Pre- and Perinatal Ischemia-Hypoxia, the Ischemia-Hypoxia Response Pathway, and ADHD Risk

Taylor F. Smith[1,2] · Rainald Schmidt-Kastner[3] · John E. McGeary[2,4] · Jessica A. Kaczorowski[1] · Valerie S. Knopik[2]

Abstract This review focuses on how measured pre- and perinatal environmental and (epi)genetic risk factors are interrelated and potentially influence one, of many, *common* developmental pathway towards ADHD. Consistent with the Developmental Origins of Health and Disease hypothesis, lower birth weight is associated with increased ADHD risk. Prenatal ischemia-hypoxia (insufficient blood and oxygen supply in utero) is a primary pathway to lower birth weight and produces neurodevelopmental risk for ADHD. To promote tissue survival in the context of ischemia-hypoxia, ischemia-hypoxia response (IHR) pathway gene expression is altered in the developing brain and peripheral tissues. Although altered IHR gene expression is adaptive in the context of ischemia-hypoxia, lasting IHR epigenetic modifications may lead to increased ADHD risk. Taken together, IHR genetic vulnerability to ischemia-hypoxia and IHR epigenetic alterations following prenatal ischemia-hypoxia may result in neurodevelopmental vulnerability for ADHD. Limitations of the extant literature and future directions for genetically-informed research are discussed.

Keywords ADHD · Prenatal · Ischemia · Hypoxia · Epigenetic · Developmental pathway

✉ Taylor F. Smith
tsmith82@calpoly.edu

[1] Department of Psychology and Child Development, California Polytechnic State University, 1 Grand Ave., San Luis Obispo, CA 93407, USA

[2] Division of Behavioral Genetics, Rhode Island Hospital and Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, RI, USA

[3] Integrated Medical Science Department, CE Schmidt College of Medicine, Florida Atlantic University (FAU), Boca Raton, FL, USA

[4] Providence VA Medical Center, Providence, RI, USA

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a chronic health condition characterized by persistent, pervasive, and developmentally inappropriate levels of inattention, hyperactivity-impulsivity, or both (American Psychiatric Association 2013). ADHD has an average prevalence rate of 5–5.5 % in youth (Polanczyk et al. 2007), is more common in males (Polanczyk et al. 2007), and generally persists into adulthood (Barbaresi et al. 2013). It is also associated with high rates of psychiatric comorbidity (Angold et al. 1999). The economic impact of ADHD in the United States is an estimated $143–$266 billion annually (Doshi et al. 2012). In order to reduce the ADHD public health burden, there is a critical need to further understand the complex origins of ADHD and early etiological pathways to neurodevelopmental vulnerability.

Comprehensive theories of ADHD (Nigg 2005; Sonuga-Barke 2002) focus on multiple neurodevelopmental pathways to ADHD and provide a framework to conceptualize phenotypic heterogeneity within ADHD. Multiple genetic and prenatal environmental risk factors for ADHD have been identified; however, it is unclear how genetic and environmental risk factors coalesce to alter ADHD risk. Researchers have begun to examine how genetic pathways may impact molecular and cellular processes and ADHD risk (Poelmans et al. 2011; Yang et al.

2013); however, there remains a significant need to understand the role of prenatal environmental risk factors in the etiology of ADHD (Nigg 2012).

Building on previous work linking prenatal hypoxia to ADHD (Lou 1996; Toft 1999), this paper focuses on the interplay between genetic, epigenetic, and environmental risk to examine molecular pathways to ADHD, with a specific focus on the ischemia-hypoxia response pathway. To this end, we first briefly review empirical evidence and theory implicating prenatal ischemia-hypoxia (e.g., preeclampsia) and perinatal ischemia-hypoxia (e.g., birth asphyxia) in the development of ADHD and other neurodevelopmental disorders. Next, we focus on the potential role of genetic and epigenetic variation in genes shown to be involved in the ischemia-hypoxia response. Last, we review the similarities between neurodevelopmental sequelae of ischemia-hypoxia and neurodevelopmental correlates of ADHD. We conclude by discussing important methodological issues in this domain and suggestions for future research. The goal of the proposed model is to partially account for etiological heterogeneity in ADHD by articulating a putative developmental pathway from pre- and perinatal ischemia-hypoxia to ADHD risk.

Lower birth weight and ADHD risk: Pre- and perinatal ischemia-hypoxia as a shared determinant

Birth weight and ADHD risk

Lower birth weight is associated with a wide-range of chronic health and behavioral conditions (Boulet et al. 2011; Gluckman and Hanson 2004) and is one of the strongest, and most studied, risk factors for ADHD (Nigg et al. 2010; Thapar et al. 2013). There is a dose–response relationship between lower birth weight and ADHD risk that is continuous in nature (Boulet et al. 2011; Phua et al. 2012; van Os et al. 2001). In addition, birth weight is associated with increased risk for ADHD over and above gestational age (Lahti et al. 2006). When examined categorically, low birth weight (<2500 g) is associated with an approximately two to threefold increase in ADHD risk (Breslau et al. 1996; Linnet et al. 2006; Mick et al. 2002) after adjusting for covariates including child sex, SES, maternal stress, parental psychopathology, substance abuse, and maternal smoking (Breslau et al. 1996; Elgen et al. 2003; Horwood et al. 1998; Indredavik et al. 2004; Linnet et al. 2006; Zubrick et al. 2000). Further, sibling comparison (Class et al. 2014) and discordant twin studies (Ficks et al. 2013; Groen-Blukhuis et al. 2011; Hultman et al. 2007) indicate that the relationship between birth weight and ADHD is not accounted for by genetic factors alone. Despite the well-established association between lower birth weight and ADHD, there is a paucity of research examining etiological pathways that both limit fetal growth and increase ADHD risk.

Prenatal ischemia-hypoxia, birth weight, and ADHD risk

The relationship between lower birth weight and ADHD is likely driven by precipitating environmental and genetic factors. Prenatal ischemia-hypoxia, or an insufficient supply of nutrients and oxygen to the developing fetus, is a primary pathway to lower birth weight (Henriksen and Clausen 2002; Kinzler and Vintzileos 2008) and prematurity (Salmaso et al. 2014). Prenatal ischemia-hypoxia is implicated in a range of neurodevelopmental disorders, including ADHD (Getahun et al. 2013; Owens and Hinshaw 2013), autism (Gardener et al. 2009; Kolevzon et al. 2007), schizophrenia (Mittal et al. 2008; Schmidt-Kastner et al. 2012; Schmidt-Kastner et al. 2006), and cerebral palsy (Derrick et al. 2007; Mwaniki et al. 2012). In particular, obstetric complications associated with reduced nutrient and oxygen supply during the prenatal period (e.g., preeclampsia) or perinatal period (e.g., birth asphyxia) increase risk for ADHD (Getahun et al. 2013; Pineda et al. 2007) and ADHD-related comorbidity (Owens and Hinshaw 2013). Furthermore, multiple prenatal environmental risk factors for ADHD (Froehlich et al. 2011), such as maternal smoking (Bush et al. 2000; Knopik 2009, 2010; Knopik et al. 2005, 2012, 2015, 2016) and maternal alcohol use (Bosco and Diaz 2012; Knopik et al. 2006) also lead to restricted fetal growth, partially through prenatal ischemia-hypoxia (Table 1). Genetically informed studies, however, demonstrate that the relationship between prenatal environmental risk factors, birth weight and ADHD is complex, and are at least partially accounted for by genetic factors (e.g., Thapar et al. 2009; Knopik et al. 2005, 2015, 2016). Taken together, ischemia-hypoxia during pregnancy and delivery results from a range of obstetric conditions and fetal exposures, which limit fetal growth, and may account for a substantial portion of the ADHD disease burden (Fig. 1).

