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Immune signaling in sex-specific neural and behavioral development: Adolescent opportunity

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Abstract

Sex differences in neural and behavioral development are integral to understanding neurodevelopmental, mental health, and neurodegenerative disorders. Much of the literature has focused on late prenatal and early postnatal life as a critical juncture for establishing sex-specific developmental trajectories, and data are now clear that immune signaling plays a central role in establishing sex differences early in life. Adolescence is another developmental period during which sex differences arise. However, we know far less about how immune signaling plays a role in establishing sex differences during adolescence. Herein, we review well-defined examples of sex differences during adolescence, and then survey the literature to speculate how immune signaling might be playing a role in defining sex-specific adolescent outcomes. We discuss open questions in the literature and propose experimental design tenets that may assist in better understanding adolescent neurodevelopment.

Introduction

Although once considered immune privileged, there is now copious evidence that the brain is influenced by unique immune signaling profiles. Microglia are the resident immune cells of the brain, but other glial cells, infiltrating peripheral immune cells and even neurons have immune signaling properties. Developmental processes mediated by immune signaling include synaptogenesis and regulating synaptic connectivity, cell and axonal migration, remodeling dendritic complexity, synaptic pruning, and apoptotic clearance [1]. Most of these processes display sex differences. In fact, some of the most fundamental sex differences require immune signaling: the male brain is masculinized by testicular androgen secretion around the time of birth, which is converted to estradiol via aromatase. Estradiol increases prostaglandin E2 immune signaling in the brain to promote male-specific microglial remodeling in multiple brain regions [2, 3]. These early life immune events give rise to sex-specific behaviors later in life. However, sex differences in neural and behavioral outcomes are not solely established in prenatal and early postnatal life. Another crucial developmental period during which numerous sex

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differences emerge is adolescence. Adolescence is a period of rapid development across the brain, most notably the dopaminergic 'reward' circuitry, and is characterized by increased exploration, risk-taking, and peer-centered social behaviors [4-7]. Adolescence begins prior to and extends beyond puberty, which brings forth secondary sexual characteristics [8], in totality encompassing multiple years in humans and multiple weeks in rodents (Fig. 1) [5, 9]. Despite the central role that immune signaling plays in establishing sex differences during prenatal and early life, how immune signaling might contribute to sex differences established during adolescence is less well studied. We propose that just as immune signaling provides a molecular framework for establishing sex differences early in life, immune signaling may also be a crucial contributor to sex differences during adolescent development (Fig. 2) that provides an opportunity for investigation.

To focus this review, we will discuss sex differences that arise from adolescent developmental plasticity in which both a behavioral/physiological outcome *and* its underlying neural mechanism has been defined. For each example, we will then survey the literature to speculate how immune signaling might be playing a role in defining the sex-specific adolescent outcome. Classification of sex-specific outcomes into groups that distinguish specific features may be helpful for a deeper understanding of sex differences [10], and thus we will further organize this discussion by type of sex difference (Fig. 3). Finally, we will discuss open questions in the literature and propose experimental design tenets that may assist in better understanding adolescent neurodevelopment.

Sex dimorphism during adolescence

We will begin with a discussion of the most stark sex differences, sex dimorphism, which we define as when a behavioral/physiological outcome and its underlying mechanistic processes both diverge by sex. The most classic example of sex dimorphism during adolescence is the effect of puberty-initiated gonadal hormones, which result in several sociosexual behaviors as well as the onset of fertility. Puberty occurs when gonadotropin releasing hormone (GnRH) release activates the hypothalamic-pituitary-gonadal axis, resulting in gonadal hormone production. The neuropeptide kisspeptin is important for puberty initiation [11-14], and may be sex-specific. In humans and other mammals, kisspeptin treatment directly stimulates GnRH neurons [15-17]. Kisspeptin neurons are predominantly found in two hypothalamic areas, the arcuate nucleus (ARC) and the anteroventral periventricular and periventricular nuclei (AVPV/PeN) [18-20]. In females, *Kiss1* and kisspeptin expression increases throughout development in both the AVPV/PeN and the ARC nuclei, particularly around puberty and first estrous [21]. In males, *Kiss1* and kisspeptin in the AVPV also increases across development, but females express more kisspeptin than do males in this region. Unlike females, males do not show a clear increase in *Kiss1* and kisspeptin expression in the ARC nucleus throughout development [17, 21, 22]. Thus, while kisspeptin appears to be important for puberty initiation in females, male puberty may be dependent on absolute changes in kisspeptin levels and involve other signaling factors. A strong relationship between immune and kisspeptin signaling is observed in adult rodents [23-25], but a recent study was the first to examine this relationship during puberty. Pro-inflammatory immune activation via lipopolysaccharide (LPS) treatment in pubertal male and female mice decreased hypothalamic *Kiss1* in both sexes, though the magnitude of

