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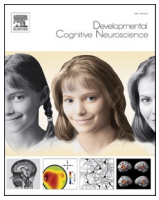

Immune signaling as a node of interaction between systems that sex-specifically develop during puberty and adolescence

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ABSTRACT

Adolescence is pivotal for neural and behavioral development across species. During this period, maturation occurs in several biological systems, the most well-recognized being activation of the hypothalamic-pituitary-gonadal axis marking pubertal onset. Increasing comparative studies of sex differences have enriched our understanding of systems integration during neurodevelopment. In recent years, immune signaling has emerged as a key node of interaction between a variety of biological signaling processes. Herein, we review the age- and sex-specific changes that occur in neural, hypothalamic-pituitary, and microbiome systems during adolescence. We then describe how immune signaling interacts with these systems, and review recent preclinical evidence indicating that immune signaling may play a central role in integrating changes in their typical and atypical development during adolescence. Finally, we discuss the translational relevance of these preclinical studies to human health and wellness.

1. Introduction

Adolescence is a period of significant physical, cognitive and psychosocial changes produced by copious developmental plasticity across biological systems, for example, neural/behavioral, endocrine, stress, and microbiome systems. Although they overlap in time, puberty and adolescence are two fundamentally distinct phases of development. Puberty occurs during adolescence and is characterized by the transition from a non-reproductive to a reproductive-state (Sisk and Foster, 2004). Because of the activation of gonadal hormone production during puberty, and thus easily quantifiable sexual characteristics, puberty is the best understood period of adolescent development, and is one of the most well characterized periods with respect to sex differences. The onset of adolescence is more difficult to estimate, as its definition is a behavioral one: increased peer-centered social behaviors, risk-taking, and exploratory behaviors (Spear, 2000; Schneider, 2013). Adolescence is typically defined to begin prior to, and extend past, puberty to the beginning of adulthood (Fig. 1) (Sawyer et al., 2018). In recent years, immune signaling has emerged as a key node of interaction between a variety of biological systems, including those in flux during adolescence (Kopec et al., 2019; Brenhouse and Schwarz, 2016; Yahfoufi et al., 2020). In fact, adverse childhood events occurring in late childhood and adolescence, but not earlier in life, were recently reported to be associated with persistent immune abnormalities (Iob et al., 2022), suggesting immune signaling may be particularly influential during the adolescent period. In this review, we have three goals. (**1**) We will integrate diverse literatures to describe how immune signaling may play a central role in sex-specific changes that occur in neural, endocrine, stress, and microbiome development during adolescence. (**2**) We will draw special attention to developmental stage *within adolescence* (pre--puberty early adolescence, mid-adolescence and onset of puberty, and post-puberty late adolescence) as a critical factor to consider in experimental designs that incorporate adolescent biology, manipulations, and/or comparisons. Finally, (**3**) we discuss the translational relevance of these data for human health and wellness.

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	Adolescence	Onset of Puberty
Humans	~10 - 24 years	Boys: ~12 years Girls: ~11 years
Rats	~20 - 60 days	Males: ~45 days Females: ~35 days
Mice	~20 - 55 days	Males: ~35 days Females: ~30 days

Fig. 1. Approximate ages of adolescence and puberty in humans, rats, and mice. Ages are approximated based on the literature (Schneider, 2013; Sawyer et al., 2018).

2. Immune contributions to early development

Microglia are the resident immune cells of the brain, and their activity drives critical brain development during early postnatal life, including promotion of myelination, synaptogenesis, and synaptic pruning (Schafer et al., 2012; Schafer and Stevens, 2013; Hughes, 2021). Both microglia and peripheral immune cells can further influence neural activity via cytokine and chemokine signaling, which can broadly be classified as either pro-inflammatory, i.e. they help stimulate an immune response, or anti-inflammatory, i.e. they control or attenuate an immune response. Common pro-inflammatory cytokine targets assessed in the literature are interleukins (IL)− 1β and IL-6, and tumor necrosis factor α (TNFα). There are also proteins associated with pro-inflammatory activity, such as immune transcriptional regulators NFκB and IκBα, and C-reactive protein, that often appear in the literature. Much of our understanding of the changes in immune response throughout the lifespan comes from research studies using lipopolysaccharide (LPS). LPS is a bacterial endotoxin derived from the cell wall of gram-negative bacteria (e.g. Escherichia coli) (Raetz and Whitfield, 2002). When administered in the periphery, LPS binds to toll-like receptor 4 (TLR4) on immune cells and activates the innate immune response by triggering an intracellular cascade of events that ultimately results in the production and release of pro- and anti-inflammatory cytokines in the blood (de Bont et al., 1998; Beaty et al., 1994). Peripheral LPS and cytokines can cross the blood brain barrier and induces neuroinflammation in the brain by activating microglial cells (Bilbo and Schwarz, 2009; Kentner et al., 2010). Immune mechanisms and their developmental timing differ between males and females as early as in utero, and are therefore poised to influence sex-specific development of behavior from birth throughout the lifespan. We will briefly review these data as a platform to ground our examination of confirmed and possible immune signaling contributions to the adolescent developmental period, which is less well studied from an immune perspective.

The placenta is the prenatal interface between maternal and fetal bloodborne signals, and itself is sex specific, with resident immune cells that respond to the changing maternal environment differently in developing males and females (Bronson and Bale, 2016; Howerton and Bale, 2012). For example, prenatal exposure to stress or maternal immune activation yields pro-inflammatory activity in the placenta of male, but not female mice (Bronson and Bale, 2014), and prenatal SARS-COV-2 infection in humans impacts placental responses in a fetal sex-specific ways (some outcomes more common in the context of male fetuses than female fetuses, and vice versa) (Bordt et al., 2021). Perinatally, hormones play an important role in masculinization of the brain. Work by Margaret McCarthy and colleagues (Schwarz and McCarthy, 2008; VanRyzin et al., 2019; Lenz et al., 2013; Amateau and McCarthy, 2002) in rats has revealed is mediated via estrogen-induced activation of a pro-inflammatory signaling pathway involving cyclooxygenase-2 (COX-2) and production of prostaglandins (in particular, prostaglandin E_2; PGE2) is necessary for masculinization of the brain by perinatal estrogens. Therefore, by birth, the brain has already been relying on immune signals to regulate its biobehavioral development with regards to chromosomal sex, which persists in postnatal development. In rats, microglial development follows sex-specific timelines, with microglia colonizing the hippocampus earlier in males than females (Schwarz et al., 2012), and neonatal female microglia displaying more phagocytic activity and higher expression of phagocytosis-related genes compared to males (Nelson et al., 2017). In a recent study synthesizing myriad transcriptional factors that together indicate developmental maturation, microglial maturation was found to follow a precocious trajectory in female mice compared to males (Hanamsagar et al., 2018). This differential microglial development may have a number of consequences on brain development in males and females. For example, during the second week of life in mice (which we liken to late infancy/early childhood (Agoston, 2017); West, 1987), females reach an earlier peak in microglial volume and phagocytic capacity within the hippocampus, which co-occurs with more axon terminals and dendritic spines in the hippocampus of females compared to males (Weinhard et al., 2018).

These data collectively lay a strong foundation for immune mechanisms playing a role in sex-specific developmental plasticity early in life, but far fewer studies have been conducted to examine the effects of immune signaling in developmental plasticity during adolescence. In the following passages, we will review changes that occur in neural, hypothalamic-pituitary-gonadal and -adrenal, and microbiome systems during adolescence, and their reported or hypothesized interactions with immune signaling. Adolescence is a protracted developmental period, but has been primarily studied in preclinical literature by comparing a mid-adolescent/pubertal age to an adult age. There is a growing appreciation that adolescence is more complex than the processes occur during puberty alone. For example, studies using prepubertally gonadectomized animals have revealed that adolescent sex differences in hippocampal CA3 pyramidal neuron structure remain, suggesting that some sex differences cannot be simply explained by the effects of circulating gonadal hormones (Scharfman and MacLusky, 2017). Furthermore, in both humans and rats clear neural and behavioral profiles associated with different developmental stages across adolescence (Kopec et al., 2018; Paus, 2005; Paus et al., 1999). We will thus discuss system changes during early adolescence prior to puberty, mid-adolescence surrounding puberty onset, and late adolescence post-puberty, as three separate phases.