Ischemia-hypoxia response (IHR)

In response to prenatal ischemia-hypoxia, the placental-fetal unit initiates a cascade of responses to preferentially allocate oxygen and nutrients to promote survival (Murray 2012). Exposure to ischemia-hypoxia leads to changes in metabolic demand (Murray 2012; Wheaton and Chandel 2011), angiogenesis (Shibuya 2008), inflammatory/immune response (Ellison et al. 2005), neuroprotective/neurotoxic systems (Myint et al. 2007), oxidative stress

Table 1 Population attributable fractions (PAF) for ischemia-hypoxia related pre- and perinatal environmental risk factors and ADHD

Risk factor	Adj. RR estimate	PAF estimate (%)
Low birth weight (<2500 g)	2.85[a]	12.8[b]
Maternal smoking	1.53[c]	7.0[b]
Maternal alcohol use/non-FAS spec	5.00[b]	2.4[b]
	Adj. OR estimate	PAF estimate (%)
Preeclampsia	1.34[d]	2.5[d]
Prolapsed/nuchal cord	1.13[d]	2.0[d]
Placental abruption	1.16[d]	0.2[d]
Breech/transverse presentation	1.13[d]	0.7[d]
Respiratory distress syndrome	1.47[d]	0.6[d]
Neonatal resuscitation	2.75[d]	0.4[d]
Apgar score of <7 at 5 min	1.31[d]	0.3[d]
Fetal dystocia	1.11[d]	0.2[d]

Adj RR adjusted relative risk, *Adj OR* adjusted odds ratio, *PAF* population attributable fraction—the percentage of ADHD cases attributed to a given risk factor. Relative risk and odds ratio estimates are derived from single studies and may overestimate the true association between a risk factor and ADHD; however, attempts were made to limit such biases (see Nigg 2006, pp. 226–241; Getahun et al. 2013)

[a] Breslau et al. 1996

[b] Nigg 2006

[c] Linnet et al. 2003

[d] Getahun et al. 2013

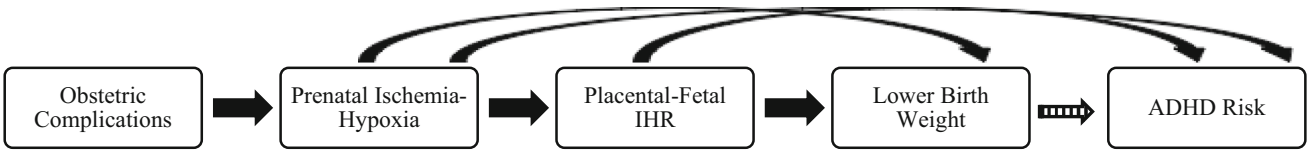

Fig. 1 Prenatal ischemia-hypoxia and the ischemia-hypoxia response are predicted to underlie the association between lower birth weight and ADHD. This model depicts how chronic prenatal ischemia-hypoxia partially determines the association between lower birth weight and attention-deficit/hyperactivity disorder (ADHD) risk. Acute pre- or perinatal ischemia-hypoxia (e.g., umbilical cord prolapse) may still contribute to ADHD risk; however, birth weight may not be affected. *IHR* ischemia hypoxia-response

(Prabakaran et al. 2004), and blood flow redistribution (Roza et al. 2008). Importantly, all of these processes are also implicated in the etiology of ADHD (Lesch et al. 2013; Lou 1996; Lou et al. 2004; Oades 2011; Oades et al. 2010; Ribases et al. 2008; Roza et al. 2008; Sanchez-Mora et al. 2010; Todd and Botteron 2001). Collectively, the ischemia-hypoxia response (IHR) may function to minimize damage to neural tissue from an ischemic-hypoxic pre- and perinatal environment.

Neurodevelopmental outcomes following ischemia-hypoxia exposure, however, are highly variable. Therefore, it is critical to identify genetic and epigenetic factors that might moderate or mediate the association between ischemia-hypoxia and ADHD. Most previous gene by environment interaction (GxE) studies in ADHD selected candidate genes that have shown an association with the disorder (see Nigg et al. 2010; for a review). This approach has a limited conceptual basis and may be related to the inconsistent findings in the ADHD GxE literature (Ficks and Waldman 2009). In contrast, candidate genes or pathways should be selected based on converging evidence from multiple sources (Dick et al. 2015), including their functional significance in relation to the putative environmental pathogen (Moffitt et al. 2005)—in this case, pre-and perinatal ischemia-hypoxia. We have shown that SNPs in angiogenic (NRP1 & NRP2), neurotrophic (NTRK1 & NTRK3), and inflammatory genes (CCBL1, CCBL2, IL16, S100B) moderate the association between birth weight centile and ADHD symptom severity (Smith et al. 2014). These genetic systems have been implicated in the ischemia-hypoxia response and analyses in BrainCloud (Colantuoni et al. 2011) suggest many of these genes are expressed in the prefrontal cortex at relatively higher levels during prenatal development compared to later

development (See Supplementary Fig. 1). This provides preliminary evidence that developmental systems involved in the ischemia-hypoxia response are associated with ADHD risk and effects likely depend on prenatal environmental influences.

Additionally, bioinformatic tools (Viswanathan et al. 2008) can assist in the identification of specific genes and genetic pathways that are implicated in the IHR. Of particular interest are genes that are functionally related to hypoxia inducible factor 1 or 2 (*HIF-1*; *HIF-2*), which regulate the cellular response to hypoxia and are expressed in the brain. HIFs promote adaptation to hypoxic conditions by regulating the transcription of IHR genes (Sharp and Bernaudin 2004), which confer neurological and vascular adaptation (Schmidt-Kastner et al. 2006; Schmidt-Kastner et al. 2012; Sharp and Bernaudin 2004). *HIF-1* is necessary for normal embryonic (Yu et al. 1999), neural, and vascular development (Tomita et al. 2003). In addition, the vascular endothelial growth factor family is the main regulator of angiogenesis (i.e., the formation of new blood vessels; Shibuya 2008; Shibuya and Claesson-Welsh 2006). The angiogenic system is implicated in ADHD etiology (Jesmin et al. 2004; Smith et al. 2014) and is upregulated in response to hypoxia, a process that is mediated by HIFs (Mac Gabhann and Popel 2008) and epigenetic mechanisms (Mimura et al. 2012; Skowronski et al. 2010). Although the IHR aims to protect neural tissue from ischemia-hypoxia, IHR effects may persist and alter susceptibility for neurodevelopmental disorders later in life.

Developmental origins of ADHD: Epigenetic programming and neurodevelopmental risk

The Developmental Origins of Health and Disease hypothesis (DOHaD; Gluckman and Hanson 2004; Mill and Petronis 2008; Nigg 2012; Swanson and Wadhwa 2008) builds on the theory of "fetal programming" (Barker 2007) and provides an integrative framework to conceptualize the interplay between environmental, genetic and epigenetic factors in determining birth and health outcomes. Briefly, DOHaD posits that the prenatal environmental influences are associated with birth outcomes. This association is presumed to be mediated by epigenetic changes which allow the developing fetus to adapt the structure and function of developmental systems to promote survival. Additionally, prenatal environmental influences may disrupt or constrain developmental plasticity (see Gluckman and Hanson 2004). To the extent that there is a mismatch between the prenatal and postnatal environments the individual may be ill-quipped to function adaptively in the postnatal environment. This mismatch confers vulnerability for later disease as the organism is functioning in an environment for which it was not epigenetically programmed to be adaptive in.

