



REVIEW ARTICLE

Neuroinflammation in preterm babies and autism spectrum disorders

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Genetic anomalies have a role in autism spectrum disorders (ASD). Each genetic factor is responsible for a small fraction of cases. Environment factors, like preterm delivery, have an important role in ASD. Preterm infants have a 10-fold higher risk of developing ASD. Preterm birth is often associated with maternal/fetal inflammation, leading to a fetal/neonatal inflammatory syndrome. There are demonstrated experimental links between fetal inflammation and the later development of behavioral symptoms consistent with ASD. Preterm infants have deficits in connectivity. Most ASD genes encode synaptic proteins, suggesting that ASD are connectivity pathologies. Microglia are essential for normal synaptogenesis. Microglia are diverted from homeostatic functions towards inflammatory phenotypes during perinatal inflammation, impairing synaptogenesis. Preterm infants with ASD have a different phenotype from term born peers. Our original hypothesis is that exposure to inflammation in preterm infants, combined with at risk genetic background, deregulates brain development leading to ASD.

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INTRODUCTION

The focus of this review is brain injury due to preterm birth and a set of neurodevelopmental disorders strongly associated with preterm birth, the autism spectrum disorders (ASD). Indeed, infants born preterm have a 10-fold higher risk to develop signs of ASD when compared to term infants.^{1–3} Of important note, preterm and term infants with ASD have not completely similar clinical phenotypes as preterm infants generally present a subcategory of ASD with social and communication inabilities but no repetitive/stereotypic behaviors.⁴ In term infants, it is largely accepted that ASD is linked to a combination of genetic and environmental factors, the relative weight of each being different for almost every infant.⁵ In preterm infants, brain injury (the so-called “encephalopathy of prematurity” or “EP”) is often secondary to neuroinflammation, which is mediated by microglia and astrocytes. EP is characterized in part by diffuse white-matter injury and synaptic abnormalities.⁶ As a great number of preterm born infants, relative to term born infants, will develop ASD, our overarching argument is that exposure to neuroinflammatory insult during the last trimester is an environmental factor of great importance to the development of ASD (Fig. 1). To provide support to our argument, we will provide a brief introduction to preterm birth and the brain injuries associated with early birth and the ASDs. We will then point to the similarities and differences in the etiology of these three disorders (preterms with cognitive impairment but no ASD, preterms with ASD, and terms with ASD), in the neurophenotypic outcomes, and also compare and contrast their neurobehavioural profiles. These differences will be key to understand for the development of viable strategies to improve the outcomes for all infants with ASDs.

PRETERM BIRTH

The World Health Organization (WHO) estimates that every year there are at least 15 million infants that are born prematurely, birth before 37 of 40 weeks completed gestation or gestational week (GW). This is ~1 in 10 infants globally that are born too early. Of these 15 million preterm born infants, close to 1 million will not survive and the majority of survivors will be left with permanent neurobehavioral deficits.^{7,8} The incidence of preterm birth is increasing in developed countries and the cause of this is unknown,⁹ although environmental factors such as air pollution are strong candidates.¹⁰ People who were born preterm tend to have lower IQ and to perform worse than aged-matched, full-term born controls in several cognitive areas such as executive functioning, language processing and working memory.^{11–16} These deficits become apparent in early childhood and are permanent, with observations having been made in large cohorts of infants born preterm through adolescence and into late adulthood.^{17,18} The severity of outcomes for individuals born preterm is directly related to the severity of the preterm birth although this is modulated by a host of factors to be discussed below (i.e., inflammation, stress, genetics). Specifically, preterm birth can be subdivided further based on gestational week at delivery as: extremely preterm (before GW 28), very preterm, (between GW 28 to 32) and moderate to late preterm (from GW 32 to 37). The majority (84%) of preterm births are classified as moderate to late preterm.⁹

The etiology of preterm birth

Approximately 45% of preterm deliveries occur with no obvious precipitating factors, i.e., spontaneously, and 25% follow a premature rupture of membrane (PPROM).¹⁹ The remaining 30%

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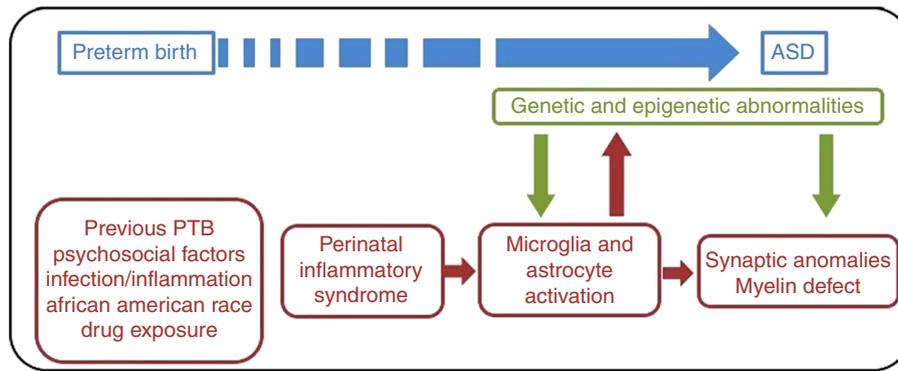


