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The impact of chronic stress during adolescence on the development of aggressive behavior: A systematic review on the role of the dopaminergic system in rodents

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ABSTRACT

Pathological aggression, frequently observed in psychiatric patients and criminal subjects, poses a major burden on the health care and criminal justice system, necessitating better aetiological models to inform targets for prevention and intervention. Emerging evidence suggests that adverse experiences during development can cause long-lasting brain alterations associated with maladaptive behaviors, such as aggression. The present review discusses, mainly based on studies in rodents, whether disruption of the mesocorticolimbic dopamine system through chronic stress-exposure during adolescence predisposes to adult aggression. Our findings suggest that chronic stress in adolescence induces prefrontal cortex (PFC) hyperdopaminergia and ultimately leads to blunted prefrontal dopamine transmission in adulthood. This, in turn, disrupts the ability of the PFC to guide adaptive, long-term focused action selection by regulating mesolimbic dopamine signaling. We propose that, especially during the dynamic and transitional period of adolescence, exposure to chronic stress could lead to excessive adaptive change, which may result in an increased vulnerability to maladaptive aggression in adulthood. We discuss how these findings in rodents may translate to humans.

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1. Introduction

Aggression has for long been a key problem for society given its enormous negative psychological and financial consequences (DeLisi et al., 2010; Krug et al., 2002). Pathological aggression is strongly associated with criminal behavior and a prominent aspect of a multitude of psychiatric disorders, including psychopathy, conduct disorder, post-traumatic stress disorder and antisocial personality disorder (Blair, 2003; Jakupcak et al., 2007). The physical and mental harm of violence and aggression has severe impact on both victims and perpetrators, which often cuts across the lifespan, affecting multiple domains of life (Brown et al., 2007; Cooley-Quille et al., 2001). Therefore, identifying causal mechanisms underlying these behaviors could significantly aid to improve preventive and treatment measures.

Human aggression has been defined broadly as ‘any form of behavior directed toward the goal of harming or injuring another living being who is motivated to avoid such treatment’ (Baron and Richardson, 1994). The ability to generate an aggressive response has evolved evolutionarily as a potential life-saving mechanism to ensure survival and is thus adaptive when serving specific functions, such as reproduction or securing access to food and shelter (Blake and Grafman, 2004). However, when aggression becomes exaggerated, persistent and is expressed out of context, it develops into maladaptive behavior with destructive consequences (de Almeida et al., 2005; Nelson and Trainor, 2007). The concept of aggression is heterogeneous and has been classified based on its different causes, modes or subtypes. Animal studies have indicated sex differences in triggers of aggression: males become aggressive while competing for mates and resources, whereas females display aggression in order to defend their young (Baron and Richardson, 2004). Also in humans, sex-specific modes of aggression have been indicated: females are more often involved in relational aggression and display more verbal and indirect aggressive behaviors, such as alienation and character defamation, whereas males display more physical aggression (Archer and Coyne, 2005; Crick and Grotpeter, 1995). Moreover, data from the Pittsburgh Youth Study, a prospective longitudinal investigation documenting developmental pathways of antisocial and delinquent behavior, suggests that the level of physical aggression in boys is highest early in life and decreases from early adolescence onwards (Loeber and Hay, 1997). More serious violence, however, peaks only in late adolescence or early adulthood, after which it decreases again (Farrington, 1986).

The most common type of classification of aggression in humans is the controlled-instrumental versus reactive-impulsive subtype. Controlled-instrumental aggression is goal-oriented and purposeful and may be the cause for higher profile incidents such as mass killings, whereas reactive-impulsive aggression is characterized by impulsivity and inappropriate aggressive responses (Nelson and Trainor, 2007). Both subtypes are hypothesized relate to different dysfunctioning brain systems: the higher cortical systems regulate controlled-instrumental aggression, while the hypothalamic and limbic systems mediate impulsive aggression (Blair, 2003; Van Goozen et al., 2007). Still, despite the theoretically meaningful and internally consistent distinction, the two subtypes are not mutually exclusive since instrumental aggressive individuals are also likely to show impulsive aggression following provocation. Consequently, a dimensional approach, considering the complex interplay between different brain structures and systems in aggression

has been proposed (Anderson and Bushman, 2002; Siever, 2008).

Moreover, a wide range of studies have demonstrated prefrontal deficiencies, such as poor executive functioning and cognitive control, as important correlates of antisocial development (Anderson et al., 1999; Brower and Price, 2001; Morgan and Lilienfeld, 2000). A meta-analysis of 43 structural and functional imaging studies examining antisocial and violent behaviors revealed a significant reduction in structure and volume of the right OFC, right anterior cingulate cortex, and left DLPFC (Yang and Raine, 2009). Based on these findings, Raine and colleagues have proposed the prefrontal dysfunction theory, which states that prefrontal brain deficits give rise to a lack of inhibitory control over aggressive behaviors (Raine, 1997).