From a DOHaD perspective, the association between lower birth weight and ADHD may arise from a milieu of obstetric complications which lead to pre- and perinatal ischemia hypoxia. The placental-fetal unit will adapt to the ischemic-hypoxic environment by altering the structure and function of developmental systems, including the brain. Further, prenatal ischemia-hypoxia may lead to neural disruption (e.g., intraventricular hemorrhage; Whitaker et al. 2011) or place constraints on neurodevelopmental processes (e.g., cerebral blood flow; Fu and Olofsson 2011). At the molecular level, the IHR response functions to promote survival in the context of cerebral ischemia-hypoxia. Consistent with DOHaD, however, the IHR response may leave ADHD-related brain regions ill-equipped to function in a nutrient and oxygen rich postnatal environment, increasing ADHD risk later in life. IHR genetic variability and ischemia-hypoxia induced epigenetic changes (described below) may confer increased risk or protection from ADHD, following pre- and perinatal environmental risk exposure (Mill and Petronis 2008).

Ischemia-hypoxia induced epigenetic effects

Epigenetic mechanisms are a primary mechanism linking adverse intrauterine environments with later risk for disease (Wadhwa et al. 2009). Epigenetic changes in DNA methylation, histone modifications, and noncoding RNA have been shown, in part, to be induced by exposure to prenatal ischemia-hypoxia and alter gene expression (Watson et al. 2010). Ischemia-hypoxia induced epigenetic alterations are maintained in the absence of HIFs (Tsai and Wu 2013; Watson et al. 2010), suggesting they may continue to impact behavioral phenotypes later in life. DNA methylation, for example, is the addition of a methyl group to a cytosine in cytosine/guanine-rich DNA regions (Maccani and Marsit 2009). When cytosines in the gene's promoter region are methylated, gene expression is generally reduced or silenced. Of note, lasting changes in global DNA methylation are observed in the rat brain following cerebral ischemia-hypoxia (Wu et al. 2013). Taken together, decreased nutrient and oxygen availability in utero may alter IHR gene expression (Schmidt-Kastner et al. 2012), through HIFs and epigenetic mechanisms, leading to altered susceptibility for ADHD and related outcomes (Wang et al. 2013).

Pre- and perinatal ischemia-hypoxia and neurodevelopmental risk

Pre- and perinatal ischemia-hypoxia leads to lasting changes in neurodevelopmental functioning, especially in males

(Mueller and Bale 2008). This phenomenon may partially account for ADHD male preponderance (Jesmin et al. 2004; Laplante et al. 2012) and persistence overtime. Thus, it is critical to understand neurodevelopmental sequelae of prenatal ischemia-hypoxia and their relation to ADHD vulnerability. We briefly address four areas we believe to be of neurodevelopmental importance below: (i) neuroanatomical alterations, (ii) neurotransmission perturbation, (iii) neuroinflammation, and (iv) cerebral vascular response.

Neuroanatomical alterations

In animal models, chronic pre- and perinatal ischemia-hypoxia is associated with reductions in brain weight, myelination, neurogenesis, synaptogenesis, and white matter damage (Bassan et al. 2010; Mallard et al. 1999), as well as delays in interneuron, astroglia, and oligodendroglia maturation (Salmaso et al. 2014). Generally, these findings persist into adulthood (Rehn et al. 2004). Numerous human studies highlight the association between fetal growth restriction (an indicator of pre- and perinatal ischemia-hypoxia) and neuroanatomical and neurocognitive outcomes. For instance, in a population-based study, lower birth weight predicted decreased anterior cingulate, caudate and total brain volume in childhood (Walhovd et al. 2012). Additionally, growth-restricted infants have reductions in overall white and gray matter compared to infants in the normal birth weight range (Brown et al. 2009; Larroque et al. 2003; Tolsa et al. 2004). These neuroanatomical findings relate to poor performance on measures of inattention and impulsivity (Peterson et al. 2003; Tolsa et al. 2004) and are consistent with neurocognitive findings in ADHD samples (Filipek et al. 1997; Kates et al. 2002; Mostofsky et al. 2002; Overmeyer et al. 2001). Furthermore, within a low birth weight cohort, immature white matter lesions and ventricular enlargement, which are suggestive of ischemia-hypoxia exposure, predicted increased risk for ADHD (Whitaker et al. 1997, 2011). Taken together, neurodevelopmental outcomes in pre- and perinatal ischemia-hypoxia animal models and human studies suggest neurodevelopmental delays or disruptions, which are functionally related to ADHD symptomatology.

Neurotransmisssion perturbation

Dopaminergic dysfunction remains of central interest for the pathophysiology and genetics of ADHD (Biederman and Faraone 2005; Castellanos and Tannock 2002; Swanson et al. 2007). The role of dopaminergic neurons, fibers, and synapses has been studied in animal models of pre- and perinatal ischemia-hypoxia (Boksa and El-Khodor 2003). Loss of dopaminergic neurons has not been observed in perinatal models, but dysfunction such as imbalances in dopamine release and abnormal receptor expression have been reported (Boksa and El-Khodor 2003; Chen et al. 1997; Ungethum et al. 1996). Bjelke et al. (1991) described increased numbers of tyrosine-hydroxylase positive, dopaminergic neurons in the substantia nigra in a perinatal anoxia model. The transcription factor HIF-1 has been related to the development of nigral dopamine neurons (Milosevic et al. 2007) and to dopamine toxicity (Lee et al. 2009). Interestingly, dopaminergic neurons of the mouse substantia nigra and ventral tegmental area express mainly ARNT as HIF-1 beta subunit and only low levels of ARNT2, contrasting with dual expression in cortical and hippocampal neuronal populations (Dela Cruz et al. 2014). We have speculated that this expression pattern may limit the reaction of midbrain dopaminergic neurons to hypoxia (Dela Cruz et al. 2014). In adult rats, lesions can be observed in the substantia nigra pars reticulata under severe ischemic conditions whereas the dopaminergic nigral neurons are resistant (Inamura et al. 1987). The human striatum is vulnerable to perinatal ischemia-hypoxia (Lou et al. 2004), and experimental studies show dysmaturation of striatal projection neurons following pre-natal hypoxia (McClendon et al. 2014). The interaction between early striatal damage and dysfunction of the dopaminergic input remains to be understood. One intriguing hypothesis (Toft 1999) is that subtle damage to frontostriatal circuitry would lead to specific deficits in sustained attention and response inhibition underlying ADHD behavioral symptoms and related functional deficits (Gau et al. 2015). Taken together, experimental evidence indicates that pre- and perinatal hypoxia can have lasting effects on the dopaminergic function, whereas neuronal death does not seem to play a role.

ADHD is also associated with altered glutamatergic transmission (Elia et al. 2012; Lesch et al. 2013). In contrast to findings related to dopaminergic functioning, prenatal ischemia-hypoxia leads to energy depletion in the fetal brain and neuronal apoptosis (cell death) from glutamate-induced excitotoxicity (Back and Rosenberg 2014). Interestingly, neuronal energy deficiency has also been proposed as a biological underpinning of ADHD (Todd and Botteron 2001).