Fig. 1 Schematic representation of the potential interplay between environmental, epigenetic, and genetic factors in the appearance of ASD signs in preterm infants

Table 1. List of factors associated with a higher risk of preterm delivery
Risk factors for preterm birth
Previous spontaneous preterm delivery
Family case of preterm delivery
Psychosocial factors (domestic violence, stress, anxiety, etc)
Maternal or fetal infections/inflammation (urinary tract infections etc)
Cervical incompetence (prior surgery, etc)
Multiple gestations
African American race
Drug use or environmental toxin exposure
Fetal growth restriction/intrauterine growth restriction

of preterm birth are due to induced labor or caesarean due to maternal or fetal conditions. More specifically, several clinical and demographic factors have been associated with preterm birth and are outlined in Table 1.

We would like to highlight a genetic paradigm is an important contributor as women are at higher risk of having a preterm delivery if they have previously experienced preterm delivery, or if they have close family members who have had a preterm delivery.²⁰ Although no candidate genes for preterm birth have yet been reported from genome-wide association studies (GWAS), another approach has been to determine associations between single-nucleotide polymorphism (SNP) and preterm birth. More than 30 SNPs in genes known to have functions in inflammation and tissue remodeling have been associated with preterm birth, PPRM or the severity of brain injury after preterm birth across a number of studies.^{21–24} More recently, Strauss et al. reviewed the literature and presented a suite of studies that support that ‘preterm birth has a polygenic basis that involves rare mutations or damaging variants in multiple genes involved in innate immunity and host defense mechanisms against microbes and their noxious products.’ These studies include whole-exome sequencing (WES) highlighting candidate genes linked to PPRM, and predominantly innate immunity genes.²⁵ This year another study has linked HSPA1L, Heat Shock Protein 70, with spontaneous preterm birth.²⁶ Mutations in HSPA1L have also been recently linked with bowel inflammation.²⁷

Psychosocial risk factors such as stress, anxiety and depression, individually or as comorbid conditions increase the risk of preterm delivery.²⁸ Also linked to the incidence of preterm birth are environmental factors such as work environment, ambient and household air pollution^{10,29} and natural disasters,²⁸ although any link between preterm birth and exposure to disaster (expected to

increase stress levels) such as terrorist attack and hurricane was not supported in a meta-analysis.³⁰

However, the single main risk factor for preterm birth is maternal–fetal infection/inflammation, with 25–40% of preterm delivery linked to infections either subsequent to PPRM or often with no prior diagnosis. The site of infection can include the chorionic space, chorion, placenta, amniotic fluid, umbilical cord, or the fetus. Infection triggers a cascade of events leading to preterm labor,^{31,32} that we understand involves the release of pro-inflammatory chemokines and cytokines which promote the production of prostaglandins that stimulate uterine contractions and the degradation of fetal membranes.^{28,31,32} It is also obvious that there is an interaction between genetic variance, i.e., single-nucleotide polymorphisms (SNPs) and preterm labor. Cohort studies have identified in various settings associations between variants in SNPs in cyclooxygenase-2 (*PTGS2*) and interleukin-6 receptor 1 (*IL-6R*) and preterm birth^{22,24} and specifically [reviewed in refs.^{33,34}]. Moreover, in a US-based case-control study, researchers demonstrated that mothers carrying a polymorphism in the promoter of the tumor necrosis factor alpha gene (*TNFA*) have increased odds of preterm delivery following infection compared to women carrying the same polymorphism and not subjected to infection.²⁸ In addition, preterm birth may be associated with intrauterine growth restriction (IUGR), also known as fetal growth restriction (FGR). IUGR/FGR is characterized by a fetus that does not grow to its genetically destined potential and the clinical diagnostic criteria for IUGR/FGR is when the birth weight is below the 10th percentile for the sex and GW of the infant.³⁵

Encephalopathy of prematurity (EP)

Between GW 18 and 40, fetal white-matter (WM) volume shows a 22-fold increase in volume, the cortical grey matter (GM) undergoes a 21-fold increase and the deep subcortical structure volume increases by 10-fold. As such, preterm birth itself is associated with disruption of the normal developmental programs via neural circuit organization³⁶ and also with events harmful to the brain directly such as inflammatory mediators (discussed further below). Specifically, MRI and post-mortem studies show in preterm born infants a constellation of injuries with diffuse white and grey matter abnormalities, including poor oligodendrocyte (OL) maturation and delayed myelination, reduced neurite formation and glial activation. In addition, generalized micro-structural changes in the cortex are found in preterm infants although the structural underpinnings of these signals are poorly understood.^{37,38} Collectively these constellation of changes is known as encephalopathy of prematurity. We expand on the descriptions of these white and grey matter injuries in following sections.