3. Pre-puberty early adolescence

3.1. Immune-neural interactions during pre-puberty early adolescence

The characteristic social, exploratory, and decision making changes that accompany entry into adolescence are thought to be in large part a result of developmental plasticity within dopaminergic 'reward' circuits in the brain, most notably in the ventral tegmental area (VTA), the nucleus accumbens (NAc) and the prefrontal cortex (PFC) (Spear, 2000; Schneider, 2013). Immune-mediated development within the reward circuitry during adolescence has only begun to be explored, but recent data suggest that sex-specific, immune-mediated developmental trajectories are important for reward circuitry development in adolescent rats. Microglia-mediated phagocytosis of synapses (i.e., synaptic pruning) occurs within the NAc reward region during pre-puberty early adolescence to regulate adolescent-typical social play behavior in both sexes (Kopec et al., 2018). Consistent with sex-specific early life developmental time courses discussed above, microglia-mediated synaptic pruning in the NAc occurred in females prior to males: at postnatal day (P)22 in females and at P30 in males (Kopec et al., 2018). Interestingly, NAc dopamine D1 receptors were a pruning target in males, but not females (Kopec et al., 2018). The female NAc pruning target, and how changes in local NAc synaptic architecture impacts circuit-level communication with other brain regions, is not yet known. These data indicate that the same immune process occurs during sex-specific

adolescent ages to regulate sex-*divergent* synaptic signaling in support of sex-*convergent* social development.

There is frequently a rapid over-expression of synapses or synaptic receptors prior to synaptic pruning during development, which is well documented for dopamine receptor expression during pre-puberty early adolescence in several reward regions in rats (Andersen et al., 1997, 2000; Tarazi and Baldessarini, 2000; Tarazi et al., 1999). In fact, dopamine receptor over-expression in the dorsal striatum was confirmed to be independent of gonadal hormones in rats of both sex via gonadectomies (Andersen et al., 2002). Adolescent dopamine receptor over-expression may be related to more recent reports of DCC-netrin-mediated dopaminergic axonal outgrowth, impulsivity, and behavioral response to addictive substances in male mice (Reynolds et al., 2018; Cuesta et al., 2020; Restrepo-Lozano et al., 2022). As yet, there is no link between synaptic overexpression and immune signaling, but microglia are important for dopamine neuron axon outgrowth earlier in life (Squarzoni et al., 2014). The intersection between microglia and dopaminergic outgrowth during adolescence remains to be explored. Since rapid or peak changes often indicate periods of heightened susceptibility to stimuli (Knudsen, 2004), these sex-specific developmental trajectories can offer insight into sex-specific influences of early life environmental exposures.

Finally, adolescence as a whole is known to be a period of vulnerability to addictive substances. Adolescents are the most likely population to be initiating drug use (SAMSHA, 2020), and the ongoing development in the reward circuitry, which is activated by addictive substances, compounds the effects of drug experimentation to promote long-lasting negative outcomes (Crews et al., 2007; Dow-Edwards et al., 2019; Spear, 2016). Interestingly, studies in rat and mouse models have revealed that there are some addictive substances that seem to have the strongest effect during pre-puberty adolescence, including delta-9-tetrahydrocannabidiol (THC) (Silva et al., 2016) and nicotine (Adriani et al., 2002; Smith et al., 2015; Yuan et al., 2015). The differential impact of nicotine during pre-puberty adolescence is supported in human epidemiology studies (Lanza and Vasilenko, 2015), and may be stronger in females compared to males across species (Lanza and Vasilenko, 2015; Chellian et al., 2020; Cross et al., 2017). Ethanol exposure also produces more long-term negative effects if administered during an early/mid adolescent time frame (P25–45) vs. a late adolescent time frame (P45–65) in rats, which appears to be a male-specific effect (Spear, 2015; Varlinskaya et al., 2020; Varlinskaya and Spear, 2006, 2004). These data further support the notion that there are unique developmental phases within adolescence (Spear, 2015). Although immune signaling is well known to be activated by addictive substances and plays a role in the process of addiction (Lacagnina et al., 2017), whether immune signaling is involved in a preferential pre-puberty early adolescent vulnerability to selected addictive substances is unknown.

3.2. Immune-HPG interactions during pre-puberty early adolescence

Gonadal hormones have widespread effects on the brain and behavior, and are re-activated during puberty via the hypothalamic-pituitary-gonadal (HPG) axis. Because levels of gonadal testosterone and estradiol are low during the HPG axis's quiescent period before puberty, behavioral differences between males and females are assumed to be negligible in juvenile animals. However, it has long been appreciated there are many opportunities for immune signaling to impact future HPG function (Grossman, 1985). Cytokines act directly and indirectly on gonadotropin releasing hormone (GnRH) neurons (Barabas et al., 2020; Wu and Wolfe, 2012). These inputs play their first role on the reproductive axis prenatally during the migration of GnRH-expressing neurons from the fetal olfactory placode, where they are synthesized, to the forebrain, where they will reside in the preoptic area of the hypothalamus. The immune mediators IL-6, monocyte chemoattractant protein 1 (MCP-1), and leukemia inhibitory factor (LIF) have been found on GnRH neurons and in cell lines modelling immature, migratory GnRH. MCP-1 and LIF were both found to induce chemokinesis (Magni et al., 2007; Zakharova et al., 2020). These data suggest a bidirectional relationship between the immune signaling and reproductive development early in the ontogeny of both systems. Indeed, neonatal LPS exposure delays puberty and alters kisspeptin expression, a protein important for puberty and fertility, in female rats (Knox et al., 2009). Whether early life is the only critical period during which immune signaling can influence pubertal timing, or if any pre-pubertal immune activation can impact puberty, is unclear. This will be particularly critical to understand, as age at puberty onset is decreasing (discussed in *Section 7*), and as we discuss herein, there are several developmental mechanisms specific to either pre-puberty early adolescence or post-puberty late adolescence that may be impacted should HPG axis be activated in aberrantly.

3.3. Immune-HPA interactions during pre-puberty early adolescence

Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, ultimately resulting in glucocorticoid release (cortisol in humans and corticosterone in rodents, hereafter collectively referred to as CORT). "Stress" is a broad term that can describe a number of different experiences, from psychosocial threat, to physical restriction or harm, to chemical stressors such as exposure to addictive substances. Stress increases during adolescence in humans due to a number of different factors in their changing family, social, and educational lives (Roberts and Lopez-Duran, 2019). HPA and sympathetic nervous system activity coordinate with the immune system to affect health and behavior; these responses are highly plastic and programmable during early life (see (Bilbo et al., 2012) for review), and manifest differently in males and females (Hanamsagar and Bilbo, 2016). Generally, early adolescent pre-pubertal mice and rats have a prolonged stress-induced CORT response relative to post-pubertal rodents, with few detected sex differences (Romeo et al., 2013, 2004a, 2004b, 2005; Romeo, 2010a, 2010b). For example, prepubertal male rats display greater and more prolonged CORT and adrenocorticotropic hormone concentrations following exposure to various acute stressors, like ether, foot shock, restraint stress (Romeo et al., 2004a, 2004b, 2005; Romeo, 2010a, 2010b).