Neuroinflammation

In response to prenatal ischemia-hypoxia and neuronal apoptosis, the immune system responds by increasing circulating pro-inflammatory cytokines, which further compromises fetal brain development (Jellema et al. 2013). Pro-inflammatory cytokines may lead to increased blood–brain barrier permeability (Kaur and Ling 2008) and excessive quinolinic acid, a glutamate receptor agonist,

which at heightened levels is neurotoxic (Myint et al. 2007). Indeed, elevated levels of circulating cytokines in perinatal development are associated with multiple neurodevelopmental deficits (e.g., Krakowiak et al. 2015), including ADHD diagnosis (Oades 2011) and ADHD neurocognitive endophenotypes (Oades et al. 2010).

Cerebral vascular response

Doppler velocimetry studies have shown that, in response to fetal hypoxia, the fetus increases distribution of blood flow to the brain (Fu and Olofsson 2006). Though this "brain-sparing flow" may confer survival advantage in the moment, it is associated with decreased vascular plasticity in the future (Fu and Olofsson 2006) and increased risk for ADHD symptoms at 3 years of age (Roza et al. 2008). Thus, fetal adaptations to prenatal ischemia-hypoxia and aberrant vascular adaptations may lead to increased vulnerability for later neurodevelopmental and behavioral problems.

Summary and research considerations

Converging lines of evidence indicate that ischemia-hypoxia is an early environmental pathogen for ADHD and related neurodevelopmental outcomes. Ischemia-hypoxia is a common element of multiple (often viewed as disparate) prenatal environmental risk factors, including low birth weight, prematurity, various obstetric complications, and maternal smoking during pregnancy (Table 1). To promote the identification of etiological pathways to ADHD, it is important to consider the physiological sequelae of prenatal environmental risk factors. From this perspective, prenatal ischemia-hypoxia may initiate one common early etiological pathway to ADHD. Further, the IHR pathway highlights regions of the genome and epigenome that are particularly relevant to the development of ADHD, especially in the context of prenatal environmental risk. Further, preliminary evidence suggests that prenatal ischemia-hypoxia may help to explain male preponderance of ADHD (Jesmin et al. 2004; Laplante et al. 2012) as well as phenotypic heterogeneity in ADHD symptomatology (Toft 1999; Gau et al. 2015), persistence (e.g., Wu et al. 2013) and comorbidity (Owens and Hinshaw 2013).To better elucidate mechanisms linking pre- and perinatal ischemia-hypoxia and ADHD, consideration should be given to the following methodological issues.

First, there is little consensus on the most appropriate indicators of pre- and perinatal ischemia-hypoxia. Low birth weight is often utilized as a general proxy for an adverse intrauterine environment. Low birth weight, however, is multifactorial and may identify individuals who are either constitutionally small or premature, but not growth restricted (Maulik 2006) and not exposed to prenatal ischemia-hypoxia. Appropriately grown individuals that are born premature do not appear to be at increased risk for ADHD (Heinonen et al. 2010). Therefore, in models of ADHD risk, it is more appropriate to utilize measures of fetal growth that adjust for gestational age as well as other covariates (e.g., sex, parity, and ancestry), such as customized birth centiles. Customized birth centiles may better capture vulnerability for ADHD due to limited nutrient and oxygen supply in utero compared to birth weight alone as they provide better estimates of growth potential. This measurement approach, however, is not proximally related to prenatal ischemia-hypoxia, prompting the need for more direct measures of prenatal ischemia-hypoxia in human studies, such as Doppler ultrasound assessment of fetal cerebral blood flow (e.g., Roza et al. 2008).

Ischemia-hypoxia related obstetric complications during pregnancy and birth (see Table 1) may provide a more accurate measure of ischemia-hypoxia exposure. Creating a weighted summary score of chronic and acute pre- and perinatal risk factors allows for ischemia-hypoxia exposure severity to be measured on a continuum (Getahun et al. 2013; Lewis and Murray 1987). In addition, directly measuring maternal-placental-fetal blood flow with Doppler ultrasound may provide a more direct measure of prenatal ischemia (Guvendag et al. 2013; Thuring et al. 2012) at the time of assessment. Further, placental pathology examination may provide researchers a physiological measure of limited placental-fetal blood and oxygen flow, which have previously been linked to autism (Walker et al. 2013). Direct measures of prenatal ischemia-hypoxia in human studies are sorely needed to increase the public health impact of research in this domain.

Second, evidence from microarray gene expression studies in brain tissue of mice implicates a wide-range of genes in the ischemia-hypoxia response, which may play an important role in ADHD etiology, especially following an adverse intrauterine environment. Therefore, a multi-omic approach is required to examine the interplay between prenatal environmental risk, genomic, epigenomic, and transcriptomic factors. This would involve integrating genomic, epigenomic and transcriptomic data within the IHR pathway. Analytical approaches for integrating multi-omic data are still in the early stages of development (Lasky-Su 2013). In addition, it is unclear how well epigenetic alternations and gene expression in the brain relate to levels in peripheral tissues (e.g., blood), which are accessible in human studies (Day et al. 2013; Tylee et al. 2013). Studies examining tissue specificity and temporal stability of IHR epigenetic and expression changes in response to ischemia-hypoxia are needed. Leveraging developmental gene expression databases (e.g., Allen

Brain Atlas; BrainCloud; BRAINSPAN) will help to target genes that are relevant to prenatal brain development.

Third, to complement epidemiological studies, there is critical need to leverage experimental and quasi-experimental designs in animals and humans, respectively. Experimental methods which leverage inbred strains of rodents provide the critical methodological control for genetic differences that otherwise obfuscate environmentally-induced epigenetic and expression differences in the IHR pathway. Genetically-informed human studies (e.g., co-twin, sibling comparisons, and children-of-twin) may help to further isolate causal prenatal environmental factors for ADHD and related neurodevelopmental disorders. Thus, utilizing epidemiological and experimental research methods in this domain will help to both identify specific pre- and perinatal environmental causes and molecular mechanisms linking prenatal ischemia-hypoxia exposure with ADHD risk.

In conclusion, prenatal ischemia-hypoxia and IHR genes and epigenetic mechanisms may initiate *one, among many,* possible developmental cascades that ultimately increases risk for ADHD and related neurodevelopmental outcomes. Multi-omic research linking prenatal ischemia-hypoxia with lasting neurodevelopmental vulnerability is needed to better elucidate the role of the IHR pathway in ADHD vulnerability. Such research may help to identify molecular mechanisms associated with neurodevelopmental risk/protection following exposure to an adverse pre- and perinatal environment. Ultimately, this research may inform preventative interventions for ADHD targeting individuals exposed to pre- and perinatal ischemia-hypoxia.

Acknowledgments Authors were supported by the following sources: T32MH19927 and RSCA award California Polytechnic State University (Smith) and DA023134 (Knopik). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veteran Affairs.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This review article does not contain any studies with human or animal subjects performed by any of the authors.

