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Neuroinflammation as a risk factor for attention deficit hyperactivity disorder

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is a persistent, and impairing pediatric-onset neurodevelopmental condition. Its high prevalence, and recurrent controversy over its widespread identification and treatment, drive strong interest in its etiology and mechanisms. Emerging evidence for a role for neuroinflammation in ADHD pathophysiology is of great interest. This evidence includes 1) the above-chance comorbidity of ADHD with inflammatory and autoimmune disorders, 2) initial studies indicating an association with ADHD and increased serum cytokines, 3) preliminary evidence from genetic studies demonstrating associations between polymorphisms in genes associated with inflammatory pathways and ADHD, 4) emerging evidence that early life exposure to environmental factors may increase risk for ADHD via an inflammatory mechanism, and 5) mechanistic evidence from animal models of maternal immune activation documenting behavioral and neural outcomes consistent with ADHD. Prenatal exposure to inflammation is associated with changes in offspring brain development including reductions in cortical gray matter volume and the volume of certain cortical areas –parallel to observations associated with ADHD. Alterations in neurotransmitter systems, including the dopaminergic, serotonergic and glutamatergic systems, are observed in ADHD populations. Animal models provide strong evidence that development and function of these neurotransmitters systems are sensitive to exposure to in utero inflammation. In summary, accumulating evidence from human studies and animal models, while still incomplete, support a potential role for neuroinflammation in the pathophysiology of ADHD. Confirmation of this association and the underlying mechanisms have become valuable targets for research. If confirmed, such a picture may be important in opening new intervention routes.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by pervasive and persistent behavioral symptoms of inattention, hyperactivity, and/or impulsivity that are extreme for age and interfere with social or academic functioning. Diagnosis requires the emergence of symptoms before twelve years of age and that symptoms present in two or more settings (APA, 2013). ADHD is common, affecting about 5% of children worldwide (APA, 2013) with boys being overrepresented, on average, approximately 2:1 (Danielson et al., 2018). The impact of ADHD is far reaching due its early onset and frequent persistence and secondary complications. Those with ADHD suffer reduced academic performance, weakened social and familial relationships, peer rejection, and long-term elevated rates of serious accidental injury, drug addiction, depression, school or occupational failure, and involvement in the criminal justice system. Cognitive problems such as subtle reduction in IQ, working memory, and executive function are also common, though not universal, in children with ADHD (Dan and Raz, 2012; Nigg, 2005; Willcutt et al., 2005) and may be related to both early environmental stressors (Wiggs et al., 2016) and genetic risk for ADHD (Nigg et al., 2018). Although ADHD is usually thought of as a childhood affliction, 50% of sufferers continue to have impairing symptoms into adolescence and 30–60% have impairing symptoms as adults (Ahmed et al., 2014). Adults with ADHD have lower socioeconomic achievement and reduced life span (Doshi et al., 2012). New insights into ADHD's etiology and new treatment possibilities are thus of keen interest.

The etiology of ADHD is complex, involving both common and rare genetic variants as well as multiple environmental risk factors. Ample evidence indicates that ADHD is highly heritable, but lacks any genes of

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major effect except in very rare cases, although individual loci are reliably associated with ADHD in meta-analysis, and multiple forms of genetic influence are implicated (Faraone and Larsson, 2019; Wiggs et al., 2016). About a third of the heritability is accounted for by common genetic variation. The proportion related to genotype by environment interaction is unknown (discussed further below). Studies of shared SnP heritability indicate that ADHD shares genetic liability with many other common psychiatric conditions including anxiety and mood disorders (Anttila et al., 2018). At the same time, early environmental factors are also implicated in the etiology of ADHD including many factors associated with increased inflammation such as maternal infection (Werenberg Dreier et al., 2016), maternal smoking (Becker et al., 2008; Biederman, 2005; Mick et al., 2002; Neuman et al., 2007; Silva et al., 2014; Thapar et al., 2013), maternal obesity and poor diet (Andersen et al., 2018; Buss et al., 2012; Chen et al., 2014; Rijlaarsdam et al., 2017; Rodriguez, 2010; Rodriguez et al., 2008; Sanchez et al., 2018; Vermiglio et al., 2004), and maternal exposure to pollutants (Thapar et al., 2013). Effect sizes for individual risk factors are generally modest and causality is still being evaluated in novel designs (Nigg et al., 2016; Thapar et al., 2013). Environmental effects are generally non-specific in that other psychiatric outcomes are also associated with these risk factors. At the same time, their association with ADHD in many instances survives statistical adjustment for co-occurring psychiatric symptoms and conditions.

Genotype-by-environment interactions are increasingly established in the field of developmental psychopathology (Kim and Leventhal, 2015; Pietropaolo et al., 2017; Pinto et al., 2015; S.M. Schaafsma et al., 2017) and are emerging in ADHD as well (Elmore et al., 2016; Nigg et al., 2010). While statistical decompositions can distinguish genetic and non-genetic influences on individual differences in a population, from a biological point of view genes and environments always act in concert. Indeed, it is well-established that environmental factors, especially those experienced during early development, can have a long-lasting influence on gene expression via epigenetic signaling and through that route on neural development. Initial evidence supports the idea that genetically susceptible individuals are more likely to develop ADHD (and other complex diseases) if exposed to certain environmental risk factors (Nigg et al., 2016; Stevenson et al., 2010). Many of these risk factors often impact genes involved in the dopamine (Becker et al., 2008; Neuman et al., 2007) and serotonin systems (Cortese, 2012; Pennington et al., 2009). Yet, the mechanism of action of these genetic and environmental influences on ADHD is not known.

In that regard, it is noteworthy that many of the early environmental risk factors for ADHD increase the inflammatory profile of the in-utero environment (Costenbader and Karlson, 2006; Shankar et al., 2011; Terasaki and Schwarz, 2016), supporting the hypothesis that exposure to inflammation during development leads to neuroinflammation and may play a role in the pathophysiology of ADHD (Costenbader and Karlson, 2006; Shankar et al., 2011; Terasaki and Schwarz, 2016). In this review, we discuss the neurobiological developmental changes involved in ADHD, with respect to their possible link to neuroinflammation as a mechanism.