Peripheral immune cells as well as microglia express receptors for CORT and the sympathetic-derived catecholamines, adrenaline and noradrenaline (Miller et al., 1994; Tanaka et al., 1997; Elenkov et al., 2000). The mineralocorticoid (MR) receptor, which binds CORT as well as aldosterone, has a permissive effect along with the adrenoreceptor to evoke pro-inflammatory activity upon acute stressors, while the glucocorticoid receptor (GR), which binds CORT with a lower affinity than MR, acts to return immune cells to homeostasis and suppresses pro-inflammatory activity in ensuing hours after an acute stress (Sapolsky et al., 2000). However, chronic stress leads to sustained high levels of CORT and therefore sustained GR binding, which can cause immune suppression in the periphery (Sapolsky et al., 2000; Dhabhar and McEwen, 1997). GR binding can also, however, prime cells for enhanced pro-inflammatory activity if the stressor occurs prior to immune challenge (Frank et al., 2007, 2012; Sorrells and Sapolsky, 2010), and microglial priming, at least in response to immune challenge, is reportedly especially long-lived when incited during early life (Bilbo and Schwarz, 2009). Consistent with this notion, rodent models of prolonged stress during adolescence have persistent immune consequences in adulthood (Bekhbat et al., 2019, 2021). While much work has been done identifying differential effects of neonatal and juvenile stress on male and female neuroimmune processes (Grassi-Oliveira et al., 2016; Ganguly et al., 2019; Gildawie et al., 2020a, 2020b; White and Kaffman, 2019), little is known about whether GR development or microglial priming is sex-specific during adolescence. One recent study, however, showed that pre-pubertal female piglets express enhanced upregulation of pro-inflammatory microglial genes in the hippocampus and

hypothalamus in response to the GR agonist dexamethasone (Murani et al., 2022), suggesting that juvenile female microglia might be more prone to GR-induced priming.

3.4. Immune-microbiome interactions during pre-puberty adolescence

The gastrointestinal (GI) tract contains approximately 1×10^{14} microorganisms (Gill et al., 2006; Qin et al., 2010), like bacteria, archaea, viruses and eukaryotic microbes that are collectively referred to as the gut microbiome. It can regulate host immunity, metabolism, neurodevelopment, and behavior (Jasarevic et al., 2017). The gut microbiome modulates central nervous system functioning through the gut-brain axis (Cryan and O'Mahony, 2011; Rhee et al., 2009). This bidirectional axis, involving endocrine, immune, and neural pathways, allows the gut microbiota to impact brain functioning and behaviour, but the extent of these communications is not fully understood yet (Cryan and Dinan, 2012; Gareau et al., 2011). Bacterial communities within the maternal vagina provide the primary inoculum that colonize the neonate gut during vaginal birth, which play an important role in offspring postnatal development and contribute to long-term health outcomes (Dominguez-Bello et al., 2010, 2016; Backhed et al., 2015; Palmer et al., 2007; Yatsunenko et al., 2012).

At pre-puberty early adolescence (weaning in rodents), the complex interactions between diet and nutrition, immune maturation, and gene-environment interactions induce further changes to the gut microbiota in mixed-sex mice (Rakoff-Nahoum et al., 2015). Interestingly, in these studies the impact of disrupted immune signaling on microbiome development was region dependent, with the highest impact in the colon occurring during pre- and early adolescence (P16, P26, respectively), and the highest impact in the small intestine occurring in mid/late adolescence (P42) (Rakoff-Nahoum et al., 2015). Host sex also modulates gut microbial composition at weaning (Markle et al., 2013; Yurkovetskiy et al., 2013). For example, weanling female mice have greater concentrations of Mucispirillum, Desulfovibrio, and Odoribacter compared to males (Rooks et al., 2014). Mucispirillum, Desulfovibrio, and Odoribacter are typically found in low concentrations in the healthy gut. An increase in the concentrations of these bacteria has been associated with inflammatory and neuroinflammatory diseases (Herp et al., 2021; Murros et al., 2021; Hiippala et al., 2020). Sex differences are also observed in humans during early infancy, girls display greater abundance of Firmicutes and reduced abundance of Bacteroidetes compared to boys (Huda et al., 2019; Martin et al., 2016; Sordillo et al., 2017). Firmicutes and Bacteriodetes are among the most abundant phyla in the human and rodent gut (Lay, 2021). While the functional implications of this sex difference warrants further investigation, it is possible that it may lead to improved nutrient availability, gut barrier functions, reduced inflammation, and greater resilience to environmental insults in females compared to males (Sanders et al., 2019; Jaggar et al., 2020). Finally, male mouse pups born to a dam that had been exposed to chronic high fat diet exhibit social deficits and gut microbiota dysbiosis (Buffington et al., 2016). Social deficits could be reversed via fecal microbiome transfer from typically developing mice if the transfer occurred during early adolescence (P28), but not late adolescence (P56) (Buffington et al., 2016). Social rescue associated with oxytocin-mediated plasticity deficits in the VTA (Buffington et al., 2016), a key node in the reward circuitry that develops during adolescence. The immune interactions associated with microbiome dysbiosis or rescue in this model are unclear, but microglia are highly sensitive to the microbiome (Thion et al., 2018). These data collectively suggest that the adolescent microbiome is not only developing during early adolescence, but may be a tractable vehicle to re-route earlier life developmental abnormalities.

4. Puberty and mid-adolescence

4.1. Immune-neural interaction during puberty and mid-adolescence

As discussed, our understanding of adolescence is by far most robust during mid-adolescence, when puberty occurs. Undergoing puberty fundamentally changes an individual's behavioral repertoire; thus unsurprisingly during puberty the brain undergoes significant reorganizing and remodeling, which are primarily driven by gonadal steroid hormones (Sisk and Foster, 2004; Levitt, 2003; Sisk and Zehr, 2005), including sex-dependent decreases in grey and increases white matter volumes in humans (Paus et al., 1999; Sowell et al., 1996; Bava et al., 2011). Adolescent boys tend to have greater white matter volume compared to girls (Perrin et al., 2008), while adolescent girls tend to have greater grey matter density in a number of cortical regions (Paus et al., 2010). There are also significant increases in hippocampal and amygdala volumes during early pubertal development across species (Giedd et al., 1999; Meyer et al., 1978; Romeo and Sisk, 2001). Several sex differences in brain structure and function can be directly linked to organizational effects of gonadal hormones during puberty. In fact, it has been proposed that the arrival of estrogens or androgens at the onset of puberty open critical periods for experience-dependent neural plasticity (Sisk and Zehr, 2005; Piekarski et al., 2017).

The effects of estrogen on drug seeking behavior at different developmental stages has been scrutinized using rodent models. In female mice, estradiol facilitates amphetamine- and cocaine-induced conditioned place preference and nigrostriatal dopamine release. Conditoned place preference for amphetamine and cocaine is diminished when females are ovariectomized, but is re-established with estradiol and progesterone treatment. Meanwhile, gonadectomized males were not affected by estrogen (Chen et al., 2003; Russo et al., 2003). In addition to establishing place preference for rewarding substances, estradiol also induces greater drug taking behavior, and this effect is determined by pubertal estrogen exposure. In gonadally intact adult females, estradiol increased cocaine self-administration. Females that were ovariectomized before puberty also self-administered more cocaine when administered estradiol in adulthood, but not if they were supplemented with estradiol during puberty (P27–37) (Perry et al., 2013). Therefore, the timing of estrogen exposure during development has programming effects on the adult response to estrogen, but it is not dependent on estrogen alone. Estrogen signaling within the NAc is necessary for this drug-induced conditioned place preference, specifically via estrogen receptor β, which induced greater cocaine conditioned place preference and cFos expression, a protein correlated with neural activity, in the NAc when activated (Satta et al., 2018). In addition to its role in early life sex differentiation, PGE2 immune signaling has been implicated in impulsive behaviors and, more specifically, the reinstatement of ethanol consumption after a period of abstinence. In a model of voluntary alcohol consumption, short periods of abstinence in mid-late adolescent female rats (P28–56) increased COX-2 and PGE2 in the dorsal striatum, and inhibiting COX-2 reduced ethanol consumption and PGE2 during reinstatement (Kline and Yamamoto, 2022). The relationship between PGE2 and impulsivity is hypothesized to be attributable to dopamine-PGE2 signaling in the striatum of male mice (Matsuoka et al., 2005). The PGE2 receptor subtype EP1 facilitates striatal dopamine D1 and D2 receptor signaling, and D1 and D2 agonists both stimulate PGE2 production (Kitaoka et al., 2007). This pathway is also related to impulsivity, as EP1-deficient male mice demonstrated more impulsive behavior, which was associated with increased dopamine turnover in the frontal cortex and striatum (Matsuoka et al., 2005). Male mice lacking EP1 also failed to demonstrate hyperlocomotion typically induced by cocaine- and D1 agonism. They also have impaired striatal dopamine signaling as indexed by reduced DARPP-32 phosphorylation at Thr34 (Kitaoka et al., 2007). These data suggest a relationship between inflammatory signaling via PGE2, also a key modulator of reproductive development, and dopamine-mediated motivated

behavior.