References

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5. Am Psychiatr Assoc, Arlington

Angold A, Costello EJ, Erkanli A (1999) Comorbidity. J Child Psychol Psychiatry 40(1):57–87

Back S, Rosenberg P (2014) Pathophysiology of glia in perinatal white matter injury. Glia 62(11):1790

Barbaresi WJ, Colligan RC, Weaver AL, Voigt RG, Killian JM, Katusic SK (2013) Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study. Pediatrics 131(4):637–644

Barker DJP (2007) The origins of the developmental origins theory. J Intern Med 261(5):412–417

Bassan H, Kidron D, Bassan M, Rotstein M, Kariv N, Giladi E, Davidson A, Gozes I, Harel S (2010) The effects of vascular intrauterine growth retardation on cortical astrocytes. J Matern Fetal Neonatal Med 23(7):595–600

Biederman J, Faraone SV (2005) Attention-deficit hyperactivity disorder. Lancet 366(9481):237–248

Bjelke B, Andersson K, Ogren SO, Bolme P (1991) Asphyctic lesion: proliferation of tyrosine hydroxylase-immunoreactive nerve cell bodies in the rat substantia nigra and functional changes in dopamine neurotransmission. Brain Res 543(1):1–9

Boksa P, El-Khodor BF (2003) Birth insult interacts with stress at adulthood to alter dopaminergic function in animal models: possible implications for schizophrenia and other disorders. Neurosci Biobehav Rev 27(1–2):91–101

Bosco C, Diaz E (2012) Placental hypoxia and foetal development versus alcohol exposure in pregnancy. Alcohol Alcohol 47(2):109–117

Boulet SL, Schieve LA, Boyle CA (2011) Birth weight and health and developmental outcomes in US children, 1997–2005. Matern Child Health J 15(7):836–844

Breslau N, Brown G, DelDotto J, Kumar S, Ezhuthachan S, Andreski P, Hufnagle K (1996) Psychiatric sequelae of low birth weight at 6 years of age. J Abnorm Child Psychol 24(3):385–400

Brown N, Inder T, Bear M, Hunt R, Anderson P, Doyle L (2009) Neurobehavior at term and white and gray matter abnormalities in very preterm infants. J Pediatr 155(1):32–38

Bush PG, Mayhew TM, Abramovich DR, Aggett PJ, Burke MD, Page KR (2000) Maternal cigarette smoking and oxygen diffusion across the placenta. Placenta 21(8):824–833

Castellanos FX, Tannock R (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3(8):617–628

Chen Y, Hillefors-Berglund M, Herrera-Marschitz M, Bjelke B, Gross J, Andersson K, von Euler G (1997) Perinatal asphyxia induces long-term changes in dopamine D1, D2, and D3 receptor binding in the rat brain. Exp Neurol 146(1):74–80

Class QA, Rickert ME, Larsson H, Lichtenstein P, D'Onofrio BM (2014) Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison. Br J Psychiatry 205(5):355–361

Colantuoni C, Lipska BK, Ye TZ, Hyde TM, Tao R, Leek JT, Colantuoni EA, Elkahloun AG, Herman MM, Weinberger DR, Kleinman JE (2011) Temporal dynamics and genetic control of transcription in the human prefrontal cortex. Nature 478:519–524

Day K, Waite L, Thalacker-Mercer A, West A, Bamman M, Brooks J, Myers R, Absher D (2013) Differential DNA methylation with age displays both common and dynamic features across human tissues that are influenced by CpG landscape. Genome Biol 14(9):R102

Dela Cruz JA, Schmidt-Kastner R, Stevens JA, Steinbusch HW, Rutten BP (2014) Differential distribution of hypoxia-inducible factor 1-beta (ARNT or ARNT2) in mouse substantia nigra and ventral tegmental area. J Chem Neuroanat 61–62:64–71

Derrick M, Drobyshevsky A, Ji X, Tan S (2007) A model of cerebral palsy from fetal hypoxia-ischemia. Stroke 38(2 Suppl):731–735

Dick DM, Agrawal A, Keller MC, Adkins A, Aliev F, Monroe S, Hewitt JK, Kendler KS, Sher KJ (2015) Candidate gene-