decrease was larger in females due to their higher baseline expression [26]. These data suggest that puberty initiation, which in turn instructs a plethora of sex differences, can be modulated by immune signaling. Indeed, studies examining patients with irritable bowel syndrome and Crohn's disease, both associated with chronic inflammation, indicate puberty is delayed, which in the case of Crohn's disease can be treated by reducing levels of the pro-inflammatory cytokine TNFα [27, 28]. These data suggest that pro-inflammatory immune signaling *can* modulate kisspeptin expression and puberty onset, but whether natural, non-sickness related immune signaling is an important regulator of kisspeptin and/or puberty has not yet been determined. Either abnormally early or late puberty onset is associated with a number of negative mental health outcomes in both sexes [29]. Female puberty onset occurs about one year earlier than was average in 1977 [30]. Thus, it is important to understand how puberty onset might be regulated, and immune signaling, activated by any number of stressors, may be important lines of research in the coming years.

There are also less obvious sexually dimorphic events occurring during adolescence. A recent report [31] found that prior to puberty, female mice have better spatial memory task performance and lower LTP threshold in the hippocampus than males, which is reversed after puberty. The behavioral and neural change in females was due to female-specific increases in α5 $GABA_A$ receptor-containing synapses, whereas the behavioral and neural change in males was not related to α5 $GABA_A$ signaling. Pro-inflammatory immune challenge via LPS or ethanol increases GABAergic signaling, at least in part through increased expression of $GABA_A$ receptors in mixed sex and male mice, respectively [32, 33]. Pharmacologically manipulating microglia was sufficient to reduce $GABA_A$ receptor levels and GABAergic signaling in response to both LPS and ethanol challenge. Whether there is a female-specific increase in microglial immune signaling that supports increased $GABA_A$ receptor-containing synapses during adolescence is unknown. Interestingly, there is also a recent report that a subset of microglia which express GABA receptors are selectively tuned to monitor and prune inhibitory synapses during normal cortical development [34]. Whether GABA-receptive microglia could instead increase synaptogenesis of GABAergic synapses is unclear, though microglia are known to induce spine formation during somatosensory development [35].

Convergent sex differences during adolescence

We define convergent sex differences to be when either (*a*) the behavioral outcome is the same or similar across sex but the underlying mechanisms diverge by sex, or (*b*) the neural mechanism is the same across sex but the resultant behavior diverges by sex. There are now several studies that show convergent sex differences in the regulation of social play during adolescence. Social play peaks during adolescence and declines into adulthood, and is considered a hallmark of adolescent development in several mammalian species; both sexes express social play, though it is typically more pronounced in males relative to females [36]. A recent study demonstrated that sex-specific immune signaling mediates social play in both sexes [37]. Complement C3, an immune protein, and microglia mediate synaptic pruning during the development of several brain regions. C3-microglia-mediated pruning also occurred in the nucleus accumbens reward region in both male and female rats, but during sex-specific periods: pre-early adolescent females (postnatal day (P)20-30)

and early-mid adolescent males (P30-38). This observation is in line with females tending to develop earlier than males during adolescence. In males, microglia-mediated pruning eliminates dopamine D1 receptors, consequently reducing social play behavior. Interfering with complement signaling increased D1 receptors and social play in males. Interfering with complement signaling also increased social play in females by the same magnitude as males, but this was D1 receptor independent. These data suggest that pruning impacts social play in both sexes, but via sex-specific synaptic receptor regulation and during sex-specific adolescent periods. Microglia-mediated pruning also occurs in the prefrontal cortex during adolescence [38, 39], but current studies have not explicitly tested whether there are sex differences in this process.