In addition, it is worth mentioning that the last half of gestation is also fundamental for the growth and maturation of peripheral organs. As such, many preterm born infants suffer from a wide range of complications including respiratory, cardiovascular, and gastrointestinal deficits.³⁹ In addition, necessary daily treatments and surgical procedures for the health of the infant can be painful. Pain has been suggested to itself impact on later cerebral and psychosocial development, but has not been linked specifically to ASD.^{40,41} It requires complex confounding variable analyses to link pain exposure to neurodevelopmental outcomes in preterm born infants as it is the sickest infants that need the greatest number of painful interventions. However, in the rat early life inflammatory pain exposure causes social behavior defects that mimics facets of human ASD behaviors.⁴²

Introduction to causes of EP

There are several factors that are thought to contribute to the evolution of EP that include the disturbance of normal development and damaging extrinsic factors. The first postulated cause of EP relates to the facts that preterm born infants have immature respiratory and cardiovascular systems. The in utero environment in which normal brain development take place has a far lower oxygen tension than the oxygen tension found ex utero. This high (relatively) oxygen environment in which premature infants then undergo the remainder of their brain development. This ex utero hyperoxia is itself considered to be detrimental for brain development, and the negative effects of hyperoxia on the developing brain has been successfully modelled.^{43,44} However, a meta-analysis has found that target oxygen saturation ranges of 85–89% versus 91–95% has no effect on mortality and neurodevelopmental impairment at 18–24 months.⁴⁵ It is also described in some cases that the ability of preterm infants to autoregulate their cerebral oxygen saturation is impaired.^{46,47} This is suggested to lead to periods of hypoxia–ischemia and reperfusion associated with the production of reactive oxygen species (ROS). However, poor cerebral autoregulation is not always observed in cohorts of preterm born infants and it is unclear what the true proportions of infants suffering from poor cerebral autoregulation is, see references and discussion in ref.⁴⁸ The primary risk factor for preterm birth and predictor for outcome is exposure to infection or inflammation^{1,2,49,50}, and for a lively discussion on the causal factors of injury in preterm infants please see ref.⁵¹ In response to infection and inflammation, the systemic immune cells produce a plethora of cytokines,^{52,53} which are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling, including the chemotactic cytokines, chemokines. Chemokines and cytokines play not only a role in the bodies response to injury and infection, but also in the carefully curates steps of normal development, such as OL maturation.^{54,55} Chief among the cytokines known to have a role in injury to the developing brain is TNF α , which has direct effects in high concentrations to injure OL and neurons.⁵⁶ As such, it is to be expected that inflammatory cytokines and chemokines have a chief role in the white and grey matter damage of EP. Cytokines are produced within the brain predominantly by microglia and astrocytes and the specific role of inflammation and these glial cells will be elaborated on below.

WHITE MATTER DEFECTS ASSOCIATED WITH PRETERM BIRTH

At the beginning of the twentieth century and through to the 1990's in high income health care systems, white-matter injury (WMI) was the most obvious and predominantly studied facet of brain damage in premature infants.⁶ In 1962, Banker and Larroche reported, in 51 infants, the presence of periventricular leukomalacia (PVL), a severe form of cystic WMI, but relative sparing of the GM. Thanks to the advances in neonatal care in high income health care systems there are fewer preterm born infants demonstrating large severe cystic WMI, and also steep reduction

in mortality among very and extremely preterm born infants.⁵⁷ Limited access to health care, both antenatal and postnatal, is still associated with worse brain injury, higher mortality and poorer outcomes for preterm born infants, especially in developing countries.⁵⁸

The panorama of injury in preterm born infants in developed countries is now described to principally involve either: (1) moderate WMI with small necrotic lesions and/or glial scars, referred to as “punctate white-matter lesion” (PWML) and diffuse signal abnormalities; or (2) mild to indeterminate WMI, showing microscopic or no necrotic lesions.^{59–61} Because there is heterogeneity in the types of WMI, the outcome for infants can vary from fine to severe motor deficits, sensory deficits, cognitive and learning impairments and behavioral disturbances.^{60,62}

The predominate cause of WMI in preterm born infants is considered to be due to the maturation arrest of OL in the absence of overt oligodendrocyte progenitor cell (OPC) death. This has been shown in human preterm cohort studies,^{63–65} in studies of moderate inflammatory injury,⁶⁶ and in studies of more severe experimental injury.^{67–69} In a cohort of human cases with severe WMI,^{70,71} OL maturation arrest has also been shown secondary to initial OPC death and progenitor proliferation. Numerous studies have demonstrated that the period between GW 28 and 32, which coincides with preterm delivery, is critical for OL maturation because pre-OL are highly vulnerable to environmental factors including inflammatory products such as cytokines and chemokines, for comprehensive reviews on this topic please refer to refs.^{72,73}

