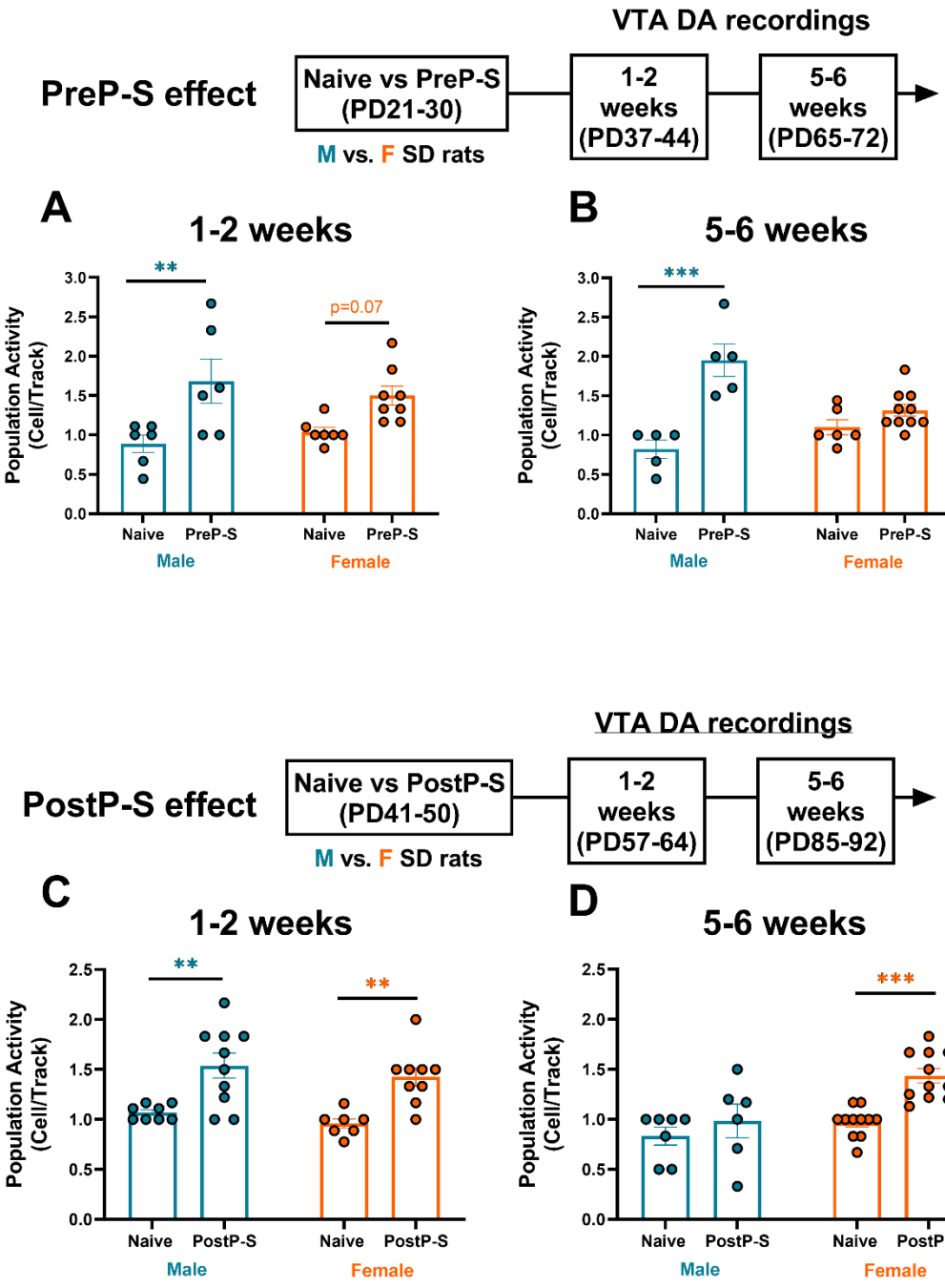

Figure S1. Age-dependent effects of PreP-S and PostP-S on ventral tegmental area (VTA) dopamine (DA) neuron population activity in rats without prior behavioral testing.

To control for potential confounds from behavioral testing and explore testing age-dependent effects, VTA DA recordings were conducted at set testing time post-stress, 1-2 weeks and 5-6 weeks, in a set of behavior-free animals. **(A)** In 1-2 weeks after PreP-S, overall an increase in DA population activity was observed in both sexes