2. Peripheral inflammation

Several lines of evidence can be marshaled to support a hypothesis that inflammation is part of a pathway to ADHD. This is not surprising when one considers the numerous associations between inflammation and CNS development and function (Bhattacharya et al., 2016). For example, GWAS studies have identified associations between ADHD and the gene for IL-1RA (Segman et al., 2002) as well as genes involved in regulation of gene expression, cell adhesion, and inflammation (Zayats et al., 2015). As another example, atopic immune disorders such as eczema (Buske-Kirschbaum et al., 2013; Liao et al., 2016; Lin et al., 2016; Schmitt et al., 2009), asthma (Fasmer et al., 2011; Instanes et al., 2017; Lin et al., 2016), rheumatoid arthritis (Instanes et al., 2017), type 1 diabetes (Instanes et al., 2017), and hypothyroidism (Instanes et al., 2017) have been associated with higher rates of ADHD diagnosis. Meta-analyses (Miyazaki et al., 2017; Schans et al., 2017; Schmitt et al., 2010) confirm that the odds of experiencing atopic immune disorders were slightly higher in children with ADHD than controls, however the effect estimates were quite variable across studies. Although these associations are variable between studies and study quality is sometimes weak, the data are consistent with a connection between the peripheral immune system and ADHD. Interestingly, recent evidence suggests that patients displaying ADHD symptomology have higher serum cytokine levels than non-ADHD controls (Anand et al., 2017; Darwish et al., 2018; Donfrancesco et al., 2016a; Donfrancesco et al., 2016b; O'Shea et al., 2014). One study reported an association between pro-inflammatory serum cytokines and ADHD symptom severity (Oades et al., 2010b). However, again, these studies are preliminary in that they included small sample sizes and were heterogeneous in the molecules examined and methodology used impairing comparisons across studies (Anand et al., 2017). Further there is evidence that patients taking psychostimulants, such as methylphenidate have lower levels of cytokines than medication-naïve patients suggesting an effect of treatment or improved symptomatology on cytokine levels (Oades et al., 2010a) that was not well-controlled in most studies. Nonetheless, more examination of cytokine levels should prove interesting.

Other isolated but intriguing findings bear note. Higher levels of antibasal ganglia antibodies (Toto et al., 2015) and antibodies against the dopamine transporter (Giana et al., 2015) are reported in populations with ADHD and are noteworthy as signs of inflammation. Furthermore, in one study, ADHD patients were observed to have elevated cerebrospinal fluid levels of the pro-inflammatory cytokine TNF-beta and lower levels of the anti-inflammatory cytokine IL-4 (Mittleman et al., 1997). Besides modulation of the central immune system by cytokines, it is possible that peripheral monocytes and other immune cells penetrate the blood brain barrier to induce neuroinflammation. Under normal conditions the blood-brain barrier separates the peripheral immune system from the CNS and prevents peripheral immune cells from entering the CNS. However, when the blood-brain barrier is compromised from injury, disease, or even marked psychological stress, peripheral monocytes can enter the CNS (Wohleb et al., 2014) and possibly alter function of neurons and other glial cells. The ability of peripheral monocytes to cross the blood brain barrier during development is supported by studies of maternal immune activation (MIA) which detect a compromised blood brain barrier in the developing offspring (Stolp and Dziegielewska, 2009).

Indirect evidence for the role of peripheral inflammation in the etiology of ADHD comes from dietary interventions. Meta-analysis has indicated that children with ADHD tend to have lower blood levels of long chain fatty acids and that ADHD symptoms are partially ameliorated in response to supplemented omega-3 polyunsaturated fatty acids (Chang et al., 2018; Hawkey and Nigg, 2014). Early omega-3 supplementation of mothers causes improved attentional development in infants (Colombo et al., 2016). Omega-3 polyunsaturated fatty acids are well documented to have anti-inflammatory properties and are beneficial in certain chronic inflammatory diseases such as rheumatoid arthritis (Yates et al., 2014). These preliminary findings suggest an association between ADHD and altered peripheral inflammatory profile, supporting the hypothesis that modulation of the neuroinflammatory environment plays a role in the pathophysiology of ADHD.

3. Neuroinflammation hypothesis

Based on the preceding, a neuroinflammation hypothesis can be developed for many forms of developmental psychopathology including ADHD. Here we define neuroinflammation as a general term for inflammation of neural tissue. It is characterized by changes in microglia, astrocytes, cytokines, chemokines, and related molecular processes

within the CNS. It is important to note that a strict definition of neuroinflammation may limit it to inflammation in response to bacteria, parasite, or viruses and a more appropriate term for inflammation, in the context we reference throughout this paper, may be microglial activation or neural immune activation. For ADHD post-mortem studies are lacking, but for some disorders post-mortem studies confirm neuroinflammation and not just peripheral tissue inflammation (Faraone and Mick, 2010; Kim et al., 2016; Monji et al., 2013; Vargas et al., 2005). Neuroinflammation is proposed to influence brain development and subsequently increase risk of neurodevelopmental disorders by acting through mechanisms including glial activation (Reus et al., 2015), increased oxidative stress (Hassan et al., 2016), aberrant neuronal development (Belmadani et al., 2006), reduced neurotropic support (Sen et al., 2008), and altered neurotransmitter function (Kronfol and Remick, 2000).

Several early risk factors that have been proposed for ADHD, including maternal infection, low birth weight, fetal alcohol exposure, maternal stress, and maternal obesity, all share an increased maternal inflammatory profile, raising the possibility that inflammation during prenatal development may play a role in the pathophysiology of ADHD (Costenbader and Karlson, 2006; Shankar et al., 2011; Terasaki and Schwarz, 2016).

During prenatal development, neurons rely on concentration gradients of specific chemoattractant factors as well as supporting glial cells to migrate to appropriate locations (Ayala et al., 2007; Barry et al., 2014). Glial cells and the process of neuronal migration are highly sensitive to the inflammatory environment, because changes in inflammatory markers alter chemoattractant gradients and glial cell functioning (Metin et al., 2008). Microglia are the primary immunocompetent cells of the central nervous system (CNS). Initially, believed to be primarily involved in pathologic states, such as reacting to infection and damage to the brain, it is now clear that microglia perform a host of additional functions within the brain including synaptic pruning, neuronal phagocytosis, and refining network connectivity during development (Cunningham et al., 2013; Eyo and Dailey, 2013; Salter and Beggs, 2014). Additionally, recent studies have indicated that microglia exhibit sex-dependent phenotypes. For example, it appears that, in rodent models, male microglia exhibit a more proinflammatory phenotype and develop at delayed rates compared to females (Hanamsagar et al., 2018; Villa et al., 2018). These sex differences in microglia phenotypes in animals raise the intriguing possibility of a mechanism for why ADHD and most other early-onset neurodevelopmental conditions affect males at overrepresented rates.