The lateral septum is also critical for social play in both sexes, via complex, sex-specific neural mechanisms. Social play increases both GABA and glutamate release in the lateral septum of both sexes. Blocking $GABA_A$ receptor signaling in the lateral septum reduces play in both sexes, but blocking glutamatergic signaling (both NMDA and AMPA signaling) reduces play in females only [40]. Additionally, blocking vasopressin receptors (V1aR) in the lateral septum increases social play in the home cage in males and decreases social play in the home cage in females [41]. Surprisingly, this was context-dependent, and blocking V1aRs in the lateral septum did not affect social play in a novel cage in either sex [42]. These data suggest there is an important and largely unexplored interaction between physical context and behavioral endpoint that can mediate sex-specific neural processing. Social play also increased dopamine release within the lateral septum in females, but not males, but blocking dopamine receptors in the lateral septum decreased social play in both sexes. The authors conclude that basal dopamine signaling in lateral septum is important for male social play, but evoked dopamine signaling in lateral septum is important for female social play [43]. Immune signaling is well known to induce vasopressin release in hypothalamus and amygdala [44-46], but this has not been examined in the lateral septum. Prenatal immune activation, which impacts social play behavior in a sex-specific manner, also reduces vasopressin mRNA levels in a sex- and region-specific manner [47] and increases microglia in the lateral septum in females [48]. In general, the role of immune signaling in the lateral septum is entirely unknown.

Just as physical context is important for the relationship between neural signaling and behavior, so too is social context. Both adult male and female rodents are particularly attuned to the opposite sex. In fact, in adult mice, ~80% of medial amygdala (MeA) neurons in both sexes preferentially respond to the opposite sex, a selectivity that only develops after adolescence. Aromotase knockout in male mice abolished this selectivity in adulthood, and early life masculinization with estradiol injections in female mice increased the number of female-responsive neurons [49]. These data suggest that in males, early life masculinization, an immune-dependent event (reviewed above), interacts with adolescent development to produce opposite-sex selectivity in the MeA. The mechanism in females is unclear. Prairie voles are an interesting species in which to study opposite sex behaviors, as they form monogamous pair bonds [50]. Peripheral immune activation with LPS can facilitate partner preference in female, but not male prairie voles [51], though the neural mechanisms underlying this effect are unclear. Taken together these data suggest that both natural and experimentally-activated immune signaling can play a modulatory role in

opposite sex-focused behaviors. Whether immune signaling is important for neuronal tuning to *any* stimulus is an open question, but would be of broad interest across neuroscience disciplines.

Quantitative sex differences during adolescence

We define quantitative sex differences to be when the behavioral outcome and its underlying mechanistic processes are the same, but either the behavior or mechanistic process differs in quantity by sex. Examples of quantitative sex differences in which there is a well-defined relationship between behavioral endpoint and underlying neural mechanism are scarce. For example, while social play is widely recognized to differ in quantity by sex (males>females), there also appears to be clear sex differences in the mechanisms underlying play, as reviewed above. One example of a quantitative sex difference was uncovered in a study examining the effects of vasopressin signaling in the lateral septum on social discrimination and investigation, rather than play. Blocking V1aRs in the lateral septum in adolescent rats did not impact social discrimination, but increased investigation of a novel vs. familiar stimulus in both sexes. However, the increase in novelty-centered investigation was larger in males than in females, which was unique to adolescent animals relative to adults [52]. It is unclear whether adolescent lateral septum vasopressin signaling is a negative regulator of novelty-centered investigation, a positive regulator of familiarity-centered investigation, or some combination. There is, however, evidence that familiarity may be more salient to female rats: female rats will engage in more social play with a familiar social partner vs. a novel partner, while male rats will play equally regardless of familiarity of conspecific [53]. There is interesting evidence in humans suggesting immune signaling is important for motivation to be near familiar vs. unfamiliar individuals. LPS injection in humans too low to induce overt sickness behaviors increased desire to be near family members vs. strangers, which was positively correlated with peripheral IL-6 pro-inflammatory cytokine levels and BOLD fMRI activity in the nucleus accumbens [54]. Moreover, a recent human neuroimaging study showed that activity in the nucleus accumbens also correlated with the shift in responsivity from a familiar (mother's) voice in childhood to a novel voice in adolescence [55]. How the neural signaling underlying familiarity-induced preference changes during adolescence has not been examined to our knowledge, but immune signaling may be a good starting point.