[Two-way ANOVA; PreP-S: $F(1, 23) = 16.28$, $p<0.001$; Bonferroni's post hoc test: PreP-S:Male, $p<0.01$; PreP-S:Female, $p=0.07$]. **(B)** In 5-6 weeks after stress, PreP-S only induced an increase of DA neuron population activity in males without affecting females [interaction: $F(1, 22)=14.53$, $p<0.01$; PreP-S: $F(1, 22)=31.34$, $p<0.0001$; Bonferroni's post hoc test: PreP-S:Male, $p<0.001$]. Similar testing-time dependent effects were found for PostP-S. **(C)** In 1-2 weeks after stress, PostP-S induced a hyperdopaminergic state in both sexes [PostP-S: $F(1, 30) = 25.61$, $p<0.0001$; Bonferroni's post hoc test: PostP-S:Male and PostP-S:Female, $p<0.01$]. **(D)** in 5-6 weeks after PostP-S, only females exhibited DA hyperactivity [PostP-S: $F(1, 31) = 12.20$, $p<0.01$; sex: $F(1, 31) = 11.05$, $p<0.01$; Bonferroni's post hoc test: PostP-S:Female, $p<0.001$]. In conclusion, most prevalent sex differences were observed in the long-term effects (i.e., 5-6 weeks after stress). Short-term effects of stress appeared uniform in both sexes, characterized by increased population activity. The pattern of sex dependence in the long-term stress effects corresponded to that measured in Figure 1 of the main text, verifying that behavioral tests were insufficient to alter adult DA neuron population activity. Data are represented in mean ± SEM; $^{**}p < 0.01$, $^{***}p < 0.001$ vs. within-sex control.

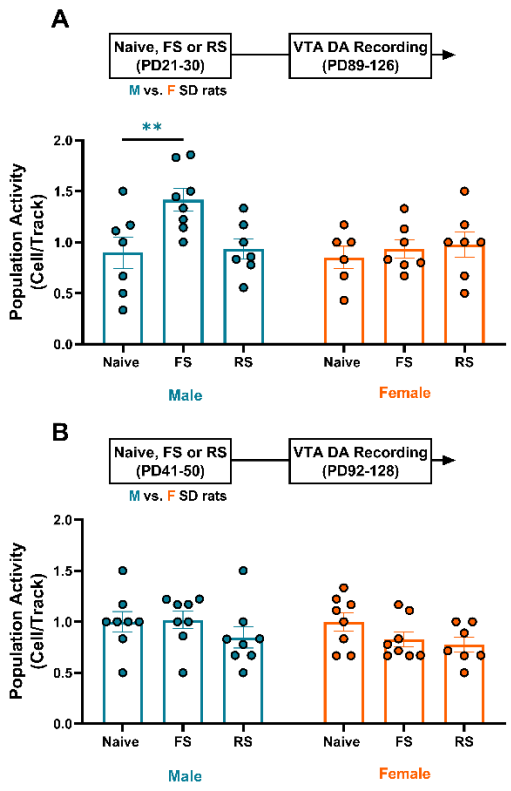

Figure S2. Effects of singular stressors on adult DA neuron population activity.

Long-term effects of daily footshock stress (FS) and three sessions of repeated restraint stress (RS) were compared. **(A)** When examined in PD21-30 (i.e., prepuberty), only FS in males was found to significantly increase adult VTA neuron population activity [2-way ANOVA; stress type: $F(2, 36) = 3.653$, $p<0.05$; Tukey's post hoc: $p<0.01$). **(B)** When examined in PD41-50 (i.e., postpuberty), no effect of singular stressors was found on DA neuron firing in either sex. Altogether, these data suggested that singular stressors were largely ineffective in altering adult VTA DA neuron population activity. Data represent mean ± SEM. **$p < 0.01$ vs. Naïve. *Blue* and *Orange* dots represent data from males and females, respectively.

plPFC-BLA spike plasticity		Male				Female			
		<3 wk		>6 wk		<3 wk		>6 wk	
		Naive	Stress	Naive	Stress	Naive	Stress	Naive	Stress
PreP-S	# of neurons	8	7	5	6	6	6	6	9
	Latency (sec)	23.5 ± 1.83	26.01 ± 1.64	22.8 ± 1.23	22.7 ± 1.74	22.71 ± 1.87	24.24 ± 1.88	25.5 ± 1.49	26.2 ± 1.23
	Current intensity (mA)	0.62 ± 0.09	0.73 ± 0.08	0.73 ± 0.10	0.81 ± 0.12	0.60 ± 0.08	0.66 ± 0.01	0.67 ± 0.05	0.88 ± 0.06
	Basal spike probability	0.68 ± 0.05	0.73 ± 0.04	0.62 ± 0.04	0.64 ± 0.09	0.64 ± 0.05	0.62 ± 0.07	0.60 ± 0.08	0.64 ± 0.05
PostP-S	# of neurons	7	6	6	9	7	11	5	7
	Latency (sec)	26.7 ± 0.82	23.7 ± 1.29	25.5 ± 0.70	27.3 ± 1.07	27.2 ± 1.08	24.6 ± 1.27	22.6 ± 1.01	21 ± 1.17
	Current intensity (mA)	0.73 ± 0.10	0.69 ± 0.09	0.69 ± 0.11	0.78 ± 0.09	0.87 ± 0.07	0.86 ± 0.06	0.75 ± 0.08	0.79 ± 0.07
	Basal spike probability	0.63 ± 0.05	0.52 ± 0.04	0.61 ± 0.06	0.70 ± 0.05	0.56 ± 0.08	0.65 ± 0.10	0.54 ± 0.03	0.62 ± 0.10

Table S2. Baseline parameters of the recorded BLA neurons responding to repeated PFC pulse stimulation.

For each stress, at each recording age (i.e., <3 wks or >6 wk), two-way ANOVA on sex and stress did not reveal any difference in latency to spike, current intensity to elicit baseline, and basal spike probability for the recorded BLA neurons.

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