The extensive involvement of microglia and astrocytes in neurodevelopment makes them a point of interest when discussing mechanistic origins of neurodevelopment disorders, such as ADHD. In rodent models of maternal immune activation (MIA), microglial and astrocytic functionality is altered to an inflammatory state (Mattei et al., 2017). These alterations, along with inflammation directly influence neural precursor cells, can affect neuronal development, potentially giving rise to subsequent behaviors often associated with ADHD such as hyperactivity and anxiety (see the animal models section below, Fig. 1).

4. Neurobiological basis of ADHD: evidence from studies in humans

While a comprehensive coverage of neurobiological correlates of ADHD and other developmental psychopathologies is beyond the scope of this manuscript (for extended discussions see (Aoki et al., 2017; Bilbo and Schwarz, 2009; Dougherty et al., 2016; Lim et al., 2015; Martin et al., 2014; Rommelse et al., 2017), here we highlight selected findings relevant to the current discussion. All the findings discussed below occur at the group level; none are robust enough to be clinically relevant or diagnostic at the individual level as yet.

4.1. Neuroanatomical changes associated with ADHD

Briefly, CNS development begins 3–4 weeks post-conception with the folding and fusing of the ectoderm to form the neural tube. Subsequently, the prenatal CNS goes through a series of maturational events including neurogenesis and proliferation, neuronal migration, synapse formation and pruning, apoptosis, and finally myelination that extends into postnatal development (Marsh et al., 2008). In typical developing individuals, cortical gray matter development is characterized by increases in volume throughout the brain until puberty followed by reductions until full brain maturation in the third decade of life. The development of cortical volume is non-linear and asynchronous, with the frontal and parietal lobe volumes peaking at about 12 years of age, the temporal lobe at about 16 years of age, and the occipital lobe at about 20 years old (Giedd et al., 1999) while subcortical structures have their own asynchronous developmental timeline (Gilmore et al., 2012). Comparatively, children with ADHD have on average an approximately 4% reduction in overall gray matter volume in both the cerebrum and cerebellum, while developmental trajectories parallel typical development (Castellanos et al., 2002). This translates to key cortical regions reaching peak volume and beginning to prune about 3 years later than what occurs in typically developing children (Shaw et al., 2007). As microglia are highly involved in developmental pruning of synapses it is highly possible that this delayed pruning is related to neuroinflammation and altered microglial function. The neuroanatomical changes discussed here and later are focused on postnatally observed changes. However, alterations in brain development are likely occurring prenatally as well. However, to date there is limited understanding of the alterations in prenatal brain development that are associated with ADHD.

Moving into more specific structures, the primary cortical areas associated with ADHD symptomology are the prefrontal cortex (PFC) (Arnsten and Rubia, 2012), orbitofrontal cortex, and anterior cingulate cortex (Amico et al., 2011). Rubia and Arnsten (Arnsten and Rubia, 2012) point out that the PFC is viewed as important in the “top-down” regulation of attention, inhibition/cognitive control, emotion and motivation. A useful and common heuristic supposition is that attention and cognitive control are regulated relatively more by the dorsolateral and inferior PFC, while motivation and affect are regulated relatively more by the orbital and ventromedial PFC. Through a series of frontal-subcortical connections, these areas are involved in processes such as executive function, motivation, emotion, and evaluative assessment of stimuli. Children with ADHD show abnormalities in the inferior PFC and its connections to striatal, cerebellar, and parietal regions (Arnsten and Rubia, 2012). Findings indicate a reduction in gray matter volume and cortical thinning in these areas in children with ADHD (Li et al., 2015; Makris et al., 2007).

Reduced volume of subcortical structures such as the basal ganglia are also implicated in ADHD. Meta-analyses suggest that differences in structure and function of the basal ganglia represent a core finding in the ADHD literature (Hoogman et al., 2017). Relating to ADHD, these structures are associated with functions such as inhibitory control of action, attention, cognition, hyperactivity, and emotional response inhibition (de Wit et al., 2012; Grabli et al., 2004; van Rooij et al., 2015). The cerebellum has also been seen as potentially important in ADHD. These findings as they relate to ADHD as well other neurodevelopmental disorders have been extensively discussed and reviewed previously in both human studies and animal models (Stoodley, 2014, 2016; Thanellou and Green, 2013).

4.2. Changes in neural function associated with ADHD

Although the monoamines glutamate, and gamma-aminobutyric acid (GABA) interact continually in complex ways, we discuss them individually for the sake of clarity.