Epidemiological studies have demonstrated that chronic stress, caused by adverse experiences during development such as maltreatment, is associated with adverse brain development and forms a major risk factor for a wide range of psychopathologies, including aggression (Cicchetti and Toth, 2005; De Bellis et al., 1999; Shields and Cicchetti, 1998). Data from the Adverse Childhood Experiences (ACE) Study – a large (N = 17,337) retrospective cohort study examining the effects of childhood abuse on health-related outcomes – suggest an “exposure-response” relationship between the number of ACEs and co morbid health domains, by demonstrating that accumulated childhood stress exposure had a graded relationship with co morbidities, such as affective, somatic, and aggression-related domains throughout life. Theoretically, the authors argue, this parallels that cumulative exposure to stress during development causes impairments in multiple brain areas and functions (Anda et al., 2006) and implies that chronic childhood stress exert its negative effects on psychopathological development through brain alterations.

Preclinical studies are particularly useful to provide insight into the stress-responsiveness of neurobiological systems, since these studies allow experimental designs to measure the direct effects of induced environmental adversity on the brain (Kaufman et al., 2000). Moreover, the short lifespan of rodents eases the use of a longitudinal design needed to detect developmental changes. The most common rodent paradigms have typically focused on “offensive” aggressive behavior, which is characterized by the initiative of the aggressor to intentionally damage the opponent through sideways threats, chasing, defensive upright postures, tail rattling and attack bites between mature males (Miczek and O'Donnell, 1978). Offensive aggression has been studied through multiple rodent models, such as resident-intruder (rat/mouse/hamster), electric stimulation of the brain (rat), isolation-induced (mouse), maternal offensive behavior (mouse/rat) along with play-fighting paradigms in juvenile rats (Olivier and Young, 2002). By reviewing these paradigms in rodents, the present study aims to gain insights into the underlying causal mechanisms of human pathological aggression. The danger of ethological comparisons across species, however, is that similar behaviors, such as aggression, could indicate convergent adaptations to certain similarities of ecology, which limits the external validity (Tinbergen, 1972). Moreover, Tinbergen has noted that humans are the only species in which fighting is often disruptive, whereas in other species, bloodshed is rare and intra-specific fighting is usually of distinctive advantage (Tinbergen, 1968). An ethological approach on studying

aggression thus requires carefulness concerning direct inferences from rodents to humans.

Preclinical studies have indicated the modulatory role of canonical neurotransmitters such as dopamine, serotonin and γ -aminobutyric acid (GABA), in the initiation and regulation of aggressive behaviors. Through transgenic mice models, single gene defects in mono-amine oxidase A (MAOA) showed altered serotonin metabolism and enhanced aggression, supporting an earlier finding by Brunner et al. (1993) reporting MAOA deficiencies in a Dutch family with abnormal impulsive aggression (Brunner et al., 1993; Cases et al., 1995). Clinical studies aimed at reducing aggressive outbursts in psychiatric patients – have predominantly targeted pharmacotherapeutic interventions with dopamine antagonists, such as haloperidol. The dopamine D2 receptor antagonist haloperidol has been shown to reduce violent outbursts in children and adolescents who display conduct disorder and aggression, but also in acutely psychotic patients (Calver et al., 2015; Campbell M et al., 1984). Despite its clinical effectiveness in reducing aggression, haloperidol has untoward sedative and other side-effects, rendering the drug less suitable for pharmacotherapy, especially in children and adolescents. Conversely, a large study conducted in Swedish ADHD patients, showed that criminality rates were reduced by 32% in males and 41% in females, when they received amphetamine-like ADHD medication – which act as a dopamine agonist – as compared to when the same patients did not receive medication (Lichtenstein et al., 2012). Moreover, methylphenidate treatment has shown clinical efficacy by reducing antisocial behavior in children with conduct disorder (Weickert et al., 2007).

These preclinical and clinical studies hint to an important role for the dopaminergic system in the etiology of pathological aggression. At the same time, in rodents (Veenema et al., 2006) as in humans (Márquez et al., 2013), exposure to adverse environments during development has shown to increase the risk for developing aggressive behavior in adulthood (Veenema, 2009). A previous comprehensive review has summarized research focussing on the sensitivity of the mesolimbic system during perinatal development and reported both hyper- and hypo-dopaminergic changes to stress (Gatzke-Kopp, 2011). Their findings indicated that both directions of change reflect adaptive adjustments during perinatal development in preparation for future environments, with brief, acute stressors leading to hyperdopaminergic changes and severe, prolonged adversities being associated with a hypodopaminergic profile. These changes in DA signalling, the authors propose, may place individuals at greater risk for developing psychopathologies.

The present review complements the previous work on chronic stress in the perinatal period, by focusing on the impact of chronic stressors on mesocorticolimbic DA signalling during adolescence and, more specifically, on how neurobiological mechanisms mediate the effect of stress in adolescence on the development of aggressive behavior. As such, this review provides a conceptual synthesis on how stress during adolescence can affect aggressive behavior in adulthood through changes in the dopaminergic system. To this end, we will systematically review studies in rodents that examine 1) how stress during adolescence influences mesocorticolimbic DA signaling and 2) the manner by which such changes in adolescence could ultimately affect aggressive behavior in adulthood.