Grey matter injury associated with preterm birth

As mention above, grey matter injury (GMI) includes a reduction in the growth of cortical and subcortical regions in EP, including the basal ganglia, thalamus, hippocampus, orbitofrontal lobe, posterior cingulate cortex, centrum semiovale and cerebellum.^{74–76} Previously, these abnormalities in preterm infants were attributed to injury related to severe WMI. However, despite a reduction in the severity of WMI (i.e., less cystic lesions), many preterm born infants still suffer from significant GM abnormalities. The presence of GMI in the absence of cystic lesions demonstrates that these GM changes are primarily development disturbances rather than secondary to destructive processes. Although it is known that during the 3rd trimester the cerebral cortex undergoes a dramatic increase in volume and gyration, results concerning GM from MRI after birth are equivocal. Some studies observed a delay in microstructural development of the GM in multiple cortical regions of brains from infants born preterm.^{37,38,77–79} Of note, it is not yet totally clear what are the neuropathological correlates of these abnormal cortical microstructure.⁸⁰ Advances in MRI-based tractography have made it possible to define a “connectome”, which is a map of neuronal connections in the brain, and compare connectivity of preterm born brains to term born brains. This has been demonstrated a connectivity reduction between thalamus and cortex in preterm infants compared to term infants.⁸¹ Moreover, infants born at term demonstrated a strong resting states network in sensorimotor cortex and cerebellum, which in preterm infants at term-equivalent age were weaker.^{76,81–83} One hypothesis concerning the correlation between white matter and grey matter damage is that WMI in part due to pre-OL maturation blockade may activate astrogliosis and axonal myelination defects in preterm brains associated with neuroinflammation. These axonal defect lead to GMI due to abnormality of the axonal physical tension.^{77,82}

Moreover, data suggest that there is also a reduction in the number of interneurons (inhibitory neurons) in preterm post-mortem brain (H. Stolp, unpublished data) and in rabbit studies.^{84,85} One hypothesis concerning the GM development delay is that preterm birth affects production, migration, survival and/or differentiation of some subsets of interneurons as well as a

blockade of neuronal maturation linked to altered dendritic spine morphology and density.⁸² It has been demonstrated in several studies that this blockade in neuronal maturity is linked to less complexity of dendrites and less synaptic activity due to disrupted maturation of dendrites.^{6,74,75,82}

PRETERM BIRTH AND NEUROPSYCHIATRIC DISORDERS

Infants who were born preterm have a 3-fold increase risk of developing a number of neuropsychiatric diseases, including those characterized by deficits in communication, attention and hyperactivity, social skills, and the severity of these are correlated to the degree of prematurity.^{86–88} Preterm born children and adults also have significantly higher scores on measures of high-intensity pleasure, perceptual sensitivity, and attention problems, and lower scores on discomfort, cuddliness, and attentional focusing.^{89–91} Overall these observations in infants born preterm are thought to be correlated to an impairment of the sensory-neuronal circuits.⁹²

Autism spectrum disorders

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), infants with ASD among other symptoms exhibit difficulty with communication and interaction with others and also show restricted interests and repetitive behaviors. ASD include infants diagnosed with PDD-NOS (Pervasive Developmental Disorder, Not Otherwise Specified), autistic disorder, and asperger syndrome. Indeed, ASD present with deficits that range in severity and are generally considered to be composed of deficits across two domains: social-communication deficits and restricted and repetitive behaviors (RRB), that can be further subdivided into repetitive sensory motor (RSM) and insistence on sameness (IS) behaviors.⁹³ Kim et al.⁹⁴ proposed recently a structural hierarchy of ASD with subcategories that distinguished between the two domains of the spectrum.

In ~35% of cases of ASD, inheritance follow a Mendelian pattern or are directly related to a genetic syndrome. The majority however of ASD is attributed to environmental factors, such as preterm delivery.⁵ Genes strongly associated with an increase of ASD risk include, fragile X mental retardation 1 (*FMR1*), neuroligin (*NLGN*), neurexin (*NRXN*), and *SHANK*.⁹⁵ These and numerous additional genes whose mutations have been associated with ASD are involved in the control of neuronal activity, and epigenetic and transcriptional regulations (see below).

Early diagnosis of ASD, during early childhood development, are now possible through several behavioral observations and clinic evaluations such as the Autism Diagnostic Observation Schedule (ADOS)^{96,97} and the Modified Checklist for Autism In Toddlers (M-CHAT).^{98,99} To highlight the prevalence of ASD in preterm born infants, positive screening using the M-CHAT is close to 6% in children who were born at term, in contrast, to 21% of children who were at an extremely low gestational age.^{100,101}

ASD in infants born preterm

As outlined above, a major neuropsychiatric deficit associated with preterm birth are the ASDs. Several studies have demonstrated an increased risk for ASD of 7- to 10-fold in preterm born infants when compared to term born infants.^{1–3,102} Specifically, preterm infant in which preterm birth was associated with chorioamnionitis have a 16-fold increased risk to develop an ASD.³ This risk remains increased even when adjusting for IQ, given that intellectual disability (ID) is increased among infants born preterm.¹ However, as ID is a common co-morbidity of ASD even among infants not born preterm the utility of excluding these patients probably gives an underestimate of the true rates of ASD in those born preterm. It is worth noting however that an association between preterm birth and ASD was not found in a cohort of Danish children born between 1990 and 1999,¹⁰³ or in

an Australian cohort born between 1980 and 1995.¹⁰⁴ These differences may relate to changes in perinatal care, as the associations between ASD and prematurity are found more reliably in cohorts born after the year 2000 [see references and discussion in ref.¹⁰⁵], where the spectrum of injury has shifted away from gross injury to diffuse and microstructural injury. A pertinent discussion on the problems of comparing early developmental milestones in infants and children born preterm with term born peers discussed whether any increase in rates of ASD might relate to delayed development rather than ASD.¹⁰⁶ However, not only are more preterm children diagnosed with ASD in infancy and as toddlers, but these diagnoses are maintained into childhood⁴ and at least into young adulthood.¹⁰⁷