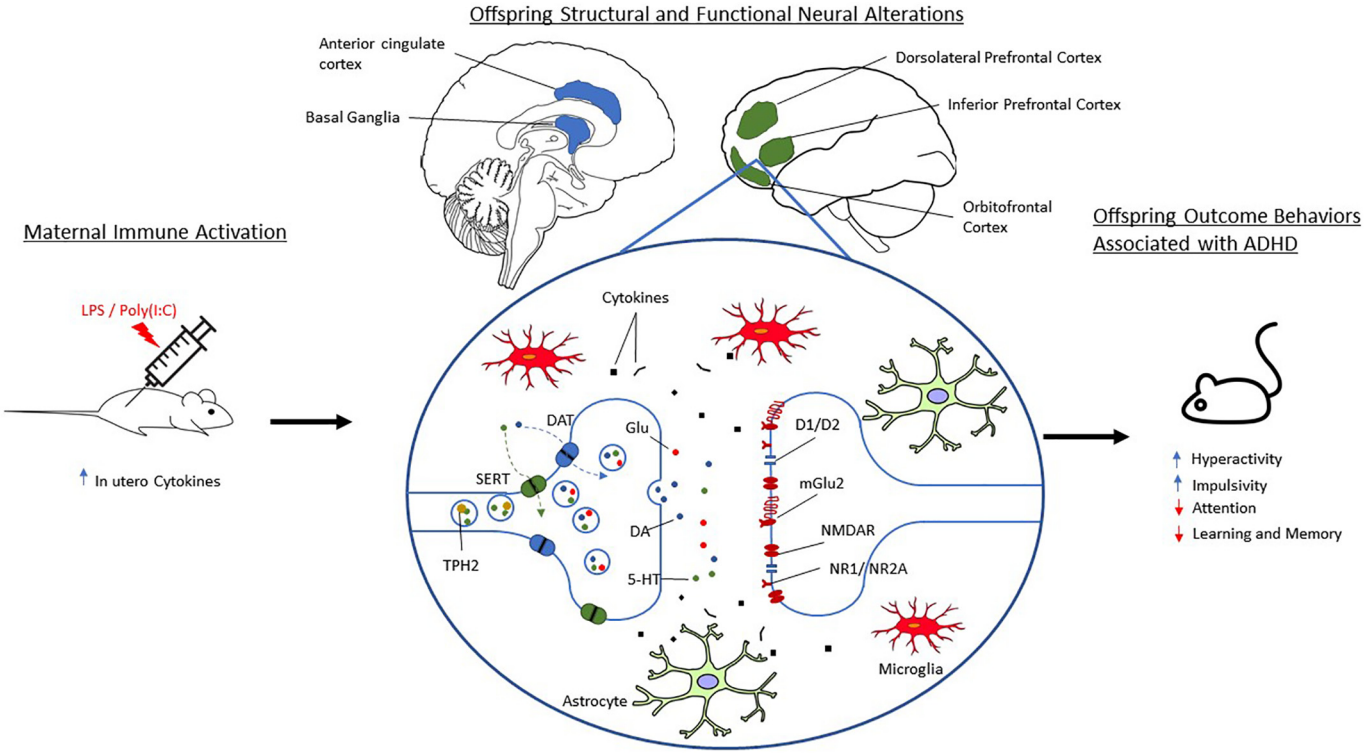

Fig. 1. Neural and behavioral changes of offspring born from mothers injected with lipopolysaccharide (LPS) or polyinosinic:polycytidylic acid (poly(I:C)) associated with changes observed in ADHD. Maternal immune activation (MIA) by LPS or poly(I:C) results in an increase of in utero cytokines altering the inflammatory environment of the developing offspring. MIA results in structural changes in volume and grey matter volume are observed in the anterior cingulate cortex, basal ganglia, dorsolateral prefrontal cortex, inferior prefrontal cortex, and orbitofrontal cortex. Functional changes observed in MIA offspring are alterations in the homeostatic levels of the neurotransmitters serotonin (5-HT), dopamine (DA), and glutamate (Glu) as well as a reduction in tryptophan hydroxylase (TPH2), the rate limiting step of 5-HT synthesis. In addition, alterations are observed in functionality of serotonin reuptake transporters (SERT) and dopamine transporters (DAT), dopamine receptors (D1/D2), metabotropic glutamate receptors (mGlu2), ionotropic glutamate receptors (NR1/NR2A), and NMDA receptors (NMDAR). Changes in these neural outcomes are associated with behavioral outcomes of increased hyperactivity and impulsivity along side decreases in attention and learning and memory.

4.2.1. Catecholamines (dopamine/norepinephrine)

Historically, ADHD was often considered a hypodopaminergic disorder (Levy, 1991; Robbins and Sahakian, 1979), where a deficiency in synaptic dopamine levels leads to clinical symptoms. Dopamine is a catecholamine synthesized mainly in the ventral tegmental area, substantia nigra, and arcuate nucleus, from the precursor amino acid tyrosine. Dopamine's role in ADHD has been supported circumstantially by pharmacological evidence that medications, like methylphenidate and amphetamines, increase levels of dopamine in the synaptic cleft, and also temporarily ameliorate symptoms of ADHD (Volkow et al., 2005). This “dopamine hypothesis” has undergone multiple, more nuanced revisions in recent years but remains a core line of thinking about ADHD (Volkow et al., 2009). Additionally, the activity of the dopamine derivative, norepinephrine (NE), has also been implicated in ADHD. The role of dopamine and catecholamines in ADHD has been previously and extensively reviewed (Del Campo et al., 2011; Volkow et al., 2009).

4.2.2. Serotonin

Recent clinical, neuroanatomical, and genetic studies provide evidence for a role for serotonin (5-HT) in the etiology of ADHD. Serotonin is a monoamine synthesized from the essential amino acid tryptophan. The main site of 5-HT synthesis in the brain is the dorsal raphe nucleus. In the dorsal raphe 5-HT is synthesized from tryptophan by the rate limiting enzyme tryptophan hydroxylase 2 (TPH2). The 5-HT system is complex, containing 14 known receptor subtypes all of which are g-protein coupled with the exception of the ligand gated 5-HT3R. Serotonin is transported from the synaptic cleft to the presynaptic neuron via the serotonin transporter (5-HTT).

Although, drugs that target dopamine and norepinephrine pathways are the first line of treatment for ADHD, up to 30% of ADHD patients do not respond to this treatment and among responders only about 50% show signs of improvement (Arnold et al., 2013). Alternative treatments for ADHD include selective-serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) and tricyclic-antidepressants (TCA) all of which target the 5-HT system (Park et al., 2014). Serotonin has been extensively shown to be an important regulator of behavioral inhibition (Crockett et al., 2009; Dayan and Huys, 2009) which has been postulated to be a core impairment in ADHD (Barkley, 1997). Pharmacological and genetic manipulation of rodent models implicates the 5-HT system in the hyperactive and impulsive dimensions of ADHD (Banerjee and Nandagopal, 2015). Children with ADHD have been reported to have lower levels of 5-HT in the blood (Coleman, 1971; Spivak et al., 1999), and reduced binding of tritiated imipramine (the non-selective 5-HT reuptake inhibitor) to blood platelets (Stoff et al., 1987). These findings led to the serotonergic hypothesis of ADHD which asserts that a reduction in available 5-HT in the synapse may contribute to clinical symptoms of ADHD (Quist and Kennedy, 2001). The serotonin system has been shown to be sensitive to exposure to inflammation with evidence from animal models (discussed in Section 5 below). Another angle by which researchers are understanding serotonin's role in ADHD is through the tryptophan synthesis pathway. These studies show that a reduction in serotonin via tryptophan depletion leads to inattention, reduced behavioral inhibition, and increased impulsivity (Banerjee and Nandagopal, 2015). Elevations in peripheral inflammation have been associated with increases in kynurenine metabolites (Pfaff et al., 2008) which competes

with serotonin for tryptophan resulting in less tryptophan available for 5-HT synthesis.

The serotonin hypothesis of ADHD is in alignment with the more well-known association of serotonin function with mood and anxiety disorders (Adler, 2007), which are strongly associated with reduced 5-HT levels (Coppen and Doogan, 1988; Eison, 1990; Sullivan et al., 2006) and often treated by medications that modulate serotonergic function. Gene by environment interplay involving the serotonin transporter is a fundamental finding in relation to mood disorders (Karg et al., 2011; Risch et al., 2009; Uher and McGuffin, 2008, 2010). However, ADHD is often comorbid with anxiety disorder, and children with ADHD are at a two-fold risk of future depression compared to children without ADHD (Meinzer et al., 2014). Further, emotional dysregulation is increasingly recognized as centrally important in ADHD (Shaw et al., 2014). In other words, it is a misconception that ADHD is purely a cognitive disorder. Thus, as ADHD is re-conceptualized increasingly as involving broader aspects of cognitive and emotional dysregulation, the role of serotonin and the frequent diagnostic overlap with emotion-related conditions begins to be meaningful.