environment interaction research: reflections and recommendations. Perspect Psychol Sci 10(1):37–59
Doshi JA, Hodgkins P, Kahle J, Sikirica V, Cangelosi MJ, Setyawan J, Erder MH, Neumann PJ (2012) Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. J Am Acad Child Adolesc Psychiatry 51(10):990–1002
Elgen I, Sommerfelt K, Markestad T (2003) Population based, controlled study of behavioural problems and psychiatric disorders in low birthweight children at 11 years of age. Obstet Gynecol Surv 58(2):103
Elia J, Glessner JT, Wang K, Takahashi N, Shtir CJ, Hadley D, Sleiman PM, Zhang H, Kim CE, Robison R (2012) Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. Nat Genet 44(1):78–84
Ellison VJ, Mocatta TJ, Winterbourn CC, Darlow BA, Volpe JJ, Inder TE (2005) The relationship of CSF and plasma cytokine levels to cerebral white matter injury in the premature newborn. Pediatr Res 57(2):282–286
Ficks CA, Waldman ID (2009) Gene-environment interactions in attention-deficit/hyperactivity disorder. Curr Psychiatry Rep 11(5):387–392
Ficks C, Lahey B, Waldman I (2013) Does low birth weight share common genetic or environmental risk with childhood disruptive disorders? J Abnorm Psychol 122(3):842–853
Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J (1997) Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 48(3):589–601
Froehlich TE, Anixt JS, Loe IM, Chirdkiatgumchai V, Kuan L, Gilman RC (2011) Update on environmental risk factors for attention-deficit/hyperactivity disorder. Curr Psychiatry Rep 13(5):333–344
Fu J, Olofsson P (2006) Restrained cerebral hyperperfusion in response to superimposed acute hypoxemia in growth-restricted human fetuses with established brain-sparing blood flow. Early Hum Dev 82(3):211–216
Fu J, Olofsson P (2011) Relations between fetal brain-sparing circulation, oxytocin challenge test, mode of delivery and fetal outcome in growth-restricted term fetuses. Acta Obstet Gyn Scan 90(3):227–230
Gardener H, Spiegelman D, Buka SL (2009) Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry 195(1):7–14
Gau SS, Tseng WL, Tseng WY, Wu YH, Lo YC (2015) Association between microstructural integrity of frontostriatal tracts and school functioning: ADHD symptoms and executive function as mediators. Psychol Med 45(3):529–543
Getahun D, Rhoads GG, Demissie K, Lu SE, Quinn VP, Fassett MJ, Wing DA, Jacobsen SJ (2013) In utero exposure to ischemic-hypoxic conditions and attention-deficit/hyperactivity disorder. Pediatrics 131(1):e53–e61
Gluckman PD, Hanson MA (2004) Living with the past: evolution, development, and patterns of disease. Science 305(5691): 1733–1736
Groen-Blukhuis MM, Middeldorp CM, van Beijsterveldt CE, Boomsma DI (2011) Evidence for a causal association of low birth weight and attention problems. J Am Acad Child Adolesc Psychiatry 50(12):1247–1254
Guvendag GE, Karcaaltincaba D, Kandemir O, Kiykac S, Mentese A (2013) Cord blood oxidative stress markers correlate with umbilical artery pulsatility in fetal growth restriction. J Matern Fetal Neonatal Med 26(6):576
Heinonen K, Räikkönen K, Pesonen A-K, Andersson S, Kajantie E, Eriksson JG, Wolke D, Lano A (2010) Behavioural symptoms of attention deficit/hyperactivity disorder in preterm and term children born small and appropriate for gestational age: a longitudinal study. BMC Pediatr 10:91
Henriksen T, Clausen T (2002) The fetal origins hypothesis: placental insufficiency and inheritance versus maternal malnutrition in well-nourished populations. Acta Obstet Gyn Scan 81(2):112–114
Horwood L, Mogridge N, Darlow B (1998) Cognitive, educational, and behavioural outcomes at 7 to 8 years in a national very low birthweight cohort. Arch Dis Child Fetal Neonatal Ed 79(1):F12
Hultman CM, Torrång A, Tuvblad C, Cnattingius S, Larsson JO, Lichtensetin P (2007) Birth weight and attention-deficit/hyperactivity symptoms in childhood and ealry adolescence: a prospective Swedish twin study. J Am Acad Child Adolesc Psychiatry 46(3):370–377
Inamura K, Olsson Y, Siesjo BK (1987) Substantia nigra damage induced by ischemia in hyperglycemic rats. A light and electron microscopic study. Acta Neuropathol 75(2):131–139
Indredavik M, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk A (2004) Psychiatric symptoms and disorders in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed 89(5):F445
Jellema R, Lima PV, Zwanenburg A, Ophelders D, De Munter S, Vanderlocht J, Germeraad W, Kuypers E, Collins J, Cleutjens J (2013) Cerebral inflammation and mobilization of the peripheral immune system following global hypoxia-ischemia in preterm sheep. J Neuroinflamm 10:13
Jesmin S, Togashi H, Mowa CN, Ueno K, Yamaguchi T, Shibayama A, Miyauchi T, Sakuma I, Yoshioka M (2004) Characterization of regional cerebral blood flow and expression of angiogenic growth factors in the frontal cortex of juvenile male SHRSP and SHR. Brain Res 2:172–182
Kates WR, Frederikse M, Mostofsky SH, Folley BS, Cooper K, Mazur-Hopkins P, Kofman O, Singer HS, Denckla MB, Pearlson GD, Kaufmann WE (2002) MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. Psychiatry Res 116(1–2):63–81
Kaur C, Ling E (2008) Blood brain barrier in hypoxic-ischemic conditions. Curr Neurovasc Res 5(1):71
Kinzler W, Vintzileos A (2008) Fetal growth restriction: a modern approach. Curr Opin Obstet Gynecol 20(2):125
Knopik VS (2009) Maternal smoking during pregnancy and child outcomes: real or spurious effect? Dev Neuropsychol 34(1):1–36
Knopik VS (2010) Commentary: smoking during pregnancy—genes and environment weigh in. Int J Epidemiol 39(5):1203–1205
Knopik VS, Sparrow EP, Madden PA, Bucholz KK, Hudziak JJ, Reich W, Slutske WS, Grant JD, McLaughlin TL, Todoro A, Todd RD, Heath AC (2005) Contributions of parental alcoholism, prenatal substance exposure, and genetic transmission to child ADHD risk: a female twin study. Psychol Med 35(5):625-635
Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, Waldron M, Martin NG (2006) Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design. Psychol Med 36(10):1461–1471
Knopik VS, Maccani MA, Francazio S, McGeary JE (2012) The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Dev Psychopathol 24(4):1377–1390
Knopik VS, Marceau K, Palmer RHC, Smith TF, Heath AC (2015) Maternal smoking during pregnancy and offspring birth weight: A genetically-informed approach incorporating multiple raters. Behav Genet. doi:10.1007/s10519-015-9750-6
Knopik VS, Marceau K, Bidwell LC, Palmer RHC, Smith TF, Todorov A, Evans AS, Heath AC (2016) Smoking during pregnancy and ADHD risk: a genetically-informed, multiple-rater approach. Am J Med Genet Part B. doi:10.1002/ajmg.b.32421
Kolevzon A, Gross R, Reichenberg A (2007) Prenatal and perinatal risk factors for autism: a review and integration of findings. Arch Pediatr Adolesc Med 161(4):326–333

Krakowiak P, Goines PE, Tancredi DJ, Ashwood P, Handen RL, Hertz-Picciotto I, Van de Water J (2015) Neonatal cytokine profiles associated with autism spectrum disorder. Biol Psychiatry. doi:10.1016/jbiopsych.2015.08.007

Lahti J, Raikkonen K, Kajantie E, Heinonen K, Pesonen AK, Jarvenpaa AL, Strandberg T (2006) Small body size at birth and behavioural symptoms of ADHD in children aged five to six years. J Child Psychol Psychiatry 47(11):1167–1174

Laplante F, Brake WG, Chehab SL, Sullivan RM (2012) Sex differences in the effects of perinatal anoxia on dopamine function in rats. Neurosci Lett 506(1):89–93

Larroque B, Marret S, Ancel P, Arnaud C, Marpeau L, Supernant K, Pierrat V, Rozé J, Matis J, Cambonie G (2003) White matter damage and intraventricular hemorrhage in very preterm infants: the EPIPAGE study. J Pediatr 143(4):477–483

Lasky-Su J (2013) A network medicine approach to psychiatric genetics. Am J Med Genet B Neuropsychiatr Genet 162(7):579

Lee DW, Rajagopalan S, Siddiq A, Gwiazda R, Yang L, Beal MF, Ratan RR, Andersen JK (2009) Inhibition of prolyl hydroxylase protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity: model for the potential involvement of the hypoxia-inducible factor pathway in Parkinson disease. J Biol Chem 284(42):29065–29076

Lesch KP, Merker S, Reif A, Novak M (2013) Dances with black widow spiders: dysregulation of glutamate signalling enters centre stage in ADHD. Eur Neuropsychopharmacol 23(6):479–491

Lewis S, Murray R (1987) Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. J Psychiatr Res 21(4):413

Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen TB, Rodriguez A, Kotimaa A, Moilanen I, Thomsen PH, Olsen J, Jarvelin MR (2003) Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. Am J Psychiatry 160(6):1028–1040

Linnet K, Wisborg K, Agerbo E, Secher N, Thomsen P, Henriksen T (2006) Gestational age, birth weight, and the risk of hyperkinetic disorder. Arch Dis Child 91(8):655–660

Lou HC (1996) Etiology and pathogenesis of attention-deficit hyperactivity disorder (ADHD): significance of prematurity and perinatal hypoxic-haemodynamic encephalopathy. Acta Paediatr 85(11):1266–1271

Lou HC, Rosa P, Pryds O, Karrebaek H, Lunding J, Cumming P, Gjedde A (2004) ADHD: increased dopamine receptor availability linked to attention deficit and low neonatal cerebral blood flow. Dev Med Child Neurol 46(3):179–183

Mac Gabhann F, Popel AS (2008) Systems biology of vascular endothelial growth factors. Microcirculation 15(8):715–738

Maccani MA, Marsit CJ (2009) Epigenetics in the placenta. Am J Reprod Immunol 62(2):78–89

Mallard E, Rehn A, Rees S, Tolcos M, Copolov D (1999) Ventriculomegaly and reduced hippocampal volume following intrauterine growth-restriction: implications for the aetiology of schizophrenia. Schizophr Res 40(1):11–21

Maulik D (2006) Fetal growth compromise: definitions, standards, and classification. Clin Obstet Gynecol 49(2):214–218

McClendon E, Chen K, Gong X, Sharifnia E, Hagen M, Cai V, Shaver DC, Riddle A, Dean JM, Gunn AJ, Mohr C, Kaplan JS, Rossi DJ, Kroenke CD, Hohimer AR, Back SA (2014) Prenatal cerebral ischemia triggers dysmaturation of caudate projection neurons. Ann Neurol 75(4):508–524