Sex divergence with unclear mechanism or behavior: Opportunities

Many adolescent data show a sex difference in either behavior or mechanism, but the behavior-mechanism relationship is not fully defined and thus does not fit clearly into one of the former three categories. These data represent an *experimental opportunity*. For example, prepubertal gonadectomy resulted in increased neuron numbers in females [56], and increased spine density in males [57]. Microglia were recently shown to be important for synaptic homeostasis during adolescence in the prefrontal cortex of male rats, which had several cognitive implications [39]. Whether immune signaling is important for sex-specific prefrontal cortex neuron numbers, to what behavioral consequence this contributes, and whether microglia also mediate synaptic homeostasis in females, are all undetermined. There are also data indicating that dopamine receptor overexpression during adolescence,

a frequent developmental program prior to pruning, is more robust in males than in females in several brain regions [58, 59], resulting in long-term sex differences in dopamine receptor expression (males>females). How this occurs and its behavioral consequences are unclear. However, dopaminergic axon outgrowth during adolescence is an important process mediated by netrin and its receptor, DCC (Deleted in Colorectal Cancer) in male mice [60]. Earlier in life, microglia are important for dopaminergic axon outgrowth [61], but whether immune signaling is important for netrin/DCC-mediated outgrowth during adolescence, and whether the process occurs in females, is unknown.

Conclusions

Several psychiatric disorders emerge during adolescence in sex-specific ways [62], and basal sex differences in neuro-immune signaling has been hypothesized to underlie sex-specific vulnerability to psychiatric disorders [63]. Studies exploring sex specific adolescent neurodevelopment are vital to our understanding and interpretation of clinical observations. Post hoc classifications of sex differences is one way to formalize collective knowledge and quickly identify opportunities to fill gaps in the literature. Existing data emphasize some key design points for future studies, including (**1**) prospective use of sex as a biological variable, (**2**) selecting behavioral tasks matched to the brain region under investigation (or vice versa) to assess mechanism-behavior concordance, (**3**) consideration of a developmental time course given that females develop earlier than males across species, and (**4**) examining physical- and social context-dependency in endpoints. We propose that immune signaling is often a good candidate mechanism to explore, as it is quickly becoming relevant to every healthy and pathological biological state, both neural or non-neural in nature.

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***** Of special interest

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Highlights

- Immune signaling is important for establishing sex differences early in life.
- Sex differences are influenced by, and emerge during, adolescence.
- The role of immune signaling in adolescent sex differences is under studied.
- Immune signaling presents an opportunity to explore adolescent sex differences.

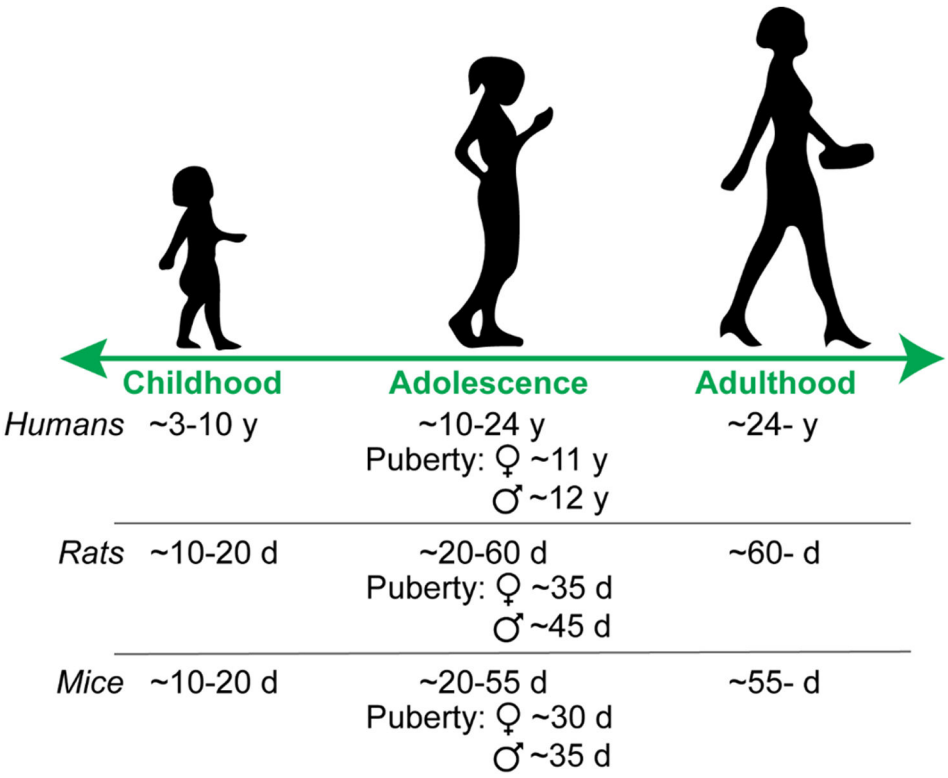

Fig. 1: Approximating adolescence across species.
Ages are broad estimates from the literature [5, 9]. y = years, d = postnatal days.