1.1. Neurodevelopmental and behavioral changes during adolescence

The term ‘adolescence’ refers to the period of gradual transition from childhood to adulthood, although the boundaries of this period are not precisely defined (Spear, 2000). The start of adolescence is marked by the onset of puberty, where reproduc-

tive organs become functional and secondary sexual characteristics emerge, whereas the end is not clearly characterized by biological boundaries. In humans, adolescence has been generally defined as between the age of 10 and 17 in girls and age 12 to 18 in boys (Arnett, 2000). Longitudinal neuroimaging research has demonstrated extensive brain development throughout adolescence, supporting the notion that this period extends until age 25 (Giedd et al., 1999; Sowell et al., 1999). Adolescence is characterized by increases in social behavior, risk-taking, impulsivity and reward sensitivity, which are linked to the drastic neurobiological and hormonal changes taking place during this developmental stage (Arnett, 1992; Brown, 2004; Gardner and Steinberg, 2005; Spear, 2000). Developmental neuroimaging research has suggested that these vulnerabilities during adolescence reflect a period of crucial neural changes in social and affective processing, which facilitate motivational learning and may serve an adaptive function (Crone and Dahl, 2012). Evolutionarily, these age-related increases in risk taking and peer affiliations are important activities, which help the adolescent to become independent and could increase the probability of reproductive success and decreases the chance of inbreeding, by emigrating from the natal family context (Schlegel and Barry, 1991; Schlegel and Barry III, 1991).

Previous studies have suggested that neurodevelopmental and behavioral changes during adolescence are similar in humans and rodents (Friemel et al., 2010). In rodents, adolescence has been defined as roughly from postnatal day 22 (P22) till P60 for female rats and from P22 till P70 for male rats, with similar definitions for mice (Adriani et al., 2002; Schneider, 2013). Moreover, peri-adolescent mice show an increased level of arousal and amount of time to search for novel compared to adult mice (Laviola et al., 1999). The onset of rodent adolescence, encompassing postnatal days P21–P28, has shown to be a sensitive period for brain maturation underlying adult aggressive behavior (Nautiyal et al., 2015) and matches closely with the onset of play behavior, agonistic behavior and the development of social hierarchies (Bartolomucci et al., 2004; Pellis and Pasztor, 1999; Terranova et al., 1998).

The importance of social play behavior for reward-related processes and stress-regulation

Social play behavior, a positively reinforcing interaction between peers, is the earliest form of non-mother-directed social behaviors (Vanderschuren et al., 1997). It is essential for the development of social competence skills, emotion regulation and cooperation and serves thus as a critical prerequisite for healthy emotional and cognitive development (Gray, 2011; Panksepp et al., 1984). Consequently, impoverished play behavior constitutes a core symptom of early neuropsychiatric disorders such as attention-deficit hyperactivity disorder (ADHD), autism and early-onset schizophrenia (Alessandri, 1992; Jordan, 2003; Møller and Husby, 2000). It has even been argued that the increase in childhood and adolescent psychopathology over the past half century is due to the decline in social play over this period (Gray, 2011). Social play has shown to be a strong reinforcer, indicating that play behavior is highly rewarding (Pellis and Pellis, 2013). Preclinical research, examining the neural substrates of social play behavior through pharmacological inactivation paradigms, revealed the involvement of prefrontal and striatal circuitries, relevant for cognitive control and reward-related processes (van Kerkhof et al., 2013). Moreover, several neurotransmitter systems, such as the opioid, cannabinoid, noradrenergic and dopaminergic system have been implicated to modulate social play behavior (Vanderschuren et al., 1997). Trezza et al. (2010) hypothesized that dopaminergic neurotransmission is particularly important when motivational properties of rewards are addressed during social play (Trezza et al., 2010). Their theory is consistent with prior studies showing that the increase in social play after exposure to cannabinoids, nicotine and ethanol

is dependent on dopaminergic neurotransmission (Trezza et al., 2009; Trezza and Vanderschuren, 2007).

Furthermore, social play may also function as an important stress-regulating mechanism. Social play deprivation, has been shown to disrupt dendritic pruning of the medial prefrontal cortex in juvenile hamsters, thereby increasing the effects of social stress in adulthood (Burlison et al., 2016). Also, studies in male Syrian hamsters have established the importance of prominent elements of social play, such as maintenance of dominance relationships and success in competitive interactions, in the development of stress-coping mechanisms (Cooper et al., 2015; Morrison et al., 2014). Moreover, it has been proposed that social play, happening in a relatively safe context, may simulate the encounter of potentially dangerous situations later in life (Spinka et al., 2001). As a consequence, this earlier experience through play fighting helps the stress-response system to adjust quicker when confronted with unpredictable events thereby facilitating stress-reduction (Pellis and Pellis, 2013).