While adolescent drug exposure in preclinical models typically spans multiple phases of adolescence, as is the case in the examples discussed above, there is evidence that short-term (5 day) morphine exposure during mid-adolescence, but not late adolescence, impacts morphine conditioned place preference reinstatement in male rats (Schwarz and Bilbo, 2013). This effect required immune signaling in the NAc during morphine exposure, and in adulthood pubertal morphine exposure increased expression of proteins involved in the pro-inflammatory TLR4 signaling cascade, specifically in microglia in the NAc. Although female rats were not examined in this study, cFos expression patterns in reward regions show an abrupt and sex-divergent shift in response to morphine exposure at mid- vs. late adolescence (Figueroa et al., 2021). These data collectively suggest that hormone exposure during distinct sensitive periods contribute to the sex differences in drug taking behavior and responsiveness to the effects of hormones in adults.

Finally, the organizational effects of neonatal and pubertal testosterone also impact impulsive choice, a PFC-dependent behavior. Male rats have been found to exhibit more impulsiveness and poorer inhibitory control than female rats (Bayless et al., 2012, 2013; Jentsch and Taylor, 2003), but this depends on the age of the test and the type of task administered. One study found that pubertal adolescent males (P40) were more impulsive than females in a novelty-seeking task, and this sex difference was not apparent in prepubertal early adolescent (P28) or adult (P80) rats (Cyrenne and Brown, 2011). Interestingly, there is now convergent evidence that microglia are playing a role in PFC development during mid-adolescence that may be related to impulsivity. In studies assessing microglial pruning of PFC synapses throughout adolescence, there was a sharp decline in microglial/dendritic spine colocalization between P39 and P50 (Mallya et al., 2019; Schalbetter et al., 2022), and ablation of microglia locally in the PFC during mid-adolescence impairs several synaptic and cognitive outcomes (Schalbetter et al., 2022), suggesting that microglia contribute to adolescent shifts in neurostructural development and synaptic homeostasis in this region. Whether this is puberty-dependent effect in males has not yet been tested. Thus, while NAc and striatal development may be primarily occurring during early adolescence, PFC development may be primarily occurring during mid-adolescence. Males or mixed sex rats and mice were used in these studies making clear conclusions about sex differences impossible; however, there is one study suggesting female PFC pruning may actually occur in late adolescence, which we will discuss in the next section.

4.2. Immune-HPG interaction during puberty and mid-adolescence

Puberty is initiated by the peptide hormone kisspeptin (KISS), which is encoded by the Kiss-1 gene (West et al., 1998; Kotani et al., 2001). KISS initiates puberty by binding to GPR54 and increasing the pulsatile secretion of GnRH from the hypothalamus (Millar et al., 2010; Rhie, 2013). Modulation of the GnRH pulse frequency is the primary mechanism through which the HPG axis is activated and the maturation of the reproductive system is initiated (Sisk and Foster, 2004; Terasawa and Fernandez, 2001). Pubertal onset can be identified by an external marker of gonadal activity which is vaginal opening in females (Ojeda et al., 2003), and the separation of the prepuce from the glans penis (i.e. preputial separation) in males (Korenbrot et al., 1977). Puberty is considered complete at the onset of the first reproductive (i.e. estrous) cycle in females and first ejaculation in males (Vandenbergh, 1967, 1969). In mice, the pubertal period can last several weeks (Vandenbergh, 1967, 1969). However, in rats, the latency between these events may be quite brief, and may last only one day (Ojeda et al., 1976; Parker and Mahesh, 1976), suggesting a very short pubertal period in this species.

Immunity and reproduction are both energetically costly processes, and crosstalk between these systems are necessary to retain adaptive homeostasis. This relationship is supported by shared receptors and molecules between neuroendocrine and immune cells. Importantly, hypothalamic neuroendocrine cells contain cytokine receptors, and immune cells contain hormone receptors (Segner et al., 2017). KISS and RF-amide related peptide (RFRP) systems are also targets that could be mediating the effects of inflammation on GnRH suppression (Lee et al., 2019). LPS exposures decreases expression of Kiss1 mRNA and increases expression of RFRP and its receptor, GPR147 mRNA while suppressing circulating leutenizing hormone (LH) (Lee et al., 2019; Iwasa et al., 2014). RFRP receptors are found on GnRH and kisspeptin neurons, so this inhibition might be dually acting on GnRH directly and on KISS neurons innervating GnRH (Iwasa et al., 2014). PGE2 also plays a role in female reproduction, as COX inhibitors have been shown to suppress LH surges and ovulation (Ojeda et al., 1975; Labhsetwar and Zolovick, 1973). In vitro experiments of hypothalamic tissue have shown that PGE2-synthesis to trigger the first GnRH release from nerve terminals. Finally, estradiol itself increases PGE2-synthesis to trigger the first GnRH surge (Ojeda and Campbell, 1982). Remarkably, removal of the thymus, where immune T cells are primarily generated, early in life reduces sexual behaviors in both sexes without altering gonadal histology, pubertal timing, or hormonal levels in either sex (Bloom et al., 1992). The data raise the possibility that peripheral T cells are important during puberty for the emergence of sexual behaviors. Together, these findings demonstrate a link between inflammatory pathways and the programming of the reproductive system in males and females before and during puberty. The behaviors required for reproduction (mounting in males and lordosis in females) are linked to reward-related circuits, so the changes due to gonadal reproductive hormones are also fundamentally tied to other rewarding behaviors, reviewed in *4.1*.

4.3. Immune-HPA interaction during puberty and mid-adolescence

There are species-specific age and sex differences in stress reactivity and responsiveness of the HPA axis. Prepubertal inbred and outbred male mice show greater and more prolonged stress-induced CORT responses compared to adult males. In contrast, inbred female prepubertal and adult mice show similar stress-induced hormonal responses (Romeo et al., 2013). However, outbred Swiss-Webster adult females display a heightened CORT response compared to prepubertal females (Romeo et al., 2013). Adult female mice typically demonstrate greater CORT response following stress exposure compared to adult male mice (Harizi et al., 2007; Goel and Bale, 2008). Similar age differences in the stress response have also been observed in rats. Moreover, adult rats exposed repeatedly to same stress display a habituated or blunted stress responses (Girotti et al., 2006; Harris et al., 2004; Helmreich et al., 1997; Magarinos and McEwen, 1995; Marti and Armario, 1997) but male pubertal rats do not experience this habituation. Instead, pubertal rats experience greater peaks of ACTH, CORT and adrenal progesterone following repeated stress (Doremus-Fitzwater et al., 2009; Romeo et al., 2006). These age and sex differences in stress responses are likely due to differences in circulating gonadal steroid hormones at the onset of puberty, as there is no sex difference in HPA axis reactivity prior to puberty (Romeo et al., 2004a, 2004b). Nevertheless, these findings suggest species-specific sex differences in HPA axis reactivity in response to acute stress and highlight that gonadal steroid hormones begin to prime adult-like patterns of stress reactivity throughout puberty.