The ASD phenotype for children born preterm is reported to differ from those born at term. Specifically, children born preterm have been reported to have significantly more impairment in social interactions, communication and total score, but not impairments associated with stereotypic behaviors,⁴ greater sensory problems,¹⁰⁸ and in another cohort have more comorbid presentation with attention-deficient hyperactivity disorder (ADHD).¹⁰⁹ A paper from this year attempted to identify whether repetitive behaviors could be used as a screening tool in toddlers born across a spectrum of gestational ages and weights.¹¹⁰ In comparison to the studies mentioned above, this paper sought to ascertain risk of suboptimal behavioral/psychological outcomes in otherwise undiagnosed children, rather than to clarify the proportion of behaviors in people with ASD based on gestational age at birth. Sifre and colleagues observed that gestational length alone did not predict the occurrence of repetitive or restricted behaviors, but that together with birth weight there was an association. However, the authors point out that their study was on a small cohort of relatively healthy born preterm infants and greater work in children at higher risk may reveal stronger links between birth timing and behavioral risk factors for ASD. A recent review has brought together these phenotypic differences together with observations on brain development,⁸⁷ to outline how preterm birth causes an unbalanced maturation rate across the brain leading to neuropsychiatric disorders such as ASD. Phenotypic subtypes related to characteristics including sensory processing are well established in ASD.^{111,112} Nuanced mathematical approaches to using rich behavioral information such as these from patients is working towards better classifications based on environmental factors such as preterm birth and genetic influences.⁹⁴

Similarities in the brain regions affected by EP and associated with ASD

Brain regions predominantly affected by preterm birth are those involved in sensory perception and social interactions,⁸⁷ see Table 2. Of note, preterm born infants show a reduction in the volume of the orbitofrontal region, an important regulator of self-monitoring and emotional self-regulation.⁷⁶ In term born infant diagnosed with ASD, the same regions are also affected.^{113–115}

The corpus callosum, also known as the callosal commissure is the largest WM structure in the human brain, consisting of 200–250 million axonal projections. The corpus callosum increases in length by approximately 25% during the last trimester, reflecting axonal growth and myelination. Thus, this region is strongly and permanently affected in the brains of infants born preterm primarily due to effects on OL maturation. Furthermore, an underdeveloped corpus callosum is commonly reported in infants with ASD¹¹⁶, and was associated with impairment in social competence and additional deficits linked to autism, specifically in measures of social responsiveness.¹¹⁷

The amygdala processes social information including emotional responses (see review¹¹⁸). Infants born preterm demonstrate a larger amygdala volume but a reduced magnitude of activation, as assessed via MRI compare to infants born at term.^{92,119–122} In term

Table 2. Comparison of brain regions affected by preterm delivery^{35,38,76,79,83} and autism spectrum disorders^{113,114,117} (ASD)

	Preterm birth	ASD
White matter		
Corpus callosum	Yes	Yes
Thalamocortical region	Yes	Yes
Cerebellum	Yes	Yes
Centrum semiovale	Yes	No
Grey matter		
Orbitofrontal region	Yes	Yes
Temporal and parietal lobes	No	Yes
Amygdala	Yes	Yes
Basal ganglia	Yes	Yes
Thalamus	Yes	No
Hippocampus	Yes	Yes
Sensorimotor cortex	Yes	No
Cerebellum	Yes	Yes

infant diagnosed with ASD, clinicians also observed an increased amygdala volume and a reduction of WM connectivity in the right amygdala.^{123,124}

The cerebellum is involved in the motor control but congenital cerebellar abnormalities are often associated with cognitive impairment. Similarly, in preterm infants, cerebellar damage was associated with poor neurological outcome including very increased risk for ASD.¹²⁵ In addition several studies have showed abnormal cerebellar structures in term infants with ASD.¹²⁶

We would also like to specifically highlight that there are shared physical characteristics between patient with ASD and those who were born preterm and suffered EP listed in Table 2. Specifically, these shared physical characteristics include fine motor deficits, poor coordination and toe walking.¹²⁷ Toe walking is considered a co-morbidity with ASD rather than a diagnostic criterion, and although what causes this is not completely understood it is possibly due to a dysfunctional vestibular system or sensory processing issues. Sensory processing issues are also common in preterm born infants,¹²⁸ possibly linking the increased presentation of toe walking in these two patient population.