1.2. The mesocorticolimbic system

The dopamine system is known to play an important role in the aetiology of aggressive behavior. Research, in both rodents and humans, has accumulated demonstrating that two of its projections, the mesolimbic and mesocortical pathways (see Fig. 1), are specifically implicated in aggression and function partially independently. The mesolimbic system plays a role in reward, motivation and emotion, while the mesocortical system is involved in cognition, working memory, planning and self-regulation (Floresco and Magyar, 2006; Pierce and Kumaresan, 2006). Dopaminergic neurons originate in the Ventral Tegmental Area (VTA) and Substantia Nigra (SN) (Groves et al., 1975). The mesocortical dopamine pathway projects from the VTA to the frontal cortex whereas the mesolimbic dopamine pathway projects mainly to the basal ganglia and medial temporal structures (i.e. nucleus accumbens; NAcc, and caudate putamen; CPu), the amygdala, hippocampus, hypothalamus, and ventral pallidum (Kauer and Malenka, 2007; Pierce and Kumaresan, 2006). The striatum, comprising the NAcc (ventral striatum) and caudate-putamen (dorsal striatum, rodent nomenclature), also receives projections from the SN in addition to the VTA. Dopamine release increases in the NAcc in anticipation of aggressive episodes (Ferrari et al., 2003; Malison et al., 1998), while during and following aggressive encounters, dopamine release increases in both the NAcc and PFC (Erp and van Miczek, 2000; Tidey and Miczek, 1996).

1.2.1. Tonic and phasic dopamine neurotransmission

According to the influential model by Grace (1995), dopamine transmission in the striatum is regulated via two processes, termed 'tonic' and 'phasic'. Tonic dopamine release constitutes 'background' dopamine release and maintains a steady-state dopamine tone, independent of stimuli. Tonic dopamine release is generated by midbrain dopamine neuron firing and modulated by corticostriatal afferents originating in the lateral PFC. In contrast, phasic dopamine release is dependent on stimuli (such as unpredicted reward and reward-predicting cues) and constitutes high-frequency 'burst' spike firing of midbrain dopamine neurons, resulting in transient high-amplitude dopamine release in the striatum. Corticostriatal afferents responsible for tonic dopamine release limit the intensity of stimulus-related phasic dopamine release in the striatum. Tonic dopamine dampens phasic dopamine release by acting on inhibitory autoreceptors located at presynaptic terminals. Diminished prefrontal function has been proposed to increase striatal dopamine release as a result of impaired negative regulation of phasic dopamine release. Consistent with this, decreased lateral PFC activity is associated with increased striatal

dopamine function in humans (Grace, 1995). This feedback mechanism might be disrupted in impulsivity (Tisch et al., 2004) and in adolescents with ADHD and/or CD (Shannon et al., 2009).

1.2.2. Heightened plasticity in the dopamine system during adolescence

The previously described increases in incentive-motivated behaviors, such as risk-taking, that characterize adolescence, are mirrored by developmental patterns of the mesocorticolimbic system, showing enhanced DA signaling in adolescence, thereby possibly facilitating these DA-modulated functional changes in behavior (Wahlstrom et al., 2010a, 2010b). Studies aimed at mapping postnatal alterations in dopaminergic neurotransmission have mostly focused on dopamine receptor signaling, dopamine synthesis and dopamine release/clearance.

A rodent study examining dopaminergic innervations demonstrated a monotonic increase from childhood (P4) to adulthood (P60) regarding the density of the dopaminergic fibers in the PFC (Kalsbeek et al., 1988). Moreover, during adolescence, D2- and D4-like dopamine receptor expression levels in rat NAcc and CPu (Tarazi et al., 1999) as well as DR1 and DR2 binding density and associated second messenger activity in rat cortex, were higher compared to earlier or later stages (Andersen et al., 2000). DAT transporter density in rat striatum also peaks during adolescence (Moll et al., 2000; Tarazi et al., 1999) and VTA dopamine neurons in adolescent rats fire faster than in adult rats (Mccutcheon et al., 2012).

In humans, Weickert et al. demonstrated that dopamine receptor expression changes in PFC throughout postnatal life are subtype-specific, with DR1 mRNA levels being highest in adolescence and early adulthood, but DR2 mRNA levels being highest in neonates (Weickert et al., 2007). These developmental changes in dopamine 1 and 2 receptor mRNA levels were replicated by a study examining both gene and protein expression in the dorso-lateral prefrontal cortex (DLPFC). This study also found that DR1 protein expression increased with age reaching a plateau during early adulthood. Moreover, monoamine oxidase A (MOA-A) and the closely linked monoamine oxidase B (MAO-B), key enzymes affecting dopamine neurotransmission through degrading dopamine, were also found to fluctuate during different stages of development. MAOA-A mRNA was highest in neonates and infants, while MAOA-A protein was highest in adolescents and adults. MAO-B mRNA increased with age and was highest in adulthood, yet MAO-B protein expression peaked during adolescence (Rothmond et al., 2012).