Mick E, Biederman J, Prince J, Fischer MJ, Faraone SV (2002) Impact of low birth weight on attention-deficit hyperactivity disorder. J Dev Behav Pediatr 23(1):16–22

Mill J, Petronis A (2008) Pre- and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): the potential role of epigenetic processes in mediating susceptibility. J Child Psychol Psychiatry 49(10):1020–1030

Milosevic J, Maisel M, Wegner F, Leuchtenberger J, Wenger RH, Gerlach M, Storch A, Schwarz J (2007) Lack of hypoxia-inducible factor-1 alpha impairs midbrain neural precursor cells involving vascular endothelial growth factor signaling. J Neurosci 27(2):412–421

Mimura I, Nangaku M, Kanki Y, Tsutsumi S, Inoue T, Kohro T, Yamamoto S, Fujita T, Shimamura T, Suehiro J, Taguchi A, Kobayashi M, Tanimura K, Inagaki T, Tanaka T, Hamakubo T, Sakai J, Aburatani H, Kodama T, Wada Y (2012) Dynamic change of chromatin conformation in response to hypoxia enhances the expression of GLUT3 (SLC2A3) by cooperative interaction of hypoxia-inducible factor 1 and KDM3A. Mol Cell Biol 32(15):3018–3032

Mittal VA, Ellman LM, Cannon TD (2008) Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications. Schizophr Bull 34(6):1083–1094

Moffitt TE, Caspi A, Rutter M (2005) Strategy for investigating interactions between measured genes and measured environments. Arch Gen Psychiatry 62(5):473–481

Mostofsky SH, Cooper KL, Kates WR, Denckla MB, Kaufmann WE (2002) Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. Biol Psychiatry 52(8):785–794

Mueller BR, Bale TL (2008) Sex-specific programming of offspring emotionality after stress early in pregnancy. J Neurosci 28(36):9055–9065

Murray AJ (2012) Oxygen delivery and fetal-placental growth: beyond a question of supply and demand? Placenta 33(Suppl 2):e16–e22

Mwaniki MK, Atieno M, Lawn JE, Newton CR (2012) Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 379(9814):445–452

Myint AM, Kim YK, Verkerk R, Scharpe S, Steinbusch H, Leonard B (2007) Kynurenine pathway in major depression: evidence of impaired neuroprotection. J Affect Disord 98(1–2):143–151

Nigg JT (2005) Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: the state of the field and salient challenges for the coming decade. Biol Psychiatry 57(11): 1424–1435

Nigg JT (2006) What causes ADHD? Understanding what goes wrong and why. Guilford Press, New York

Nigg J (2012) Environment, developmental origins, and attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 166(4):387–388

Nigg J, Nikolas M, Burt SA (2010) Measured gene-by-environment interaction in relation to attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 49(9):863–873

Oades RD (2011) An exploration of the associations of pregnancy and perinatal features with cytokines and tryptophan/kynurenine metabolism in children with attention-deficit hyperactivity disorder (ADHD). Atten Defic Hyperact Disord 3(4):301–318

Oades RD, Myint AM, Dauvermann MR, Schimmelmann BG, Schwarz MJ (2010) Attention-deficit hyperactivity disorder (ADHD) and glial integrity: an exploration of associations of cytokines and kynurenine metabolites with symptoms and attention. Behav Brain Funct 6:32

Overmeyer S, Bullmore ET, Suckling J, Simmons A, Williams SC, Santosh PJ, Taylor E (2001) Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. Psychol Med 31(8):1425–1435

Owens EB, Hinshaw SP (2013) Perinatal problems and psychiatric comorbidity among children with ADHD. J Clin Child Adolesc Psychol 42(6):762–768

Peterson B, Anderson A, Ehrenkranz R, Staib L, Tageldin M, Colson E, Gore J, Duncan C, Makuch R, Ment L (2003) Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics 111(5):939

Phua DY, Rifkin-Graboi A, Saw SM, Meaney MJ, Qiu A (2012) Executive functions of six-year-old boys with normal birth weight and gestational age. PLoS One 7(4):e36502

Pineda DA, Palacio LG, Puerta IC, Merchan V, Arango CP, Galvis AY, Gomez M, Aguirre DC, Lopera F, Arcos-Burgos M (2007) Environmental influences that affect attention deficit/hyperactivity disorder: study of a genetic isolate. Eur Child Adolesc Psychiatry 16(5):337–346

Poelmans G, Pauls D, Buitelaar J, Franke B (2011) Integrated genome-wide association study findings: identification of a neurodevelopmental network for attention deficit hyperactivity disorder. Am J Psychiatry 168(4):365

Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164(6):942–948

Prabakaran S, Swatton JE, Ryan MM, Huffaker SJ, Huang JT, Griffin JL, Wayland M, Freeman T, Dudbridge F, Lilley KS, Karp NA, Hester S, Tkachev D, Mimmack ML, Yolken RH, Webster MJ, Torrey EF, Bahn S (2004) Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. Mol Psychiatr 9(7):684–697

Rehn A, Van Den Buuse M, Copolov D, Briscoe T, Lambert G, Rees S (2004) An animal model of chronic placental insufficiency: relevance to neurodevelopmental disorders including schizophrenia. Neuroscience 129(2):381–391

Ribases M, Hervas A, Ramos-Quiroga JA, Bosch R, Bielsa A, Gastaminza X, Fernandez-Anguiano M, Nogueira M, Gomez-Barros N, Valero S, Gratacos M, Estivill X, Casas M, Cormand B, Bayes M (2008) Association study of 10 genes encoding neurotrophic factors and their receptors in adult and child attention-deficit/hyperactivity disorder. Biol Psychiatry 63(10):935–945

Roza SJ, Steegers EA, Verburg BO, Jaddoe VW, Moll HA, Hofman A, Verhulst FC, Tiemeier H (2008) What is spared by fetal brain-sparing? Fetal circulatory redistribution and behavioral problems in the general population. Am J Epidemiol 168(10):1145–1152

Salmaso N, Jablonska B, Scafidi J, Vaccarino FM, Gallo V (2014) Neurobiology of premature brain injury. Nat Neurosci 17(3):341–346

Sanchez-Mora C, Ribases M, Ramos-Quiroga JA, Casas M, Bosch R, Boreatti-Hummer A, Heine M, Jacob CP, Lesch KP, Fasmer OB, Knappskog PM, Kooij JJ, Kan C, Buitelaar JK, Mick E, Asherson P, Faraone SV, Franke B, Johansson S, Haavik J, Reif A, Bayes M, Cormand B (2010) Meta-analysis of brain-derived neurotrophic factor p.Val66Met in adult ADHD in four European populations. Am J Med Genet B Neuropsychiatr Genet 153B(2):512–523

Schmidt-Kastner R, van Os J, Steinbusch H, Schmitz C (2006) Gene regulation by hypoxia and the neurodevelopmental origin of schizophrenia. Schizophr Res 84(2–3):253–271

Schmidt-Kastner R, van Os J, Esquivel G, Steinbusch HW, Rutten BP (2012) An environmental analysis of genes associated with schizophrenia: hypoxia and vascular factors as interacting elements in the neurodevelopmental model. Mol Psychiatr 17(12):1194–1205

Sharp FR, Bernaudin M (2004) HIF1 and oxygen sensing in the brain. Nat Rev Neurosci 5(6):437–448

Shibuya M (2008) Vascular endothelial growth factor-dependent and -independent regulation of angiogenesis. BMB Rep 41(4):278–286