NEUROINFLAMMATION

Neuroinflammation is defined as the mechanism of central nervous system (CNS) inflammation that occurs in response to trauma, infections, and/or neurodegenerative diseases.¹²⁹ Two key cells involved in neuroinflammation are microglia and astrocyte, described below. In addition, immune cells from the peripheral system also produce cytokines and can themselves invade the brain following blood–brain barrier disruptions and participate in neuroinflammation.¹³⁰

Microglia

Microglia are the resident immune cells of brain and spinal cord derived from erythromyeloid precursors from the yolk sac that migrate to the neuroepithelium during early embryonic development to become effectors of brain development and brain homeostasis.^{131–133} Microglial express a plethora of receptors such as receptors of cytokines/chemokines, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) membrane receptor to detect environmental modifications (see below). Microglia have been found to exist in all species with a nervous system.¹³⁴

In the human and the mouse, microglia initially reside in the areas of the developing WM tracts, and proliferation in these zones begins early in development.^{135,136} In humans, there is proliferation of these immature amoeboid microglia during GW 10–16 and diffusion of these cells throughout the developing brain from the middle of the second trimester (approximately week 25).¹³⁷ In the mouse proliferation occurs during the first two postnatal weeks with a peak at postnatal day (P)14 and adult numbers around P21. In the mouse and the human the turnover of microglia is very slow, and these cells live for at least 3 years in the uninjured mouse,¹³⁸ and up to 20 years in the human.¹³⁹ The peak window of vulnerability for EP is a critical period for microglia because they are still located in the developing WM.^{135,140}

During development, immature amoeboid microglia adopt a ramified homeostatic state and form in adulthood a network specialized for local surveillance. The long cellular processes of microglia continuously scan their environment to detect disruptions in homeostasis using their battery of receptors for DAMPs, PAMPs, cytokines and factors in the extracellular matrix. Microglia are capable of switching rapidly to an activated profile if any modification is detected. The concept of activation includes a loss of homeostatic functions, to be discussed below. In response to altered homeostasis, such as brain injury or disease, activated microglia can exhibit graduated morphological transformation toward an amoeboid appearance that resembles the phagocytic macrophage. Via striking shifts in the transcriptional program of the cell, microglia also change their expression of receptors, enzymes and trophic factors and can migrate towards an area of injury and proliferate. It is increasingly recognized that there is considerable heterogeneity of microglial activation states in the brain. As such, the specific nomenclature of activation states and their specific roles in the brain are matters of debate,¹⁴¹ and this undoubtedly arises from developmental differences in microglial responses¹⁴² and also differences dependent on the specific nature of the brain injury (compare and contrast^{143,144}). However, to aid study and description of these plastic cells we can distinguish three main phenotypes: (i) The pro-inflammatory phenotypes with increased expression of several pro-inflammatory enzymes or cytokines used as markers: *NO synthase inducible 2 (Nos2)*, *Cyclooxygenase 2 (Ptgs2)* and *Tnfa*; (ii) The anti-inflammatory and pro-regenerative phenotype, which overexpress marker such *Cd206*, *lectin galactosidase-binding soluble 3 (Lgals3)* and *insulin-like growth factor 1 (Igf1)*; and (iii) The immuno-regulatory phenotype often associated with pro-inflammatory stimulation probably to resolve inflammation expressing different markers such as *Il1rn*, *Suppressor of cytokines signaling 3 (Socs3)* and *Sphk1*.¹⁴⁵ Importantly, these phenotypes can overlap and transition between them is possible, if not always complete, at least in vitro.¹⁴⁵

In addition to their immune functions, microglia have specific and critical roles during normal brain development and thought out life. During neurogenesis, microglia promote selective neural precursor cell (NPC) death in several regions by producing ROS and by phagocytosis of the extraneous cells;¹⁴⁶ but in contrast, microglia also support the survival of layer V neurons¹³⁶ and support OL maturation by expressing IGF1.¹⁴⁷ In the WM, microglia cells are also known to promote axon fasciculation, whereby neighboring axons travelling together adhere to each other and to be important in normal myelination.¹⁴⁷ Microglia also contribute to circuit assembly by controlling the laminar position of somatosensory interneurons.^{136,148,149} Another major function of microglia during development are their crosstalk with mechanisms of synapse formation and pruning. Recent evidences demonstrated that microglia at P8–10 promote filopodia formation (future synapse) by contact-induced Ca²⁺.¹⁵⁰ Moreover, from P8 to P21, microglia promote synaptic pruning by tagging weak synapses with complement system that are then phagocytosed.¹⁵¹ This increases the strength and the plasticity of synapses. It is

worth noting that a disturbance in each of these normal neurodevelopmental functions have been linked to ASD.^{133,150,152–157} In preterm post-mortem brains, our team previously demonstrated that around cystic lesions microglia cell number is increased compare to term brains. This suggest that microglial activation maybe a key component of WMI and we propose also GMI.^{64,158–160} This association between microgliosis and injury has been observed in models of perinatal brain injury^{66,161–167} and reviewd in ref.¹⁶⁸ Transcriptomic analysis of microglia in our mouse model of EP showed that not only they were polarized towards a pro-inflammatory phenotype but also that many transcripts corresponding to normal function of microglia during brain development were significantly down-regulated.¹⁶⁹ This suggests that these immature microglia abandon their developmental and homeostatic functions due to an inflammatory stimulus

Astrocytes

Astrocyte are the most numerous glial cell type. Neocortical astrocytes arise from two separate pools.¹⁷⁰ Astrocytes found in the deep cortical layers and the WM arise from radial glial cells towards the end of neural proliferation.¹⁷¹ These radial glia are neural stem cells and have a role in guiding migrating neurons. Astrocytes of the superficial cortical layers are primarily derived from glial precursors that multiply in the subventricular zone and then migrate into the cortex.