These findings across species suggest that throughout development, and especially during adolescence, multiple components of the dopamine system undergo considerable structural changes, which may contribute to a higher plasticity and sensitivity to stressors.

1.3. The stress-response and its mediators

Stress is generally defined as any stimulus that may disrupt the homeostasis of an organism and can elicit physiological and behavioral responses that allow an organism to react to possible danger (Chrousos, 2009; Cullinan et al., 1995; Pacák and Palkovits, 2001). The stress response is an adaptive mechanism enabling modification of behaviors in dynamic environments through modulation of neuronal function and plasticity (de Kloet et al., 2005). It has become increasingly clear that this evolutionarily conserved system is highly complex and orchestrated with a diverse set of stress mediators, such as monoamines, neuropeptides and steroids (Joëls and Baram, 2009). Since each stressor is unique, a highly coordinated and efficient stress response system, encompassing high temporal, spatial and context specificity is required.

Fig. 1. Mesocorticolimbic dopaminergic pathways in the rodent brain.

Simplified schematic of the mesocorticolimbic dopamine pathways in the rodent brain. Dopaminergic neurons originating in the ventral tegmental area (VTA) project to the basal ganglia and medial temporal structures in the mesolimbic pathway (black arrows), such as the nucleus accumbens (NAcc, ventral striatum), caudate-putamen (CPu, dorsal striatum), amygdala, hippocampus and hypothalamus. The striatum is also innervated by dopaminergic neurons originating in the substantia nigra (SN). The mesocortical pathway (blue arrow) projects from the VTA to the prefrontal cortex (PFC). Tonic 'background' dopamine release in the NAcc from midbrain dopamine neurons is modulated by glutamatergic afferents originating in the PFC (red arrow). Tonic dopamine activity in the NAcc negatively regulates phasic dopamine 'burst firing' by the VTA, which occurs in response to stimuli, such as reward or reward-predicting cues.

Stressful stimuli trigger the activation of the hypothalamic-pituitary-adrenal-axis (HPA-axis), considered to be the key effector of the stress response (Cullinan et al., 1995). From the paraventricular nucleus of the hypothalamus (PVN) corticotropin-releasing hormone (CRH) is secreted, which stimulates the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland. In turn, ACTH stimulates the production of glucocorticoids (cortisol in humans). Via a negative feedback loop, glucocorticoid activity inhibits both the hypothalamus and the pituitary gland. Activation of the HPA-axis eventually results in a rise in plasma glucocorticoid (GC) levels, which can have molecular, structural and functional effects in the brain by inducing long-term potentiation through altered gene expression or epigenetic modifications (McEwen, 2007). Eventually, these changes can lead to structural remodeling of neuronal architecture and allow for successful adaptation of an organism. However, these changes can be maladaptive when stress exposure is extended, and can predispose to psychopathologies, such as depression or drug abuse (Belujon and Grace, 2011; Hammen, 2005).

The processes underlying stress together are called "allostasis", which is the process of maintaining homeostasis by active means (e.g. secreting stress hormones). When the harms done by the allostatic process are greater than the benefits of the maintenance of homeostasis this is called "allostatic load or overload", which usually occurs when a stress response is excessive or prolonged. It is thought that especially during perinatal and juvenile development, the brain is sensitive to allostatic load making stress a major risk factor for psychopathology (McEwen, 2007). The three-hit concept of vulnerability and resilience to stress-related mental disorders holds that gene-environment interactions are essential in the proper processing of stress. Genetic factors (hit-1) interact with the early-life environment (hit-2), resulting in a particular pattern of gene expression. This pattern of gene expression can lead to a higher risk of psychiatric symptoms (vulnerability) in the later-life environment (hit-3), but the same pattern of gene

expression in the same individual may lead to a decreased risk of psychiatric symptoms (resilience) in another later-life environment (Daskalakis et al., 2013).

Glucocorticoid receptors (GRs) mediate the cellular effects of glucocorticoids (Kitchener et al., 2004). GRs are abundant in dopamine projection regions, such as the PFC, striatum and hippocampus and are, to a lesser degree, also expressed in the VTA (Morimoto et al., 1996). While it is clear that the dopamine system reacts strongly to stress, the exact mechanisms of how glucocorticoids affect the dopamine system are not well characterized. Most studies have focused on the effect of GCs on the dopamine system, but only few examine the influence of dopamine signaling on the HPA-axis and GR-mediated activity. Through negative feedback, dopamine release in the ventromedial PFC has been shown to play an important role in preventing excessive activation of the HPA-axis during stress (Sullivan and Dufresne, 2006). Adolescence in particular seems to be a sensitive period for the impact of stressors on the dopamine system. In rats, a prolonged and heightened corticosterone response to stress is observed in adolescents compared to adults (Romeo and McEwen, 2006). Also in humans, age-related differences in glucocorticoid receptor (GR) mRNA levels have been reported, with increased GR mRNA in the prefrontal cortex during adolescence and mature adulthood compared to infancy, young adulthood and senescence (Perlman et al., 2007).