There are also age and sex differences in immune response during puberty, as the immune system undergoes maturation during puberty (Holder and Blaustein, 2014). In addition to pro-inflammatory cytokine induction, LPS increases COX-2 and prostaglandins (Beutler and Poltorak, 2000) and induces HPA axis activation by triggering the release of CORT (Suzuki et al., 1986; Sorrells and Sapolsky, 2007). Adult male mice display more sickness behavior and greater hypothermia following LPS treatment compared to their pubertal counterparts. Furthermore, both male and female adult mice display more pro-inflammatory cytokines following LPS treatment compared to pubertal mice, while pubertal mice display greater anti-inflammatory cytokines compared to

adult counterparts at 10 h post-injection (Cai et al., 2016). Adult female mice show greater serum CORT concentration compared to adult males and pubertal males and females at two hours post-LPS exposure (Girard-Joyal et al., 2015). LPS-treated adult male and female mice also display increased cFos expression in a number of forebrain regions compared to saline-injected controls. However, no difference in cFos expression was found between pubertal saline- and LPS-treated mice (Girard-Joyal et al., 2015). Follow-up studies suggest that while the pubertal mice appear hyporesponsive to immune challenge based on their peripheral immune response compared to adults, they mount a more rapid central immune response compared to adults following LPS treatment. For example, pubertal males displayed greater IL-1β, TNFα, and IL-6 mRNA expression in the PFC at 2 h compared to their adult counterparts, whereas adult males display greater cytokine mRNA expression at 8 h following LPS treatment (Sharma et al., 2018). These findings are consistent with other work showing a discrepancy between peripheral and central immune responses following infection (Sharma et al., 2018; Carvey et al., 2009). However, the direction of the age difference in central immune response appears to be species-specific. In rats, LPS treatment stimulates a more robust increase in IL-1β, IL-6, TNFα, and IκBα expression in the hippocampus, paraventricular nucleus, and amygdala of adult males relative to adolescents. Similarly, an ethanol exposure induced greater IL-6 and IκBα expression in the paraventricular nucleus and amygdala of adult male rats relative to adolescent counterparts (Doremus-Fitzwater et al., 2015).

Pubertal female CD1 mice display more activated microglia following LPS treatment than adult counterparts (Holder and Blaustein, 2014), suggesting that females are more sensitive to immune challenges during puberty/adolescence than in adulthood. Indeed, pubertal exposure to stress or immune challenge can cause enduring adverse effects on reproductive and non-reproductive behaviors, particularly in females. For example, exposure to a variety of stressors like heat, immobilization, or ether, during puberty, causes long-term negative effects on reproductive capacity in female mice (Paris et al., 1973). Similarly, pubertal exposure to shipping stress or LPS causes a long-lasting decrease in sexual receptivity in inbred and outbred mice, even following treatment with estradiol and progesterone. These effects were limited to mice exposed to shipping stress or LPS at 6 weeks of age, during the stress-sensitive pubertal period, as mice exposed to these stressors at younger or older ages did not display any change in sexual receptivity (Laroche et al., 2009a, 2009b; Ismail and Blaustein, 2013; Ismail et al., 2011). Moreover, social instability stress during puberty, in which the rat undergoes social isolation and a change of cage mate, increases anxiety-like behaviour and decreases social interaction in adult male rats (Green et al., 2013), suggesting that stressful experiences during puberty can have long-lasting effects on future stress responses in adulthood. Moreover, socially isolated adolescent male mice display reduced basal CORT levels but heightened CORT reactivity to a novel stressor compared to non-isolated controls (Ros-Simo and Valverde, 2012). Pubertal LPS treatment also causes an enduring increase in depression-like and anxiety-like behaviors, alters hippocampus-dependent learning and memory processes (Kolmogorova et al., 2019) and increased Parkinson-like behaviour (Girard-Joyal and Ismail, 2017) in a sex-dependent manner. The mechanisms underlying these LPS-induced enduring behavioral changes remain unknown.

4.4. Immune-microbiome interaction during puberty and mid-adolescence

Gut microbial diversity is highest during puberty and adolescence (Lozupone et al., 2012), with adolescent children displaying greater abundance of Bifidobacterium and Clostridium compared to adults (Agans et al., 2011). Research in mice shows that pubertal males display greater abundance of Bacteriodetes, Actinobacteria, and Candidatus Saccribacteria phyla compared to adult males. Similarly, pubertal females display greater Bacteriodetes, Cyanobacteria, and Candidatus Sacchribacteria phyla, and lower abundance of Firmicutes phylum, compared to adult females (Murray et al., 2020). While very few reports explore sex differences in gut microbiome profile during puberty and adolescence, the increase in gonadal steroid hormones during puberty appears to contribute to sex differences in the gut microbiota (Ober et al., 2008). Analyses of mouse microbial composition shows greater bacterial diversity in pubertal females compared to males (Yurkovetskiy et al., 2013). While sex differences in the gut microbiota are normal, they may play a role in the sex-dependent development and presentation of various diseases (Kim et al., 2020).

Exposure to pubertal stress alters the mouse gut microbiome in a sex-dependent manner. Treatment with LPS induces greater abundance of Verrucomicrobia phylum and reduced abundance of Bacteriodetes and Candidatus Saccharibacteria phyla in pubertal males and females compared to saline-injected controls. LPS-treated pubertal males also showed greater abundance of Deferribacteres and reduced abundance of Actinobacteria phyla compared to saline controls (Murray et al., 2020).

Stress-induced changes to the gut microbiota is referred to as gut dysbiosis and can lead to the development of various metabolic and inflammatory diseases, including obesity, Type 2 diabetes, intestinal bowel disease, anxiety, and depression (Murray et al., 2019; de Vos et al., 2022). However, LPS-induced changes in gut microbial composition are mitigated by pubertal probiotic treatment (Murray et al., 2020, 2019). These findings suggest that exposure to probiotics during puberty renders the gut more resilient to immune challenges, but the mechanism underlying the protective effects of probiotic remain to be investigated.

5. Post-puberty late adolescence

5.1. Immune-neural interaction during post-puberty late adolescence

Given the delayed maturation of several brain regions, including the frontal lobe (Gogtay et al., 2004), late adolescence following puberty and preceding adulthood, is an important period of neurodevelopment during which future circuitry and function is shaped. The maturation of amygdalo-cortical axonal projections begins to plateau in late adolescence (P45) (Cunningham et al., 2002), indicating a neurodevelopmental shift post-puberty that may underlie function such as affect regulation that have been shown to be driven by connectivity between the frontal lobe and amygdala (Banks et al., 2007). Post-pubertal adolescence is not only relevant in cortical development, however. For instance, in male rats different proteins associated with dopamine signaling reach peak expression in late adolescence (P45) in striatal and prefrontal regions involved in goal-directed behavior, while dopamine fibers continue to mature into adulthood (Naneix et al., 2012). This suggests that changes in the dopamine pathway between puberty and adulthood may drive the development of decision-making behavior.