Neuroanatomical evidence is consistent with a role for the serotonergic system in ADHD. Serotonergic neurons project from the raphe nuclei throughout the cerebral cortex including robust projections to brain structures associated with ADHD such as the orbital frontal cortex (OFC). A reduction in serotonin levels in the OFC is associated with reduced emotional regulation, inhibition, and reversal learning all of which are correlates of ADHD (Clarke et al., 2007). The dorsomedial PFC is sensitive to reduced tryptophan availability (Evers et al., 2006). These studies suggest that the serotonergic system could be involved in ADHD by influencing orbitofrontal-striatal neurocircuitry.

Serotonin is involved in modulating the dopaminergic system. Serotonergic terminals can take up exogenous L-DOPA and convert it to dopamine (Stansley and Yamamoto, 2013). Also, several serotonin receptor subtypes (5-HT1BR, 5-HT1DR, and 5-HT6R) influence dopamine transmission in the mesolimbic pathway (Valentini et al., 2013; Yan and Yan, 2001). Lastly, 5-HT plays an important role in brain development which is distinct from its role in the mature brain. During development 5-HT is synthesized by the placenta from maternal derived tryptophan (Velasquez et al., 2013) making 5-HT an important link between the early environmental factors, inflammation and brain development. In summary, ample evidence indicates a potential role for 5-HT in ADHD. It is reasonable to propose that 5-HT modulation of the dopamine system and regulation of early brain development are mechanisms by which 5-HT influences risk of ADHD.

4.2.3. Glutamate/GABA

Recent evidence supports a role for the neurotransmitters glutamate (Glu) and gamma-aminobutyric acid (GABA) in the etiology of ADHD. Glutamate is the main excitatory and GABA is the main inhibitory neurotransmitter throughout the brain. GABAergic and glutamatergic neurons project to many areas and structures within the central nervous system (CNS) (Morales and Root, 2014; Soiza-Reilly and Commons, 2011). Importantly for ADHD, glutamatergic and GABAergic neurons project to the striatum where they influence dopamine neurotransmission (Ferreira et al., 2009; Tritsch et al., 2012), suggesting that alterations to these systems could have an important role in ADHD (Miller et al., 2014).

Proton magnetic resonance spectroscopy (MRS) has been used in ADHD research to noninvasively obtain quantitative measurement of differences in regional brain biochemistry between ADHD patients and controls (Novotny et al., 1998). Increased levels of Glu have been detected in children with ADHD using MRS in the frontal (Moore et al., 2006), prefrontal (MacMaster et al., 2003), subcortical (Bollmann et al., 2015) and striatal (Carrey et al., 2007; MacMaster et al., 2003) brain regions as compared with controls. Although most of these differences did not reach significance in a recent meta-analysis (Perlov et al., 2009). MRS studies in adult ADHD patients report both increases and decreases in Glu. Some studies observed increases in basal ganglia (Ferreira et al., 2009) and left cerebellar (Perlov et al., 2010) regions, while other studies, in contrast, reported decreased levels in the basal ganglia (Maltezos et al., 2014), right ACC (Perlov et al., 2007), and a left mid-frontal region (Dramsdahl et al., 2011). A study done by Bollmann et al. (2015) showed differences in glutamate levels in ADHD children which normalizes with brain maturation in adult patients, suggesting a developmental timing effect in ADHD patients as they transition from adolescence to adulthood (Bollmann et al., 2015). The inconsistent reporting of glutamate levels in ADHD patients in the literature could be explained by that fact that glutamate is ubiquitous through-out the CNS with innervation to many regions and nuclei. Additional research is required to provide a more definitive hypothesis to the differences observed in glutamate/glutamine in ADHD patients.

Research on the GABAergic system's involvement in ADHD is relatively limited. GABA has been associated with impulsivity in men suggesting a link to ADHD (Boy et al., 2011). Studies indicate that GABA levels are reduced in ADHD children (Edden et al., 2012), with one study showing increased GABA levels in adult patients (Bollmann et al., 2015). However, these differences did not obtain significance in a meta-analysis comparing measurement of brain GABA levels across psychiatric disorders (Schur et al., 2016). A study utilizing an animal model of ADHD, the spontaneous hypertensive rat (SHR), observed reduced tonic levels of GABA in the hippocampus (Sterley et al., 2013). These studies similarly suggest that a reduction in GABA may be associated with childhood ADHD with a possible transition to increased levels when ADHD persists in adulthood. Additionally, genetic manipulation studies in mice found that knocking out the Gad67 enzyme, an enzyme involved in the synthesis of GABA, and the GABA transporter 1, resulted in mild hyperactivity as well as impaired attention (Chen et al., 2015; Smith, 2018). However, the limited available evidence precludes the ability to draw significant conclusions about the role of GABA in ADHD.

In summary, extensive literature provides support for highlighting both structural and functional changes in the brain associated with ADHD. Functionally, many of the neurotransmitter systems interact in complex ways that may converge on a common end point of aberrant dopamine transmission in ADHD relevant brain structures. In the next sections we will discussion how inflammation experienced during development may influence these structural and functional systems associated with ADHD pathology.

5. Animal models support link between developmental exposure to inflammation and changes in cognition and behavior

Evidence for the link between prenatal neuroinflammation and subsequent offspring behavioral changes is substantial. To investigate the association between exposure to inflammation during development and offspring behavior investigators induce inflammation during specific periods of development. The most common models induce maternal immune activation (MIA) by systemic (intraperitoneal (IP) or subcutaneous (SC)) administration of polyinosinic:polycytidylic acid (poly(I:C)) an agonist to the toll-like receptor-3 (TLR3) that models a viral infection, lipopolysaccharide (LPS), an agonist to the TLR4 that models a bacterial infection, bacteria such as streptococcus that commonly cause infection during pregnancy, or a combination of these agents to pregnant animals. These animal models of systemic prenatal infection induce changes in offspring behavior that may be reminiscent of aspects of human neurodevelopmental disorders, including behaviors interpreted as anxiety-like behavior (Arsenault et al., 2014; Makinson et al., 2017; Penteado et al., 2014; W. Schaafsma et al., 2017), sustained attention (Vuillermot et al., 2012), cognitive flexibility (Bitanihirwe et al., 2010), and social behavior (Bitanihirwe et al., 2010; Machado et al., 2015; Malkova et al., 2012; Smith et al., 2007) establish the proof of concept for maternal inflammation influencing offspring behavior

via alterations in neural development. Below we will examine the evidence linking prenatal inflammation to models of attention, activity level, and impulse control.