In the human neocortex, astrocytic proliferation begins at around GW 24, with a peak at around GW 26–28. The exact date at which the production of astrocytes ends is not known, but it could be supposed that the major part of astrocytic production is over by the end of a normal pregnancy. This peak in the production of astrocytes at around GW 26–28 could be of particular importance for preterm newborns. Indeed, astrocytes have important roles in development and homeostasis, including in axonal guidance, the stimulation of neuronal growth, synapse formation, the transfer of metabolites between blood vessels and neurons, the establishment of the pattern of certain brain structures, the production of extracellular matrix components, the production of trophic factors, neuronal survival, myelination, and the maintenance of the blood–brain barrier. For example, experimentally blocking astrocyte production temporarily in the neocortex of rodents induces an increase in programmed cell death in neurons and long-term changes in neocortical synaptic equipment.¹⁷² As expected, based on the human data, in the mouse astrocytes are present before birth and proliferate during the first week and then elaborate their characteristic fine processes, the time equivalent to the human last trimester. Astrocytic processes are then in contact with the newly forming synapse.¹⁷³

Astrocytes express receptors for DAMPs and PAMPs, such as bacterial and viral pathogens.^{174,175} In a healthy brain, astrocytes release modulatory factor including TGF- β that are thought to promote an anti-inflammatory environment.¹⁷⁶ However, in response to injury or infection astrocytes will participate in neuroinflammation by releasing pro-inflammatory cytokines in response to microglial activation. Reactive astrocytes are also involved in the protecting neurons during neuroinflammation by reducing elevated extracellular glutamate¹⁷⁷ and by modulating microglial activation. However, by contributing to the release of toxic molecules, they can also induce brain damage.^{173,178–181} Furthermore, there is a well-recognized interplay between microglia and astrocytes in both driving¹⁸⁰ and resolving¹⁷⁶ brain injury dependent on the circumstance. In developing brain, systemic inflammation activates maturing astrocytes that directly impairs OL maturation¹⁸⁰ supporting that inflammation is a deleterious environmental factor leading to brain maturation impairments and neurodevelopmental disorders.

Neuroinflammation in EP and ASD

As previously described above, preterm delivery is often induced by maternal–fetal infection/inflammation.^{19,32,182} Parturition itself is a process mediated by inflammatory products.^{183,184} As such, it is overt stimulation of early parturition by aberrant inflammation that has a role in linking maternal–fetal infection/inflammation and preterm birth. In addition to driving preterm birth, exposure to maternal–fetal infection/inflammation is also a leading factor in the presence and severity of brain injury/neurodevelopmental disturbance in the infant^{2,185,186} and reviewd in refs.^{72,187} The maternal immune system reacts to the threat by releasing pro-inflammatory chemokines and cytokines in the blood vessel. These molecules then reach the developing fetus, which responds by expressing the same pro-inflammatory molecules even if not directly exposed to the infection. Thus the fetus will develop a systemic inflammation, that leads to a neuroinflammation.⁷² In preterm infants, neuroinflammation is the main cause of WMI: the pro-inflammatory molecules released by microglia is extremely toxic to pre-OL as describe above, and pro-inflammatory microglia profile disrupt its normal developmental function described below.¹⁵⁶ Recently, some clinical data suggest that there is a correlation between neonatal increase of blood pro-inflammatory cytokines in term born and developing ASD later on.^{156,188,189} Moreover, data from post-mortem brains on term born diagnose with ASD demonstrate an increase in microglial and astroglial activation in brains tissues in cortex, cerebellum and WM.¹⁹⁰ These data are additional arguments that underlie perinatal systemic inflammation as a major environmental factor in the development of ASD.

SIMILAR CAUSAL FACTORS IN PRETERM BIRTH AND ASD

Sex dimorphism in ASD and preterm infant brain injury

Sexual dimorphism in outcome is common in infants with ASD and those born preterm.^{109,191,192} The “male disadvantage hypothesis” of Naeye et al.¹⁹³ refers to the observation that females have a better survival rate compared to males facing same environmental factors. During development, there are two key levels of sexual dimorphism: (1) primary sex determination at the fertilization; (2) the secondary sex determination, after birth, occur in response to hormone secreted by sexual organs.¹⁹⁴ During pregnancy, genetic and epigenetic differences between the sexes modulate placentogenesis. This sex-dependent variations in placental structure and function can lead to a differential response to stressors.¹⁹⁵

Two recent studies in Australia and the UK have shown no difference in the rates of preterm birth between the sexes.^{196,197} However, clinicians routinely report developmental difference with males have a higher incidence of brain lesions and respiratory and cardiovascular deficits.^{191,198,199} Moreover, there is also a sex disparity to infection and inflammatory response in preterm birth.²⁰⁰ It is worth noting that there are striking sex differences in the microglia^{201–203} and astrocytes^{204–206} of mice and humans, that is independent of sex hormones. Given the important role of neuroinflammation in brain injury of the preterm infant these differences might explain in part the propensity of males to do worse than females.