Considerable increases in substance use, anxiety, and depressive symptomology occurs in late adolescence (Van Oort et al., 2009; Zapert et al., 2002; Smith et al., 2009). Clinical work has demonstrated important gender differences in symptom onset, where the likelihood of developing anxiety- and depressive-related symptoms is greater in post-pubescent girls (Dekker et al., 2007; Letcher et al., 2012; Ohannessian et al., 2017), while substance use tends to be more prevalent in boys (Young et al., 2002) during this period. PFC synaptic pruning is substantially increased in post-pubertal adolescence (P56) compared to puberty (approximately P35) in female mice (Evrard et al., 2021), while PFC pruning may occur earlier in males (discussed in previous section). Notably, prevention of this developmental shift in dendritic spine density instigates increases in anxiety-like behavior, signifying that typical neurodevelopment in late adolescence is a key factor in adolescent mental health post-puberty. Female PFC pruning has not (yet) been tied to microglia as it has been in males and mixed sex groups. This remains an open question. Alternatively, microglial contact with NAc dopamine receptors also peaks in late adolescence (P54) in females, but not male

rats (Kopec et al., 2018), which may result in as yet undetermined sex-specific alterations in behavior. Clinical work also shows that alcohol use in post-pubescent adolescents (15–17 years) corresponds with gender-specific deviations in PFC volume (Medina et al., 2008). In post-pubertal adolescent female mice, when estrogen is high during proestrous, binge-like ethanol exposure reduces long-term depression (LTD) in the hippocampus more than during low-estrogen phases. Although these adolescents had begun puberty, their response is distinct from adult and prepubertal females, demonstrating that hippocampal LTD is uniquely sensitive to estradiol and ethanol during postpubertal adolescence (Rabiant et al., 2021).

Finally, food seeking behavior is also regulated by estradiol and age. Over adolescence, male rat sensitivity for palatable food reward peaks at late adolescence (P50) and declines by adulthood (Friemel et al., 2010). This pattern was not seen in adolescent females, but adult females generally consume more palatable food than adult males (Marshall et al., 2017). In a paradigm associating a tone with delivery of sucrose solution, adolescent and adult female rats more quickly acquired Pavlovian approach than males, and male and female adolescents exhibited less sucrose seeking behavior than adults (Hammerslag and Gulley, 2014). In this experiment, adolescent rats were tested on P30, which is typically before full pubertal onset in males and females, so the shift to higher sucrose seeking in adults could be due to changes that occur due to puberty. Typical fluctuations in estrogen mediate sucrose seeking. On days with high estrogen, for example, females exhibit less reward seeking behavior, and ovariectomized females demonstrate increased reward seeking, which can be reversed with estradiol administration systemically or directly to the VTA (Richard et al., 2017). There are currently no data tying immune signaling with adolescent changes in food intake, but those interactions certainly exist in adult male rats (Park et al., 2008) and would be an interesting topic for future study.

5.2. Immune-HPG interaction during post-puberty late adolescence

To our knowledge, there is no literature on differential HPG function, development, or modulation specifically during the late adolescent, post-puberty period prior to young adulthood. However, after the initial development of the HPG system, glial cells continue to impact the reproductive axis, and inflammation is known to impair reproductive function in females (Barabas et al., 2020). The effects of inflammation on reproduction via GnRH and LH secretion occur through various mechanisms (Wu and Wolfe, 2012). LPS-induced inflammation suppresses the HPG axis by inhibiting GnRH and LH pulsatile secretion and disturbing the ovarian response to gonadotropin stimulation (Lee et al., 2019; Smith et al., 2021). IL-1β is the most effective modulator of GnRH and subsequent LH secretion (Barabas et al., 2020; Kalra et al., 1998). Systemic injection of IL-1β inhibits spontaneous cFos expression in GnRH neurons and reduces LH levels (Matsuwaki et al., 2014; Rivier and Vale, 1990). Intracerebral ventricular injection of IL-1β also down-regulates GnRH and GnRH receptor mRNA expression in the hypothalamic preoptic area and median eminence (Herman et al., 2012; Kang et al., 2000). Cytokines and immune mediators may also act directly on GnRH neurons, as microarray analysis has revealed that receptors for IL-1β and TNF-α, and prostaglandin are expressed on individual GnRH neurons (Jasoni et al., 2005). Microglia and astrocytes are found in close proximity to GnRH neurons in the preoptic area, as shown by double immunolabeling, which gives them optimal positioning for regulating immune responses on GnRH activity (Fujioka et al., 2013; Pellegrino et al., 2021). GnRH neurons in the preoptic area form long-term associations with astrocytes early in development (Pellegrino et al., 2021). Astrocytes play a role in neuronal development and secretory activity by secreting PGE2 to induce GnRH firing (Clasadonte et al., 2011). However, how astrocytes mediate GnRH during inflammation has not been explored. During an inflammatory event, estradiol exerts feedback on GnRH to mediate the effects of inflammation. At the beginning of the rise in estradiol, LPS prevents the LH surge that would be triggered by estradiol. Later in the cycle, closer to the peak of estradiol, LPS does not have an effect. This low-estradiol-dependent effect occurs by decreasing GnRH in the preoptic area to block preovulatory estradiol rise (Barabas et al., 2020). These data collectively demonstrate that immune signaling can modulate HPG function post-puberty, but whether there would be unique consequences in late adolescence relative to adulthood remain to be determined.

5.3. Immune-HPA interaction during post-puberty late adolescence

Post-puberty adolescence has been shown to be a unique period of HPA axis activity, where late adolescent (P50), but not early adolescent or adult, male rats exposed to stress display increased levels of CORT (Jankord et al., 2011). Clinical work points to important gender differences in late adolescent HPA axis changes. Post-pubertal girls demonstrate higher levels of basal circulating CORT than boys (Reynolds et al., 2013) not observed prior to or during puberty (Netherton et al., 2004). These gender-dependent changes in HPA axis development suggest that post-pubertal adolescence is a key sensitive period where environmental disruptions could have long-term consequences, specifically in girls. Evidence suggests that behavioral changes in post-pubertal adolescence may be, in part, regulated by changes in the HPA axis. For example, HPA reactivity modulates the increase in internalizing behavioral problems in late adolescent boys (Nederhof et al., 2015) and higher levels of CORT is associated with increased rates of depressive symptomology in girls, but not boys (Adam et al., 2010). In contrast, animal work has demonstrated a lasting depressive phenotype in females exposed to post-pubertal stress with a concurrent decrease in circulating CORT (Wulsin et al., 2016), suggesting that HPA axis changes in either direction may have lasting effects.

Work by Chiang and colleagues has elucidated the relationship between peripheral cytokine expression and HPA axis changes in post-pubertal adolescent humans. For instance, they found that major life events and daily interpersonal stress during late adolescence (18–20 years old) was associated with decreased CORT levels (Chiang et al., 2019a). No associations, however, were found between stress and circulating IL-6, suggesting that immune reactivity may not play a role in stress-induced changes in the HPA axis in late adolescence. Further assessment, however, revealed that increased symptoms of depression were associated with expression of glucocorticoid receptors and NF-κB that was independent of gender, implicating both immune and HPA axis changes in late adolescents experiencing depression (Chiang et al., 2019b). In rodents, while post-pubertal (P44) immune challenge via LPS exposure increased CORT levels in both males and female rats, this increase was higher in animals treated with LPS in adulthood (McCormick et al., 2020). Further, stress in late adolescence has been shown to prime the neuroimmune response to adult LPS treatment in males only; however, this effect was not associated with HPA changes (Pyter et al., 2013).

5.4. Immune-microbiome interaction during post-puberty late adolescence

Post-puberty adolescence may also be a period of change for various microbiomes throughout the body. After being similar throughout childhood, the oral microbiome of twins diverges in late adolescence into early adulthood, but does not seem to differ between girls and boys (Stahringer et al., 2012). Post-pubescent girls, however, have been found to be especially impacted by changes in the fecal microbiome (Leong et al., 2020). This may suggest that environmental factors affecting microbiota become more impactful in post-pubertal adolescence. Unfortunately, further evidence regarding microbiome changes in post-pubertal adolescence is lacking, primarily focusing on the distinction between pre-puberty and post-pubertal adulthood (Yatsunenko et al., 2012; Yurkovetskiy et al., 2013). These findings point to differences between early adolescence and adulthood in microbiome

diversity and lay the foundation for future work to identify the unique contributions of the post-pubertal stage of adolescence prior to the emergence of adulthood.