5.1. Evidence from animal models that exposure to prenatal inflammation leads to behavioral changes modeling aspects of ADHD

Deficits in certain kinds of attention are relevant to ADHD and other neurological disorders associated with dopamine deficiency (Del Campo et al., 2011). However, isolation of different attention systems in animal models are limited, so the relationship between prenatal maternal immune activation and offspring inattention has only been examined in a limited number of studies. One group used a signaled probability sustained attention task to examine cognitive and decision-making processes in adult rats exposed to a single dose of poly(I:C) during fetal development, but failed to detect an effect of MIA on any of the cognitive processes assessed (Bates et al., 2018). Two studies by the same group measured attentional shifting by examining the persistence of latent inhibition in a conditioned freezing paradigm. The first study noted abnormalities in attentional shifting in adult male, but not female, mice treated prenatally with a high dose of poly(I:C) (Bitanihirwe et al., 2010). These findings were followed up by the examination of the interaction between prenatal immune activation and deficiency in *Nurr1* a transcription factor essential for the development of dopamine neurons which is also implicated in ADHD (Vuillermot et al., 2012). This study noted impairments in both sustained attention (using the two-choice discrimination test) and attentional shifting in adult male mice that were exposed to prenatal immune activation and had genetic *Nurr1* deficiency (Vuillermot et al., 2012).

Activity level is much more readily simulated in animal models, although animal models to date have not effectively modeled the social cost associated with hyperactivity in human children with ADHD. Also, the setting of the measurement (i.e. home cage versus behavioral testing apparatus) and the novelty of the situation as well as the choice of animal model can greatly influence the results. In children with ADHD hyperactivity is somewhat inhibited in novel situations (Sagvolden and Sergeant, 1998; Sleator and Ullman, 1981). Thus, it would be ideal if an animal model of ADHD displayed hyperactivity in their home cage or after acclimation to the testing environment, but not necessarily during novel or stressful testing paradigms. A very limited number of studies have assessed locomotor activity in the home cage in rodent offspring exposed prenatally to inflammation. One study reports an increase in locomotor behavior in the home cage as measured by telemetry in young male mouse offspring exposed to poly(I:C) during gestation (Missig et al., 2018). Likewise, a second study observed increased locomotor behaviors in their home cage as documented via coding of videography in male mice offspring exposed to the influenza A virus during gestation (Miller et al., 2013). However, another study which used a photobeam system to measure activity of rat offspring exposed to poly(I:C) observed no group difference in locomotion in the home cage (Missault et al., 2014) and a fourth study observed a reduction in home cage activity in young adult mouse offspring exposed prenatally to LPS as measured by passive infrared monitoring (W. Schaafsma et al., 2017). Several studies report increased locomotor activity in the open field or other novel testing environments such as the elevated plus maze in offspring exposed to inflammation during gestation. These results appear to be gender dimorphic, and context and age dependent.

A study that induced gestational inflammation via prenatal exposure to Group B Streptococcus noted increased total distance travelled in male, but not female offspring at P20 in the open field (Allard et al., 2017), but that female, and not male offspring exhibited increased total distance travelled at P105-110 in an elevated plus maze (Allard et al., 2018). Offspring exposed to LPS during prenatal development were more active in the open field test at 20 months of age (Golan et al., 2006). In the study examining the interaction between prenatal immune activation and genetic *Nurr1* deficiency, described above, prenatal immune activation and *Nurr1* deficiency exerted additive effects on spontaneous locomotor hyperactivity in the open field test (Vuillermot et al., 2012). Lastly, male, but not female, mouse offspring exposed to inflammation induced by prenatal stress exhibited locomotor hyperactivity in a novel, stressful environment. This behavioral phenotype was ameliorated by treatment of the mother with non-steroidal anti-inflammatory drugs and was associated with alterations in D1 and D2 receptors (Bronson and Bale, 2014).

In summary, these animal studies in rodents suggest that male offspring locomotor activity appears to be particularly responsive to maternal immune activation. However, the current findings are not entirely consistent; only two of the studies that report hyperactivity in maternal immune activation models actually measured locomotor activity in the home cage, which is potentially the most valid measure of changes in activity expected in an animal model of ADHD.

Impulsivity is another key feature of ADHD which has several animal model analogues although each model has notable limitations. Two studies report alterations in an impulsivity in offspring exposed to prenatal inflammation. One study noted that adult female, but not male, rats exposed to group B streptococcus during gestation displayed increased locomotion and entries in the open arms of an elevated plus maze potentially indicating decreased inhibition (Allard et al., 2018). Also, social intrusiveness is a diagnostic feature associated with impulsivity in ADHD (APA, 2013) and a second study noted that young adult female rats exposed in-utero to group B streptococcus displayed hyper-social behavior during late puberty, whereas males were hypo-social compared to same-sex controls (Bergeron et al., 2013).

ADHD is also associated with cognitive problems such as impaired working memory and reduced executive function (Willcutt et al., 2012). A number of animal models of prenatal exposure to inflammation report impairments in learning and memory. Young adult mice prenatally exposed to LPS were slower to learn a T-maze but had similar memory retention for the test as controls (W. Schaafsma et al., 2017). Prenatal LPS treatment impaired neurogenesis and performance in the novel object recognition test in adult rat offspring (Graciarena et al., 2010), learning to associate a cue with the platform in the Morris-water maze (Golan et al., 2005), and learning to avoid a foot shock in the Passive avoidance test (Golan et al., 2005). Gestational LPS exposure was associated with impaired spatial learning and memory in the radial arm water maze primarily in female mice (Li et al., 2016). In murine models, prenatal poly(I:C) exposure impaired working memory in a matching-to-position paradigm in the dry maze (Vuillermot et al., 2012), spatial recognition memory in the Y maze (Giovanoli et al., 2015), performance in the novel object recognition task (Ozawa et al., 2006), and rate of route-based learning when visible cues were unavailable in the Cincinnati water maze (Vorhees et al., 2012).

In summary, rodent models provide evidence of developmental exposure to inflammation being associated with behavioral changes; some of these may be related to features of ADHD (Fig. 1) such as behaviors interpreted as reflecting inattention (Bitanihirwe et al., 2010; Vuillermot et al., 2012), motor activity (Miller et al., 2013; Missig et al., 2018), impulsivity (Allard et al., 2018; Bergeron et al., 2013), and impaired learning and memory (Golan et al., 2005; Graciarena et al., 2010; Li et al., 2016; W. Schaafsma et al., 2017; Vuillermot et al., 2012). However, inconsistent behavioral findings across studies remain a limitation, likely due to variations in the gestational age of maternal immune activation, the type of inflammatory event, and doses of the inflammatory inducing agent across studies. Future studies that characterize locomotion in the home cage, reinforcer discounting, unwarned alerting (arousal), and inattention and impulsivity in maternal immune activation studies will be helpful.