ASD, like many neurodevelopmental disorders including consequences of prematurity, shows a clear sex bias with male-to-female ratio around 4:1.²⁰⁷ The real basis for this sex-ratio is still unknown but studies have mostly focused on genetic and epigenetic factors controlling primary sex determination period reviewed in Schaafsma and Pfaff.²⁰⁸ On the other hand, factors affecting the secondary sex determination period such as hormones and environmental stress during pregnancy could also be at play.^{208,209} As a consequence of these mechanisms, girls could be either better protected against the initial insult and/or they could have a better resilience than boys (reviewed in Szatmari²⁰⁹).

Epigenetic factors

We would like to highlight that epigenetic factors such as microRNA (miRNA) and chromatin remodeling proteins are emerging to increase the robustness of developmental programming. miRNA are a class of non-coding RNA that regulate gene expression and there is increasing evidence that they have a critical role in conferring robustness to cell fate programs in other cell types.^{210,211} Evolutionary, miRNA have been demonstrated to respond strongly to environmental stress; thus, a modification in miRNA expression due to environmental factors during development could impact their function.^{210–212}

In EP, and more specifically in OPCs, this could lead to a sustained inhibition of myelination transcription factors, resulting in a blockade of the differentiation process, and thereby WMI. More generally, recent explorations have strongly supported a role for epigenetic mechanisms in OL differentiation and integrity in sustaining major changes in transcriptional networks, nuclear chromatin components, histone acetylation and methylation events, actors of DNA methylation and miRNA, all of which are sensitive to environmental insults.^{213–220} For a specific and detailed description of the molecular mechanisms regulating OL maturation in the context of WMD in preterm infants, please see ref.⁷³

In ASD, an epigenetic dimension have also been add to the risk factors including MeCP2 or other methyl binding proteins (MBDs), histone deacetylases (HDACs), chromodomain-helicase-DNA-binding Protein 8 (CHD8) or imprinted loci (IGF-1/H19) (reviewed in ref.²²¹).

ANIMAL MODELING OF NEUROINFLAMMATION AND SIGNS OF ASD

As described, numerous genes predominantly involved in synapse function have been associated with the development of ASD. Genetically modified mouse models for each of these genes has shown that these capture some aspects of behavioral defects that are reminiscent of clinical signs observed in ASD, even if transposing behavioral abnormalities observed in mice to infants with ASD is challenging. These studies have also verified synaptopathies and connectivity deficits and many describe specific regional alteration such as the hippocampus and cortex.²²² However, the cerebellum is strongly associated in poor outcomes in preterm born infants²²³ and with ASD²²⁴, but only few animal studies have looked for cerebellum alteration in mouse models for ASD. Future studies should have stronger interest in cerebellum dysfunction in ASD mouse model.

Over the past 20 years as the spectrum of injuries in preterm born infants has reduced in severity and our epidemiological studies have improved in their specificity, new models of injury to the preterm born infant have been developed. These have revolved around inflammation,⁶⁶ hyperoxia²²⁵ and hypoxia²²⁶ and there have been indications that the outcomes in these models has relevance for the neuropathology and outcomes in infants with ASD. Specifically, low level exposure to inflammation during development is associated with changes in genes associated with synapse structure and function,²²⁷ and synaptic density is reduced by hyperoxia and chronic hypoxia. Furthermore, behaviors including reduced social play behavior and increased repetitive grooming are impaired in a recently described model combining the injuries of inflammation and hypoxia.²²⁸ A limitation so far has been that a great majority of testing for outcomes in models of perinatal brain injury has focused on learning and memory with a lack of social interaction testing that could potentially make stronger relevance for ASD.

CONCLUSION

In conclusion, we formulated an argument that the development of ASD is linked to genetic and environmental factors. One

of environmental factor is preterm birth and the associated processes of brain developmental disturbance induced by neuroinflammation that is observed in many preterm born infants. We specifically highlight that behavioral testing indicates that infants born preterm with ASD, when compared to term infants with ASD, have a subcategory of ASD with social and communication inabilities but no repetitive/stereotypic behaviors. Understanding these differences will be key to understand for the development of viable strategies to improve the outcomes for all infants with ASDs. The first step in moving towards this understanding is building enhanced animal models that encompass genetic and environmental factors. These studies need to include comprehensive neuropathological, imaging and behavioral outcome measures looking for similarities and differences relevant to term and preterm born infants with ASD.

Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The first author (C.B.) is a PhD student affiliated to the PhD School Bio Sorbonne Paris Cité.

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