Recent work also points to an immune-microbiota relationship, where post-pubescent teenagers (14–18 years) with enriched oral microbiota had increased depressive- and anxiety-related symptomology that was moderated by circulating levels of C-reactive protein (Simpson et al., 2020). Further, immune challenge via LPS exposure in rats was found to have a sex-dependent impact on the fecal and colon microbiome, with differences in microbiota families in late adolescence (P46) vs. adulthood (McCormick et al., 2020). Immune signaling may, therefore, act as a key contributor to microbiome changes during late adolescence that has lasting behavioral impacts dependent on sex/gender.

6. Translational importance

The incidence of psychiatric mental illnesses, including anxiety, mood disorders, eating disorders, personality disorders, psychosis and substance abuse, increase substantially during puberty and adolescence (Paus et al., 2008). Major depression and bipolar disorder typically emerge during adolescence, with the peak age of 14 years for these mental disorders (Avenevoli et al., 2015; Kessler et al., 2005). However, the factors contributing to early onset of mental illnesses remain unclear. One possible explanation for the emergence of mental illness during adolescence is that the rapid neurodevelopment results in a heightened vulnerability of the CNS to certain biological/environmental factors including stress and inflammation (Holder and Blaustein, 2014; Kane and Ismail, 2017; Andersen, 2003). Immune signaling is likely to play a role in developmental vulnerability to mental health disorders, and in fact the number of infections requiring hospitalization during development is positively correlated with mental health disorder-associated behaviors (Kohler-Forsberg et al., 2019). We will briefly review two contemporary situations in which the interaction between immune signaling and biological systems undergoing adolescent development may be relevant for improving human health and wellness.

6.1. SARS-COV-2 and social isolation during adolescence

The role of immune signaling during adolescent development finds further clinical relevance in the COVID-19 pandemic, where isolation has been enforced around the globe to curb viral transmission. In many areas, continued or intermittent restrictions due to rapidly mutating viral variants have extended enforced isolation in adolescents. Moreover, it will be many years before the lasting impacts of COVID-induced isolation on these individuals. We can therefore look to animal research to glean the potential sex-dependent, long-term consequences of adolescent social isolation and the role of immune signaling. In rats, adolescent social isolation has been found to alter reward- and motivation-related behavior in a sex-dependent manner, where pair-housing reduces cocaine self-administration in females, but not males (Westenbroek et al., 2013). Another study in mice, however, reported increased cocaine-seeking in males only (Fosnocht et al., 2019), which may speak to strain differences and complicate translatability to the human experience. Evidence also suggests that post-weaning social isolation alters immune-microbiota interactions (Dunphy-Doherty et al., 2018) and has been found to be sex-dependent (Lopizzo et al., 2021). Further, social isolation increases microglia number (Schiavone et al., 2009) and activation (Wang et al., 2017); however, this has been demonstrated in both males and females (Hermes et al., 2006). Direct evidence regarding the role of immune signaling on reward-related behaviors is limited; however, hippocampal microglia signaling has been found to regulate isolation-induced depressive-like behavior (Wang et al., 2017). Finally, studies in male mice suggest that social isolation is more detrimental if occurring at early adolescent stages vs. later adolescent stages (Makinodan et al., 2012; Locci et al., 2017).

Across age in humans, the perceived quality and quantity of relationships was reduced following shelter-in-place and lockdown orders during the initial wave of the pandemic (Buecker, 2022). This perceived reduction in social interaction was more prominent in men than women, suggesting potential gender-dependent effects of social isolation on relationships. Given existing data linking loneliness and symptoms of depression and anxiety in children and adolescents (Laursen and Hartl, 2013; Loades et al., 2020), this age range may be at heightened risk of adverse mental health outcomes following COVID-induced social isolation. Several studies have found an increase in self-reported loneliness in adolescents during COVID-19 that was associated with a decline in mental health (Alt et al., 2021; Cooper et al., 2021; Rogers et al., 2021; Lee et al., 2020). Adolescents aged 14–17 years (~mid-adolescence) reported a decrease in contact with friends, resulting in strained relationships and a perceived reduction in social support, which was associated with increased loneliness, anxiety, and depressive symptomology (Rogers et al., 2021). In contrast, these adolescents also experienced an increase in time spent with family. Notably, adolescents with closer relationships with their parents reported lower levels of loneliness and those from lower income households reported more familial conflict. This suggests that socioeconomic status plays an important role in the impact of COVID-induced isolation on adolescents.

Researchers have predicted that COVID-related loneliness and changes in mental state may impact adolescent substance use (Sarvey and Welsh, 2021). While the rate of adult binge drinking (Weerakoon et al., 2021), substance use (Czeisler et al., 2020; Horigian et al., 2021), and opioid overdose (Slavova et al., 2020) increased substantially in the first months of the pandemic, there is a lack of data relating specifically to adolescent increases in substance use and how effects may differ between girls and boys. Moreover, increased loneliness in adolescents experiencing enforced isolation was associated with elevated CORT levels at waking (Jopling et al., 2021), implicating the HPA axis in the response to social isolation during lockdown and suggesting a potential role for neuroimmune signaling. While direct evidence linking COVID-induced isolation with immune response is lacking, past work indicates that lonely individuals had a larger immune response following a stress exposure (Jaremka et al., 2013). Moreover, exposure to COVID itself can result in enhanced cytokine levels in children and adolescents, despite the lower rates of infection in this age range (see (Jiang et al., 2020) for review). Given the link between depression, loneliness, and substance use in adolescence (see (Ingram et al., 2020) for review), it will be critical for future studies to determine how immune signaling underlies the sex- and gender-dependent effects of COVID-induced isolation.

6.2. Decreasing age at puberty

The age of pubertal onset in girls, defined by age of thelarche, has declined at a rate of 3 months per decade from 1977 to 2013, with median ages of Tanner Breast stage 2 ranging from 8.8 to 13.2 years old in studies from around the world (Eckert-Lind et al., 2020). The timing for the initial onset of puberty has important implications for physical and mental health, and racial disparities in the vulnerability to earlier puberty escalates the importance of understanding the risks associated with early puberty. It is well-established that early puberty is more prevalent in Black girls compared to other races, and the association between early life household instability and earlier puberty was found to be stronger in Black girls compared to White, Hispanic, Latinx, and Asian/Pacific Islander girls (Aghaee et al., 2020). This study defined early puberty as menarche before age 12. Bliel et al (Bleil et al., 2017). proposed a preliminary model representing racial disparities in risk factors, such as early life adversity, as mediators of the pathway by which differences in puberty timing may arise. More research is beginning to address this gap in knowledge regarding differences in health outcomes between races, but further study is needed to elucidate specific

mechanisms in different populations.

Puberty occurs during a significant period in social development, making both early and late deviations from typical acquisition of pubertal milestones psychologically distressing. Early maturing girls are at a greater risk for affective disorders, including depression, anxiety, and eating disorders, as well as earlier drug use and behavioral disorders (Angold et al., 1998; Mendle et al., 2019). In a large cross-sectional study of Black children with high trauma exposure, girls showed a strong association between early puberty and anxiety symptoms when controlling for different levels of trauma exposure (Stenson et al., 2021). Boys who begin puberty earlier are more susceptible to externalizing symptoms than girls, while late-maturing boys show more depressive symptoms (Graber, 2013). These may be mediated by other psychological factors, including self-esteem, psychological distress, and social interactions, but no clear pattern has emerged to identify a single psychological mediator of these disorders (Ge, 1996; Kaltiala-Heino et al., 2003; Orr and Ingersoll, 1995).

Most cases of central precocious puberty are deemed idiopathic and stem from early pulsatile GnRH release. Peripheral precocious puberty is due to abnormal sex steroids production at the level of the gonads is more rare (Carel et al., 2004). Atypical pubertal timing raises several health concerns, including heightened risk for breast, ovarian, endometrial, and prostate cancers as well as cardiovascular disease, diabetes, and infertility (Golub et al., 2008). The most direct clinical impacts of early or delayed puberty are related to growth and bone health. For example, precocious puberty causes bones to mature more rapidly, leading to a shorter final stature in untreated girls. precocious puberty can be treated with GnRH agonists, with the main outcome measure for treatment being adult height compared to predictions based on bone age at the time of puberty (Jung et al., 2014).