5.2. Evidence from animal models that prenatal exposure to inflammation results in changes in brain structure consistent with ADHD

With advancements in brain imaging techniques it is now possible to directly relate changes in brain structure and development associated with neurodevelopmental disorders in humans to animal models. A number of cross-sectional and a few longitudinal MRI studies in rodent models of maternal immune activation provide evidence for subtle, but long-lasting, abnormalities in brain structure consistent with the neuroanatomical changes noted in children with ADHD (Fig. 1). Decreased overall brain volume was reported with prenatal exposure to poly(I:C) in adult mice (da Silveira et al., 2017). Similar to the reduction in gray matter volume documented in children with ADHD (Castellanos et al., 2002), a reduction in cortical gray matter was noted in rhesus monkeys whose mothers were infected with influenza during pregnancy (Short et al., 2010). The most marked reductions in gray matter were observed bilaterally in the cingulate and parietal areas, and white matter was noted to be reduced in the parietal lobe (Short et al., 2010). Prenatal exposure to inflammation has been documented to result in reductions in volume of cortical areas associated with ADHD. Prenatal exposure to poly(I:C) (Piontkewitz et al., 2012) reduced the volume of the prefrontal cortex, consistent with observations in children with ADHD (Arnsten and Rubia, 2012), and reduced the volume of the hippocampus in adult mice. Exposure to polyriboinosinic-polyribocytidylic acid (POL) during gestation decreased the volume of the anterior cingulate cortex, hippocampus, amygdala, striatum, nucleus accumbens and lateral ventricles in rat offspring (Crum et al., 2017). In contrast, prenatal POL exposure resulted in larger volume in the thalamus, ventral mesencephalon, brain stem and major white matter tracts relative to controls (Crum et al., 2017). To date no studies have identified alterations in subcortical structures such as the basal ganglia (Hart et al., 2013; Nakao et al., 2011) associated with ADHD pathology in rodent models of maternal immune activation. It is important to note that the developmental timing of the maternal immune challenge induces distinct changes in the offspring brain and few studies investigate multiple challenge time points in a single study.

5.3. Exposure to maternal immune activation during gestation alters the function of neurotransmitter systems associated with ADHD

5.3.1. Dopamine

The dopaminergic system is known to be sensitive to inflammation during development as animal studies utilizing a model of maternal immune activation show aberrant dopamine transmission through reduced spontaneous firing rate and population activity, as well as reduced dopamine transport and receptors in both the PFC and subcortical regions (Baharnoori et al., 2013; Luchicchi et al., 2016). Additional evidence is observed in a study performed by Straley et al. (2017), where dopaminergic-driven behaviors are altered in rat offspring. However, the behavioral results were not associated with a loss in dopaminergic neurons suggesting inflammation is influencing behavior by functional changes to the dopamine system during development (Straley et al., 2017). More evidence for dopaminergic system sensitivity to inflammation is observed in a model of maternal stress-induced inflammation that produced behaviors related to ADHD. Researchers observed that administration of maternal non-steroidal anti-inflammatory drugs resulted in amelioration of behaviors associated with dopamine dysregulation (Bronson and Bale, 2014). This study also observed altered expression of the D1 and D2 dopamine transporters in male offspring suggesting a functional change in dopamine transmission rather than a loss of neurons. In a model of maternal inflammation induced via poly(I:C) injection reduced expression of sonic hedgehog protein was observed (Khalil et al., 2013). As sonic hedgehog protein is very important in the maturation of dopaminergic neurons (Wang et al., 1995), a reduction in this protein could lead to an underdeveloped dopamine system. Other neurotransmitters important in the neurobiology of ADHD including serotonin and glutamate have also been shown to be sensitive to the inflammatory environment (discussed below).

5.3.2. Serotonin

Animal models provide direct evidence that inflammatory factors influence the development of the 5-HT system. Much of the evidence comes from mouse models of prenatal exposure to inflammation. Overall, these studies indicate that exposure to inflammation during fetal development reduce neural 5-HT levels. In mouse offspring, LPS exposure decreased overall cerebral levels of 5-HT, down regulated mRNA expression of TPH2, and 5-HTT in whole brain homogenates (Hsueh et al., 2017), and decreased the number and size of TPH2 positive neurons in the dorsal raphe (Hsueh et al., 2017). In murine models, exposure to LPS (Depino, 2015) and poly(I:C) (Winter et al., 2009) decreased 5-HT levels in the hippocampus. In contrast, one study found that prenatal poly(I:C) exposure increased 5-HT levels in the hippocampus (Abazyan et al., 2010). The levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were reduced in the nucleus accumbens and lateral globus pallidus by prenatal poly(I:C) exposure (Winter et al., 2009) and prenatal flu exposure decreased 5-HT and 5-HIAA levels in the cerebellum (Fatemi et al., 2008; Winter et al., 2008). Prenatal exposure to the flu in a mouse model also reduced serum 5-HT levels, particularly in the male offspring, and increased 5-HT metabolism in female offspring (Miller et al., 2013). Interestingly, the vast majority of studies report a decrease in 5-HT synthesis and neuron number with exposure to prenatal inflammation regardless of the developmental timing of the immune challenge (Meyer and Feldon, 2009).

The 5-HT system plays a critical role in brain development, including neurogenesis, neuronal migration and synaptogenesis (Daws and Gould, 2011; Kannan et al., 2011). Thus, alterations in 5-HT synthesis are likely to contribute to impairments in overall brain development. One mechanism by which inflammation reduces 5-HT synthesis is by influencing the availability of its precursor tryptophan through the kynurenine pathway. An increase in kynurenine metabolites has been reported in animal models of maternal inflammation (Pfaff et al., 2008; Zavitsanou et al., 2014). As the kynurenine pathway competes with 5-HT for tryptophan, an increase in this pathway results in less tryptophan available for 5-HT synthesis. Epigenetic mechanisms are also reported to contribute to the reduction in 5-HT synthesis as prenatal exposure to poly(I:C) alters histone acetylation of the 5-HTT promoter in the hippocampus of adult mice (Reisinger et al., 2016).