Shibuya M, Claesson-Welsh L (2006) Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis. Exp Cell Res 312(5):549–560

Skowronski K, Dubey S, Rodenhiser D, Coomber B (2010) Ischemia dysregulates DNA methyltransferases and p16INK4a methylation in human colorectal cancer cells. Epigenetics 5(6):547–556

Smith TF, Anastopoulos AD, Garrett ME, Arias-Vasquez A, Franke B, Oades RD, Sonuga-Barke E, Asherson P, Gill M, Buitelaar JK, Sergeant JA, Kollins SH, Faraone SV, Ashley-Koch A, Consortium I (2014) Angiogenic, neurotrophic, and inflammatory system SNPs moderate the association between birth weight and ADHD symptom severity. Am J Med Genet B Neuropsychiatr Genet 165B(8):691–704

Sonuga-Barke EJ (2002) Psychological heterogeneity in AD/HD—A dual pathway model of behaviour and cognition. Behav Brain Res 130(1–2):29–36

Swanson JD, Wadhwa PM (2008) Developmental origins of child mental health disorders. J Child Psychol Psychiatry 49(10):1009–1019

Swanson JM, Kinsbourne M, Nigg J, Lanphear B, Stefanatos GA, Volkow N, Taylor E, Casey BJ, Castellanos FX, Wadhwa PD (2007) Etiologic subtypes of attention-deficit/hyperactivity disorder: brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. Neuropsychol Rev 17(1):39–59

Thapar A, Rice F, Hay D, Boivin J, Langley K, van den Bree M, Rutter M, Harold G (2009) Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. Biol Psychiatry 66(8):722–727

Thapar A, Cooper M, Eyre O, Langley K (2013) What have we learnt about the causes of ADHD? J Child Psychol Psychiatry 54(1):3–16

Thuring A, Maršál K, Laurini R (2012) Placental ischemia and changes in umbilical and uteroplacental arterial and venous hemodynamics. J Matern Fetal Neonatal Med 25(6):750

Todd RD, Botteron KN (2001) Is attention-deficit/hyperactivity disorder an energy deficiency syndrome? Biol Psychiatry 50(3):151–158

Toft P (1999) Prenatal and perinatal striatal injury: a hypothetical cause of attention-deficit–hyperactivity disorder? Pediatr Neurol 21(3):602–610

Tolsa C, Zimine S, Warfield S, Freschi M, Sancho R, Lazeyras F, Hanquinet S, Pfizenmaier M, Huppi P (2004) Early alteration of structural and functional brain development in premature infants born with intrauterine growth restriction. Pediatr Res 56(1):132

Tomita S, Ueno M, Sakamoto M, Kitahama Y, Ueki M, Maekawa N, Sakamoto H, Gassmann M, Kageyama R, Ueda N, Gonzalez FJ, Takahama Y (2003) Defective brain development in mice lacking the Hif-1alpha gene in neural cells. Mol Cell Biol 23(19):6739–6749

Tsai YP, Wu KJ (2013) Epigenetic regulation of hypoxia-responsive gene expression: focusing on chromatin and DNA modifications. Int J Cancer 134(2):249–256

Tylee D, Kawaguchi D, Glatt S (2013) On the outside, looking in: A review and evaluation of the comparability of blood and brain-"omes". Am J Med Genet B Neuropsychiatr Genet 162(7):595–603

Ungethum U, Chen Y, Gross J, Bjelke B, Bolme P, Eneroth P, Heldt J, Loidl CF, Herrera-Marschitz M, Andersson K (1996) Effects of perinatal asphyxia on the mesostriatal/mesolimbic dopamine system of neonatal and 4-week-old male rats. Exp Brain Res 112(3):403–410

van Os J, Wichers M, Danckaerts M, Van Gestel S, Derom C, Vlietinck R (2001) A prospective twin study of birth weight discordance and child problem behavior. Biol Psychiatry 50(8):593–599

Viswanathan G, Seto J, Patil S, Nudelman G, Sealfon S (2008) Getting started in biological pathway construction and analysis. PLoS Comput Biol 4(2):e16

Wadhwa PD, Buss C, Entringer S, Swanson JM (2009) Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin Reprod Med 27(5):358–368

Walhovd KB, Fjell AM, Brown TT, Kuperman JM, Chung Y, Hagler DJ Jr, Roddey JC, Erhart M, McCabe C, Akshoomoff N, Amaral DG, Bloss CS, Libiger O, Schork NJ, Darst BF, Casey BJ, Chang L, Ernst TM, Frazier J, Gruen JR, Kaufmann WE, Murray SS, van Zijl P, Mostofsky S, Dale AM, Pediatric Imaging, Neurocognition, Study Group (2012) Long-term influence of normal variation in neonatal characteristics on human brain development. Proc Natl Acad Sci USA 109(49):20089–20094

Walker C, Anderson K, Milano K, Ye S, Tancredi D, Pessah I, Hertz-Picciotto I, Kliman H (2013) Trophoblast inclusions are significantly increased in the placentas of children in families at risk for autism. Biol Psychiatry 74(3):204

Wang X, Meng FS, Liu ZY, Fan JM, Hao K, Chen XQ, Du JZ (2013) Gestational hypoxia induces sex-differential methylation of Crhr1 linked to anxiety-like behavior. Mol Neurobiol 48(3):544–555

Watson JA, Watson CJ, McCann A, Baugh J (2010) Epigenetics, the epicenter of the hypoxic response. Epigenetics 5(4):293–296

Wheaton WW, Chandel NS (2011) Hypoxia 2. Hypoxia regulates cellular metabolism. Am J Physiol Renal Physiol 300(3):C385–C393

Whitaker A, Van Rossem R, Feldman J, Schonfeld I, Pinto-Martin J, Tarre C, Shaffer D, Paneth N (1997) Psychiatric outcomes in low-birth-weight children at age 6 years: relation to neonatal cranial ultrasound abnormalities. Arch Gen Psychiatry 54(9):847–856

Whitaker AH, Feldman JF, Lorenz JM, McNicholas F, Fisher PW, Shen S, Pinto-Martin J, Shaffer D, Paneth N (2011) Neonatal head ultrasound abnormalities in preterm infants and adolescent psychiatric disorders. Arch Gen Psychiatry 68(7):742–752

Wu X, Sun J, Li L (2013) Chronic cerebrovascular hypoperfusion affects global DNA methylation and histone acetylation in rat brain. Neurosci Bull 29(6):685–692

Yang L, Neale BM, Liu L, Lee SH, Wray NR, Ji N, Li H, Qian Q, Wang D, Li J, Faraone SV, Wang Y, Psychiatric GCAS (2013) Polygenic transmission and complex neuro developmental network for attention deficit hyperactivity disorder: genome-wide association study of both common and rare variants. Am J Med Genet B Neuropsychiatr Genet 162B(5):419–430

Yu AY, Shimoda LA, Iyer NV, Huso DL, Sun X, McWilliams R, Beaty T, Sham JS, Wiener CM, Sylvester JT, Semenza GL (1999) Impaired physiological responses to chronic hypoxia in mice partially deficient for hypoxia-inducible factor 1alpha. J Clin Invest 103(5):691–696

Zubrick S, Kurinczuk J, McDermott B, McKelvey R, Silburn S, Davies L (2000) Fetal growth and subsequent mental health problems in children aged 4 to 13 years. Dev Med Child Neurol 42(01):14–20