Earlier age at puberty could be due to a number of environmental factors experienced during childhood. Because pubertal shifts are particularly evident in developed countries, trends towards earlier puberty are thought to be due to improved living standards, namely their effects on nutritional status. Rapid weight gain in childhood is associated with earlier breast development and menarche in girls, whereas low weight is associated with delays in puberty and reproductive suppression. In boys, higher weight has been associated with later pubertal maturation (Soliman et al., 2014). Endocrine disrupting chemicals (EDCs), both naturally-occurring and synthetic, can interfere with hormonal functioning and alter pubertal timing. The EDCs most widely implicated in puberty are bisphenol A (BPA), phlalate esters, pesticides, polychlorinated biphenyls, and flame retardants (Rasier et al., 2006). Girls diagnosed with idiopathic precocious puberty have been found to have higher levels of urinary BPA or phalates (Bulus et al., 2016; Durmaz et al., 2014; Supornsilchai et al., 2016). Many of these EDCs exert their effects on the HPG axis by mimicking naturally-occurring estrogens and androgens, acting as agonists of estrogen receptors or antagonists of androgen receptors (Combarnous and Nguyen, 2019). EDC exposure, prenatally and postnatally, can impact pubertal development in males and females (Greenspan and Lee, 2018), and accumulating exposure to combinations of chemicals creates similar risk (Kortenkamp, 2007). EDCs use is regulated in many countries, but there is still a lack of consensus on how EDCs are identified and strategies to monitor and reduce exposures worldwide (Kassotis et al., 2020).

In addition to their HPG effects, EDCs have been linked to altered immune responses in children and adults, which can lead to immune-related diseases. For example, BPA concentrations in children 3, 5, and 7 years old were associated with increased asthma (Donohue et al., 2013). In mice, BPA exposure during pregnancy was shown to activate innate and adaptive immune system pathways in offspring until the second generation (F2) (Sowers et al., 2020). Additionally, polychlorinated biphenyls (PCBs) have been shown to have immunosuppressive effects, and developmental exposure is implicated as a cause of immune deficiency in children (Serdar et al., 2014). Interestingly, in rats, PCB exposure in utero altered the expression of immune related genes in the hypothalamus and PFC differently in males and females (Liberman et al., 2020). Rodent work has also found that EDC exposure alters microglial colonization in several brain regions, and in sex-specific ways (Rebuli et al., 2016). These immune-related consequences may be due to direct influence of EDCs on immune cell signaling pathways in addition to their indirect estrogenic effects.

Finally, childhood adversity, particularly familial instability and lower socioeconomic status, has been linked to early puberty onset in girls (Jorm et al., 2004; Moffitt et al., 1992). In fact, in one study early pubertal timing mediated the association between lower socioeconomic status and poor attention (Stumper et al., 2020). Experiencing familial stress as well as early pubertal maturation predicts greater depression and anxiety symptoms after puberty (Rudolph and Troop-Gordon, 2010; Winer et al., 2017). Stressful childhood experiences are thought to precipitate atypical pubertal timing by altering HPA axis development, but no specific link between adversity, stress, and sexual maturation has been identified. Because childhood adversity and precocious puberty both pose greater risk for psychiatric disorders later in life, and these two vulnerabilities may be causally linked, it is crucial to understand the mechanistic links between environmental factors leading to disrupted interconnected HPA and HPG axes and the impacts of immune modulation.

7. Conclusions

In summary, age, sex, and interaction between biological systems are important factors to consider when assessing adolescent and pubertal outcomes across species. We propose that immune signaling, though less well studied during adolescence, may be crucial to enact adolescent developmental outcomes and mediating the interaction between experience and adolescent development.

7.1. The importance of intersectionality

Although we organized this review to emphasize unique developmental periods within adolescence, it would be remiss to not note the intersectionality between the biological systems we chose to survey. Neural, HPG, HPA, and microbiome developmental plasticity does not occur in a vacuum, and in fact each of these systems is intimately tied with one another. This is especially evident in the face of stressors or other environmental or situational challenges during development, which can simultaneously alter both the long-term developmental trajectory and acute function of all of these biological systems. We have noted several areas of overlap as we discussed the adolescent developmental trajectories of, and immune interaction with, each of these systems, but it is worth noting that overlap more discretely here as proof of principle. For example, we discussed how peripheral immune activation via LPS (or, in theory, any other stimulus capable of activating TLR4s) alters the diversity of the gut microbiome (Murray et al., 2020), increases CORT levels (Suzuki et al., 1986; Sorrells and Sapolsky, 2007), modulates KISS expression levels (Lee et al., 2019; Iwasa et al., 2014), and can modulate immune signaling in the brain (Sharma et al., 2018; Carvey et al., 2009). These systems should be viewed as links in a chain: if you pull on one link, you pull them all, even if only indirectly. As such, plasticity in one system is undoubtedly going to have consequences on another system, and may in fact be a result of upstream plasticity in a system not being assessed.

Likewise, development is a fluid progression through various stages, with earlier developmental events serving as a foundation for later maturation. Early life developmental events certainly provide a foundation for adolescent development. For example, prenatal exposure to stress or maternal immune activation yields pro-inflammatory activity in the placenta of male, but not female mice, with an associated male-specific increase in PFC dopamine D1 receptor expression, NAc dopamine D2 receptor expression, and hyperactivity in adult offspring (Bronson and Bale, 2014). While the PFC and NAc undergo copious

development during adolescence, their developmental trajectories do not start and stop within adolescence. Similarly, male rats castrated soon after birth, at P1 or P6, have reduced social play, but males castrated at P20 demonstrate normal social play behaviors (Beatty et al., 1981). Early life hormone signaling (via immune mechanisms) organize future adolescent social play behavior, but we have also reviewed that pre-puberty early adolescent immune mechanisms in the NAc also impact social play behavior. We argue that earlier adolescent periods should be more thoroughly assessed for their organizational effects on later adolescent periods. For example, NAc and striatal synaptic development appears to occur primarily during pre-puberty early adolescence, while PFC synaptic development occurs later. Does NAc synaptic development impart foundational effects on which PFC synaptic development occurs, or are they two independent events? It is equally likely that early adolescent development may impact later adolescent development, which in the case of precocious puberty may become an increasingly prevalent question in society. One thus needs to consider not just intersectionality between co-developing biological systems, but intersectionality between an early life and later life developmental periods, both within the same system and between systems.

7.2. Musings and lessons learned from the current state of adolescent biology

Finally, we would like to impart some lessons that we learned as we crafted this review:

1. Adolescence should not just be a euphemism for puberty. There are clear, gonadal hormone-independent events during adolescence that occur both prior to and after puberty.
2. PGE2 and COX signaling may be a ubiquitous upstream developmental event by which immune signaling can modulate multiple different biological systems.
3. Because males and females often have divergent developmental trajectories, it is prudent to conduct a developmental time course to ensure that development in both sexes can be appropriately captured.
4. Relatedly, when administering a manipulation during adolescence, consider comparing its impact across adolescent stages, as one might gain more specific insights to direct future studies, which we have observed with addictive substances and social isolation.
5. When possible, assessing other biological systems could provide important information. For example, have KISS or corticotropin releasing hormone levels changed in the hypothalamus in your model, reflecting HPG or HPA axis changes, respectively?
6. Time courses after a single challenge, e.g. LPS, at different stages of adolescence may be a good way to probe developmental plasticity across systems.

In sum, to better understand adolescent development and its consequences for health outcomes, it will be important to unite cross-disciplinary scientific expertise to assess multiple biological systems in parallel.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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