2. The effects of adolescent stress on the dopamine system

The most commonly used paradigms to examine the effect of stressors during adolescence in rodents are social defeat, isolation, restraint, and exposure to aversive environments. Various studies have assessed the effect of chronic stressors during adolescence on the dopamine system in adulthood (See Table S1 for an overview). Adolescent chronic stress results in decreases in basal dopamine levels (Watt et al., 2009), dopamine D2 recep-

tors (Wright et al., 2008), dopamine turnover (Watt et al., 2014), and higher DAT expression and binding (resulting in enhanced synaptic DA clearance; Novick et al., 2015, 2011) in the medial PFC in adulthood. These changes in the dopamine neurophysiology suggest a downregulation of the mesocortical system. In addition, amphetamine-induced mPFC DA release is attenuated following social defeat in adolescence, suggesting that stress blunts DA PFC DA transmission (Burke et al., 2013, 2011). With respect to the mesolimbic system, Novick et al. (2011) reported higher dopamine D1 receptor binding in the caudate-putamen, which is in contrast with the lower levels of dopamine D2 binding found in mesocortical areas (Wright et al., 2008). Also, opposed to the attenuated amphetamine response in the mPFC, the NAcc core shows an enhanced amphetamine response (Burke et al., 2013, 2011), suggesting increased dopamine sensitivity in the NAcc after chronic adolescent stress. Likewise, chronic stress induced during the entire period of adolescence and young adulthood results in an increased dopamine release and uptake by DAT in the NAcc after electrical stimulation (Yorgason et al., 2013), suggesting increased dopamine system kinetics, which may produce greater dopamine responses. One study reported contrasting effects regarding monoamine content, turnover, and biosynthesis in both mesolimbic and mesocortical brain areas following adolescent social defeat, but did observe increased levels of social anxiety in adulthood (Vidal et al., 2007).

Overall, these findings indicate that chronic stress taking place in adolescence generally results in a decreased dopamine activity/functioning in adult PFC through reduced dopamine levels and turnover, D2R's, higher DAT expression and binding, and amphetamine-induced DA release (Burke et al., 2013, 2011; Novick et al., 2015, 2011; Watt et al., 2014, 2009; Wright et al., 2008). In addition, the specificity of the mesocortical pathway in the response to adolescent stress may be due to the increased sensitivity of the adolescent PFC to stress, as a consequence of increased glucocorticoid receptor expression during this period (Perlman et al., 2007), a prolonged and heightened corticosterone response to stress compared to adults (Romeo and McEwen, 2006), as well as a higher PFC dopamine response to stress compared to the striatum and NAcc (Abercrombie et al., 1989). These factors could increase the vulnerability and reactivity of the PFC and its dopamine system to stress.

3. The effect of dopamine system changes during development on aggressive behavior in adulthood

There are few studies that have examined how alterations in the dopamine system occurring during development can persist into adulthood and affect adult aggressive behavior (See Table S2 for an overview). Nearly all have used pharmacological interventions to mimic the dopamine system hyperactivation induced by chronic stress during the developmental stage indicated. Yu and colleagues (2014) in particular have studied the effect of dopamine system changes in all three developmental stages of childhood, adolescence, and adulthood in rats. To our knowledge, this is the only study that investigated the effect of childhood dopamine system changes in relation to adult aggression. In this study, the effects of increased monoamine availability (through MAOA blockade) and dopamine availability (through DAT blockade) on behavioral outcomes during adulthood (>P90) were tested during each of the developmental stages. Strikingly, only peri-adolescent (P22–P41) MAOA or DAT blockade increased adult aggressive behavior and an increased dopaminergic response to amphetamine in adult rodents was observed, suggesting altered dopamine system functioning. The authors conclude that this stage, which constitutes the pre-pubescent phase until mid-adolescence, is a sensitive period during

which dopamine and serotonin bi-directionally modulate adult aggression. Moreover, direct activation of the VTA dopaminergic neurons by optogenetic stimulation increases isolation-induced aggressive behavior, proving that the altered dopamine functioning and aggression are causally linked during adulthood. In contrast, MAOA and DAT blockade during childhood or adulthood did not affect aggressive behavior in adulthood. Likewise, Suri et al., 2015 have induced a DAT blockade in adolescent mice (P32–P41) and demonstrated that this is sufficient to increase adult isolation-induced aggression and an altered dopamine response to amphetamine. Furthermore, Harrison et al. (2000) and DeLeon et al. (2002) have chronically administered cocaine in adolescent hamsters (P28–P56), which increases monoamine availability by blocking monoamine transporters and is associated with dopamine-related changes in the brain. Both report an increase in aggressive behavior using the resident-intruder test in late adolescence/young adulthood (P57).