5.3.3. Glutamate/GABA

While there is inconsistency in the degree and direction of change within the glutamatergic and GABAergic systems in ADHD patients, evidence suggests that alterations in these systems occur in the development of ADHD. Animal studies that model maternal inflammation indicate that proper development of the glutamatergic system is sensitive to inflammatory factors. Inflammation during development alters glutamatergic and GABAergic receptor expression and function in the offspring. Increased expression of $GABA_A$ receptors in the hippocampus and amygdala as well as decreased expression of the metabotropic glutamate receptor, mGlu2, in the frontal cortex is observed in mouse offspring born to either stressed or poly(I:C) injected mothers during pregnancy (Holloway et al., 2013; Nyffeler et al., 2006). Another study found that the ionotropic glutamate receptors NR2A, NR1, and NMDAR are altered in a sex dependent manner. Male offspring displayed increased NMDAR and NR2A binding in the striatum and cortex, which was accompanied by increased mRNA expression for NR2A and NR1 receptors (Rahman et al., 2017). In addition to neuronal changes within functionality of the glutamatergic neurons, glial cells play a crucial role in maintaining and regulating this system. Maternal inflammation disrupts normal glial functioning leading to dysfunctional regulation of glutamate transmission. Multiple studies using different species of

animals document an activation of microglia and astrocytes in response to maternal inflammation that leads to dysregulation in glutamate homeostasis (Roumier et al., 2008; Weaver-Mikaere et al., 2013; Zhang et al., 2016). Finally, evidence suggests that inflammation affects the glutamatergic system through epigenetic means. In a study by Tang et al. (2013), offspring born to mothers injected with LPS or poly(I:C) during pregnancy, showed decreases in promotor-specific histone acetylation and corresponding gene expression (Tang et al., 2013).

6. Conclusion

Substantial indirect and circumstantial evidence supports a hypothesis that neuroinflammation plays an important albeit non-specific role in the pathophysiology of ADHD. Promising new technologies and tools such as positron emission tomography (PET) using a radiotracer specific for activated microglia (Boerwinkle and Ances, 2018) will allow future studies to more directly assess neuroinflammation in patients with ADHD in a noninvasive manner. Alterations in the peripheral inflammatory profile are observed in several neurodevelopmental disorders (Kim et al., 2016; Landaas et al., 2010; Monji et al., 2013; Vargas et al., 2005), including ADHD, but this non-specificity is not surprising in light of increasing evidence that the psychiatric nosology does not carve nature at its joints but rather reflects multiple overlapping dimensions and syndromes which may have overlapping etiological pathways.

ADHD appears to be associated with increased serum cytokines and comorbidity with atopic immune disorders. Additional mechanistic evidence is gathered from observations of the behavioral and neural outcomes of animal models of MIA (Fig. 1). These studies noted abnormalities in behavior consistent with ADHD such as hyperactivity, impulsivity, and inattention. Along with these behavioral changes prenatal exposure to inflammation is associated with changes in brain structures consistent with those observed in imaging studies of patients with ADHD. Animal models of prenatal exposure to inflammation observed a reduction in cortical gray matter volume and reductions in the volume of cortical areas associated with ADHD including the PFC and anterior cingulate cortex. In addition to structural changes, alterations in neurotransmitter systems including the dopaminergic, serotonergic, glutamatergic and GABAergic systems are observed in the ADHD population. Animal models of MIA provide strong evidence that the development and function of these neurotransmitters systems are sensitive to exposure to in utero inflammation. Prenatal exposure to inflammation produced changes in receptors, enzymes, and homeostatic levels of related neurotransmitters.

While ADHD is functionally characterized by a reduction in available dopamine in the synapse, dysfunction of other neurotransmitter systems may modulate dopamine system function. Serotonin, glutamate, and GABA modulate dopamine transmission and are hypothesized here to be important as well. If one or all of these systems are altered, it could lead to aberrant dopamine transmission. Evidence from animal models of maternal immune activation are intriguing but preliminary due to inconsistencies across experiments. One important question concerns the timing of the maternal immune activation during development. The developmental timing of the maternal immune challenge induces distinct changes in the offspring brain and behavior and few studies investigate multiple challenge time points in a single study.

This review presents accumulating evidence for a possible role of neuroinflammation in the progression of ADHD. Specifically, we focus on the impacts of exposure to inflammation during in-utero development. However, exposure to environmental factors, such as maternal smoking and pollutant exposure, that trigger inflammation during the early postnatal period and childhood also influence risk for neuropsychiatric disorders including ADHD. It is noteworthy that in addition to ADHD a number of neuropsychiatric disorders including ASD (Vargas et al., 2005), schizophrenia (Monji et al., 2013), depression (Kim et al., 2016), anxiety, and bipolar disorder (Landaas et al., 2010) have also been associated with exposure to an increased peripheral and/or central inflammatory response during perinatal development. This elevated inflammatory response is thought to be triggered by a number of environmental factors during perinatal development. The environmental insults associated with ADHD appear to be similarly shared in predicting other neuropsychiatric disorders. In the case of ADHD, the majority of the evidence pertains to peripheral inflammation due to an absence of post-mortem studies. It is interesting that for schizophrenia and ASD both post-mortem studies (Bayer et al., 1999; De Picker et al., 2017; Vargas et al., 2005) and neuroimaging studies using PET and a radiotracer for microglia (Doorduin et al., 2009; Suzuki et al., 2013) provide direct evidence for persistent neuroinflammation in some subjects compared to controls. However, this evidence is still preliminary as most of these studies have a small sample size making them prone to bias and confounding factors.

We therefore propose that these perinatal insults are acting through a common inflammatory pathway. That is consistent with the artifact of comorbidity among neuropsychiatric disorders (notably, here, ADHD and mood and emotion disorders (Adler, 2007)). In addition to the need for prospective and confirmatory studies of several kinds, several issues need more exploration. First, how does the developmental timing, duration and degree of the in utero inflammatory insult influence certain brain areas and neurotransmitter systems, and thus the behavioral phenotype. Second, how do genetic and environmental risk factors interact or synergize to mediate the influence on brain development and the risk for each specific neuropsychiatric disorder or its sub-domains (e.g., negative valence, controlled attention)? Third, how do sex-specific phenotypes of microglia and sex-differences in the timing of microglial development seen in animals (Hanamsagar et al., 2018; Villa et al., 2018) relate to sex differences in neurodevelopmental conditions like ADHD?

Overall, understanding how inflammation fits in to ADHD pathophysiology holds promise for an exciting new formulation of the disorder. If we can clarify how these processes are functioning in the case of a common and pervasive condition like ADHD, new avenues will be opened for novel therapeutic interventions.

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