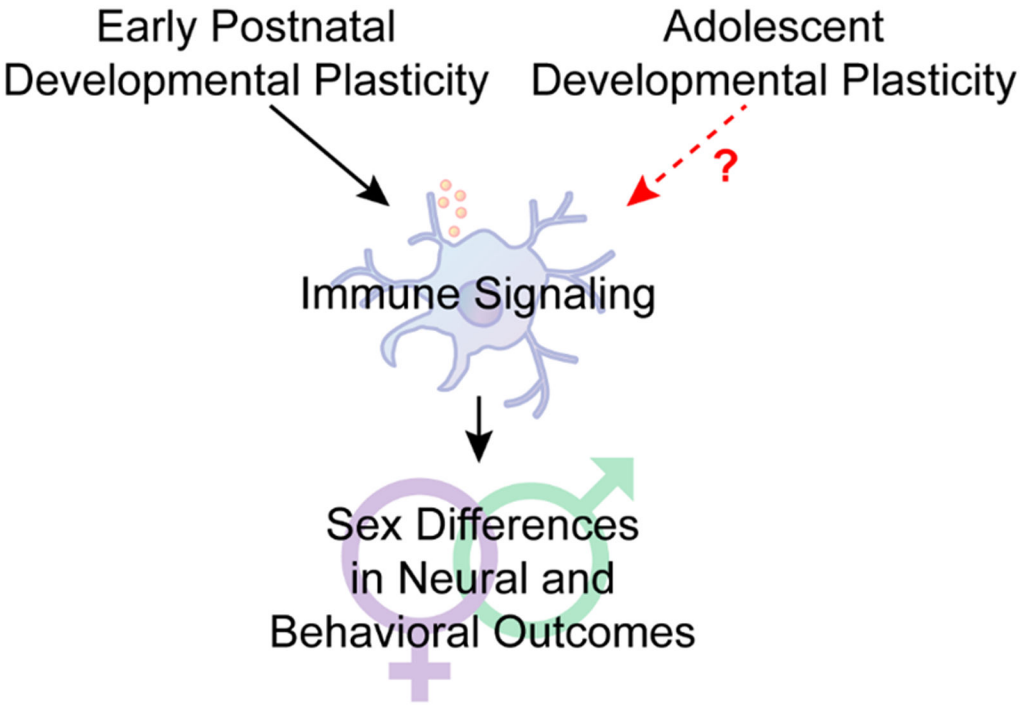

Fig.2: Immune signaling in sex-specific neural and behavioral development: Adolescent opportunity.

Sex differences are established by early life developmental plasticity, and immune signaling is now known to be a critical signaling intermediary for establishing sex-specific neural and behavioral outcomes. Adolescence is also a developmental period in which important sex differences emerge. Far fewer studies have been focused on whether immune signaling is also an intermediary for establishing sex-specific outcomes during adolescence. In this review, we discuss a variety of well characterized sex differences that emerge during adolescence, and then draw attention to literature that predicts ways in which immune signaling may play a role in the sex difference.

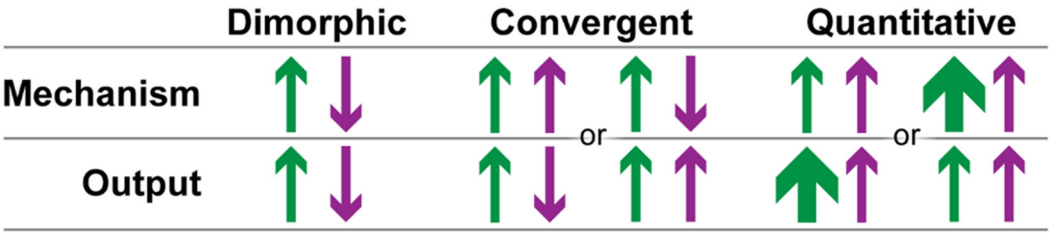

Fig. 3: Different categories of sex differences.

We review examples of sex differences that emerge during adolescence that fall into categories discussed, e.g., in [10]. We define dimorphic sex differences as both the behavioral/physiological output, and its underlying neural mechanism, diverge by sex. Convergent sex differences are when either the same neural mechanism results in divergent outputs (left), or divergent neural mechanisms support a convergent output (right). Quantitative sex differences are when both the neural mechanism and output are the same, but either the mechanism or output is greater in one sex.