In sum, interventions that chronically hyperactivate the monoamine or dopamine system during adolescence, thereby mimicking chronic stress-induced dopamine hyperactivation, may increase adult aggressive behavior (DeLeon et al., 2002; Harrison et al., 2000; Suri, 2015; Yu et al., 2014). Still, while chronic monoamine or dopamine system hyperactivation during adolescence is associated with adult aggression, these studies have not assessed the dopamine system functioning in adulthood that may underlie the observed aggressive behavior. Márquez et al. (2013) have nevertheless found that peri-adolescent stress (P28–P42) induces increased MAOA gene expression and promoter acetylation in adult PFC (P90). Since such increase in MAOA in the PFC results in decreased monoamine availability, which in turn is related to aggressive behavior, peri-adolescent stress may predispose aggressive behavior during adulthood (Márquez et al., 2013). In the light of the role of the PFC in the regulation of tonic and phasic dopamine release in the striatum, reduced dopaminergic functioning in PFC may decrease tonic dopamine release in the striatum and consequently lead to increased phasic dopamine release in the striatum. Impaired cortical functioning, either caused by trauma, tumors, or neurodegeneration, results in disinhibited aggressive behavior (Pardini et al., 2011) and reductions in frontal cortex activity have been correlated with impulsive aggression (Lee et al., 2008; Yang and Raine, 2009). Also, orbitofrontal PFC activity is generally decreased during aggressive behavior in healthy human subjects (Davidson et al., 2000). Not only is reduced frontal cortical functioning associated with aggressive behavior, but striatal dopamine is also released during aggressive encounters (Ferrari et al., 2003) and NAcc dopamine receptor blockade diminishes aggressive responses in rodents with DAT knockout (Couppis and Kennedy, 2008). This results in reduced striatal dopamine clearance, which in turn is associated with reactive aggression following mild social contact (Rodríguez et al., 2004). In addition, amphetamine-induced dopamine release in the striatum is positively correlated with impulsive antisociality in human subjects (Buckholtz et al., 2010a). Lastly, low dopamine D2/D3 autoreceptors in the NAcc have been reported in highly impulsive individuals, which can lead to diminished dopamine regulation by feedback inhibition, and enhanced dopamine neuron firing and dopamine release in response to stimuli (Buckholtz et al., 2010b). Together, these findings support the theory that mesolimbic hyperactivation and mesocortical hypoactivation increase the likelihood of displaying aggressive behaviors.

4. Conclusions and future directions

In this review, we discuss how chronic stressors during adolescence affect the dopamine system in rodents and subsequently, how these stress-induced changes affect adult aggressive behavior.

Fig. 2. Neurobiological model describing dopamine system changes underlying the impact of adolescent stress on adult aggression.

During adolescence, chronic stress will result in a hyperactivation of the mesocortical dopamine system due to a heightened responsivity to stress in the PFC during this developmental stage. This mesocortical hyperactivation will lead to a long-term compensatory downregulation of the mesocortical dopamine system, likely through the activation of presynaptic dopamine D2 receptors. This hypodopaminergic mesocortical system will result in diminished regulation of tonic and phasic dopamine release in the mesolimbic system. The mesolimbic dopamine hyperreactivity can in turn increase aggressive behavior.

Based on the discussed findings, we propose a neurodevelopmental model in which chronic upregulation of the dopamine system during adolescence due to stressors can impact on adult aggression, by inducing a long-term compensatory downregulation of the mesocortical dopamine system. Downregulation of the mesocortical system disrupts the regulation of tonic and phasic dopamine release in the mesolimbic system, and may consequently lead to increased aggressive behavior. Fig. 2 depicts a simplified schematic representation of the impact of adolescent stress on adolescent and adult dopamine systems, and its consequences on aggressive behavior. These underlying mechanisms may in part explain aggressive behavior during adulthood following chronic stress during adolescence.

The reduced capacity of the PFC to regulate mesolimbic DA signaling, as described in our model, is in line with prefrontal structural and functional deficits reported in imaging studies examining aggressive behavior. Prefrontal dysfunction effects may be even more pronounced during adolescence, given the social and cognitive overload in this period, requiring complex decision making and maintenance of social status while inhibiting an increasing sex drive and rebellious behaviors (Raine, 2002). We propose that, especially during the dynamic and transitional period of adolescence, these neurobiological changes reflect adaptive adjustments to environmental threats to prepare an individual for the future environment. As a consequence, exposure to chronic stress during adolescence may lead to excessive adaptive change, which in turn, may result in an increased vulnerability to aggression in adulthood.

Although the reviewed studies indicate that stress-induced dopaminergic changes lead to increased adult aggression, much remains to be elucidated with regard to the exact etiological mecha-

nisms. Since adolescence is a developmental stage characterized by an increased prevalence and incidence of aggressive and criminal behavior (Moffitt, 1993), and a disruption of the dopamine system is associated with aggression, future studies should examine whether adolescent rodents also show acute increased aggression following stressors or pharmacological interventions. Also, studies that assessed how dopamine system changes during development affect adult aggression, have not investigated which dopamine system changes in adulthood may underlie the observed aggressive behavior. Furthermore, while a long-term compensatory downregulation of the mesocortical system is observed following chronic stressors, the mechanism and timing of the transition from chronic hyperactivation during adolescence into the downregulation in adulthood are still unclear. For these reasons, sophisticated future study designs, investigating multiple developmental trajectories are needed.

Most of the discussed findings originate from studies on male rodents, few studies have investigated the effect of stressors on the dopamine system in females, and none have assessed the effect of dopamine alterations in female subjects in relation to adult aggression. Garret and Wellman (2009) found opposite morphological changes in mPFC in male and female rodents following adolescent stress, which might be explained by the hormone estrogen. There is a complex interplay between stress and sex hormones (Sinclair et al., 2014) and gender-specific responses to stress have been observed in the mesolimbic dopamine system (Trainor, 2011). Therefore, the importance of including female subjects in experiments is becoming clearer, especially with regard to the differences in dopamine-related disordered behaviors, including aggression.

Testosterone has been implicated in ‘male-typical’ behaviors, such as impulsivity and sensation-seeking (Campbell et al., 2010). High testosterone levels have been found in populations characterized by high aggression. While a multitude of studies suggest a correlation between testosterone and impulsivity and aggression, the relationship has not always been replicated (Archer, 2006). Interestingly, testosterone is known to positively regulate dopamine neurotransmission. Studies report that males are more prone to schizophrenia, which can be caused by a pathologically high activation of the dopaminergic system, whereas females are more prone to depression (Sinclair et al., 2014). The role of estrogen in dopamine transmission is less clear, since studies documented that estrogen can both exaggerate and reduce dopamine transmission. These conflicting findings may be due to the several factors than can influence the effect of estrogen on the dopamine system, such as dose, time of testing, and duration of exposure (Barth et al., 2015). Also, the exact underlying mechanism for a gender-specific difference in a dopaminergic stress-response is still largely unclear, and a better understanding on the interplay between stress and sex hormones on the impact on the dopamine system is therefore needed.

As such, although the disrupted regulation of the corticostriatal dopamine system independently seems to be an important causal mechanism in the etiology of aggressive behavior (Buckholz, 2015), it is important to consider the close connection it holds with other systems. For example, impulsive aggression has been suggested to be the result of dysfunctional interactions between serotonin and dopamine systems in the prefrontal cortex. Still, while MAO-A blocks both serotonin and dopamine metabolism, an increase in aggressive behavior is observed (Yu et al., 2014). The dopamine system therefore seems to be dominant over the serotonin system. To unravel how stress can impact aggression by describing the underlying neurobiological mechanisms, it is necessary to assess the multiple systems involved and the complexity of the interactions between them.

Finally, it is important to understand how the changes observed in animal dopamine systems translate to changes in human dopamine systems. The phylogenetically old mesolimbic dopamine system has shown to be considerably similar between humans and rodents. Yet, the phylogenetically new mesocortical system shows species-specific differences with regard to the dopaminergic innervation of the PFC. For example, the anatomical distribution of dopamine input in rodents and primates is different, as well as the expression of different dopamine receptor subtypes (Berger et al., 1991). This makes the translation of animal models to human models not straightforward. Moreover, many researchers have questioned the homology between specific prefrontal regions in the rodent and human brain (Preuss, 1995; Uylings et al., 2003; Wise, 2008). Cytoarchitectonic studies have indicated that since the rodent prefrontal cortex is entirely made up of agranular cortical areas, it lacks homologous granular cortices, such as the human dlPFC. Nevertheless, the rodent infralimbic cortex is considered homologous to Brodmann's Area (BA) 25, which lies within the vmPFC (Wise, 2008). Additionally, the rodent mOFC is considered homologous with the human mOFC (Preuss, 1995). It has been proposed that the rodent prelimbic cortex is homologous to BA 32, and thus corresponds to the human mPFC/vmPFC (Wise, 2008). Still, others have suggested that the medial frontal cortex of the rat has functional similarity to the primate lateral prefrontal cortex (Birrell and Brown, 2000; Uylings et al., 2003). Despite the relatively undifferentiated forebrain of rodents, we argue that considering the significant comparable networks and functional overlap, these studies can shed light on the functioning of the human PFC.

In sum, the present review systematically considered rodent studies examining the impact of chronic stressors during adolescence on mesocorticolimbic DA signaling, and the mechanisms

through which such changes could ultimately affect aggressive behavior in adulthood. Notably, prefrontal cortical neurons show heightened responsivity to stress throughout adolescence, a developmental period that is also characterized by dramatic shifts in mesocorticolimbic dopamine (DA) signaling. Given this developmental parallel, and bearing in mind the known involvement of mesocorticolimbic DA signaling in aggressive behavior and related cognitive processes, we argue that chronic stress during adolescence may predispose to adult aggression by disrupting prefrontal regulation of mesolimbic DA signaling.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neubiorev.2016.10.009>.

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