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TOPICAL REVIEW

The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome

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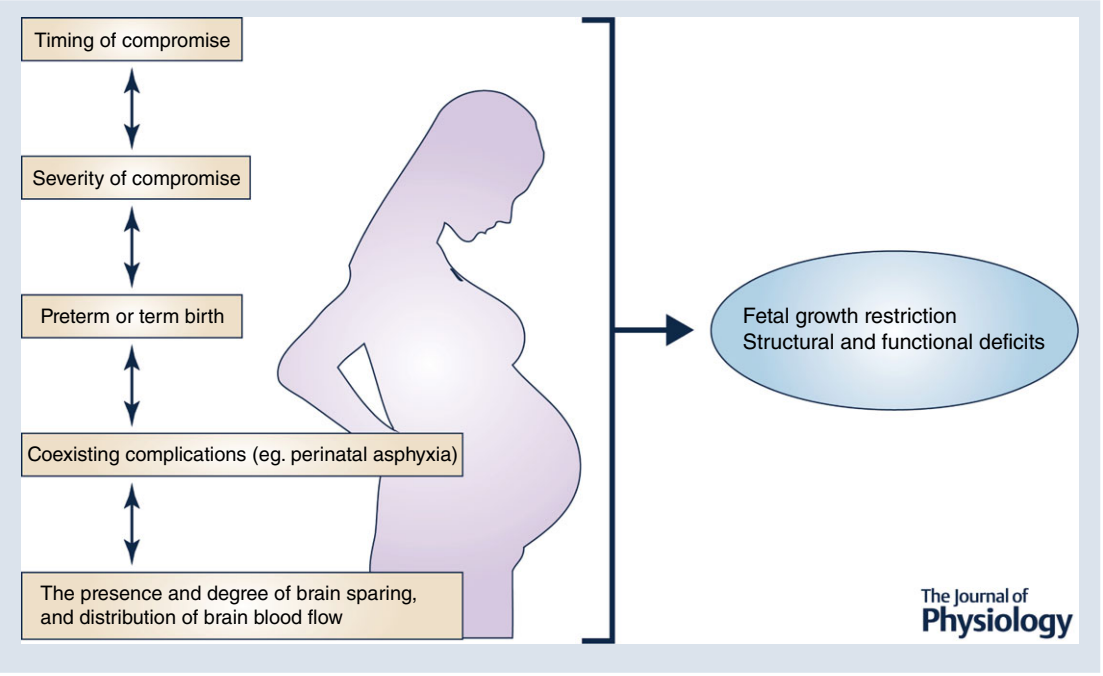

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Abstract Fetal growth restriction (FGR) is a significant complication of pregnancy describing a fetus that does not grow to full potential due to pathological compromise. FGR affects 3–9% of pregnancies in high-income countries, and is a leading cause of perinatal mortality and morbidity. Placental insufficiency is the principal cause of FGR, resulting in chronic fetal hypoxia. This hypoxia induces a fetal adaptive response of cardiac output redistribution to favour vital organs, including the brain, and is in consequence called *brain sparing*. Despite this, it is now apparent that brain sparing does not ensure normal brain development in growth-restricted fetuses. In this review we have brought together available evidence from human and experimental animal studies to describe the complex changes in brain structure and function that occur as a consequence of FGR. In both humans and animals, neurodevelopmental outcomes are influenced by the timing of the onset of FGR, the severity of FGR, and gestational age at delivery. FGR is broadly associated with reduced total brain volume and altered cortical volume and structure, decreased total number of cells and myelination deficits. Brain connectivity is also impaired, evidenced by neuronal migration deficits, reduced dendritic processes, and less efficient networks with decreased long-range connections. Subsequent to these structural alterations, short- and long-term functional consequences have been described in school children who had FGR, most commonly including problems in motor skills, cognition, memory and neuropsychological dysfunctions.

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Abstract figure legend The structural and functional deficits that are associated with fetal growth restriction in human infants are dependent on a number of important factors, including the timing of the onset of placental insufficiency and subsequent fetal hypoxia and hypoglycaemia, the severity of fetal compromise, whether the FGR infant is born preterm or at term, whether coexisting complications are present, and the cerebrovascular responses including whether brain sparing is evident and the severity of brain sparing, as well as the spatial redistribution of brain blood flow.

Abbreviations ACA, anterior cerebral artery; AGA, appropriate for gestational age; DTI, diffusion tensor imaging; FA, fractional anisotropy; FGR, fetal growth restriction; IQ, intelligence quotient; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PI, pulsatility index; RD, radial diffusivity; SGA, small for gestational age.

Introduction

Many neurodevelopmental disorders of motor and cognitive function have their origins in the antenatal period. Suboptimal fetal growth is likely to be a key factor underlying altered brain development. Specifically, fetal growth restriction (FGR), broadly describing the fetus that does not grow to its genetically destined potential (Kingdom & Smith, 2000; Resnik, 2002), is a critical pregnancy compromise that is strongly linked to neurodevelopmental deficits. Depending on the definition used, FGR complicates 3–9% of all pregnancies in high-income countries, but the incidence is reportedly sixfold greater in low-income countries such that worldwide FGR may affect up to 30 million infants per year (de Onis *et al.* 1998; Bernstein *et al.* 2000; Lackman *et al.* 2001; Fang, 2005; Chauhan & Magann, 2006; Figueras & Gratacos, 2014). FGR is associated with preterm birth, perinatal death and, for survivors, an increased risk of motor and sensory neurodevelopmental deficits, cognitive and learning impairments, and cerebral palsy (Blair, 2000; Marlow, 2000; Gagnon, 2003; Yanney & Marlow, 2004; van Wassenaer, 2005; Guellec *et al.* 2011; von Beckerath *et al.* 2013). The implementation of neuroprotective treatments can only occur in response to careful characterisation of the abnormalities in brain development that arise due to FGR, first requiring the identification of infants at greatest risk for neurodevelopmental impairment secondary to poor fetal growth.

There is no internationally recognised clinical definition for intrauterine or fetal growth restriction (IUGR or FGR). This is unfortunate, as it does not allow appropriate consideration of the distinction between poor fetal growth due to pathological compromise (true FGR), and those infants who are constitutionally small. Traditionally, the diagnosis of FGR described an infant with birth weight below the 10th percentile for their sex and gestational age (Kingdom & Smith, 2000), with more recent definitions incorporating measure of placental pathology with abnormal umbilical artery Doppler flow velocimetry during pregnancy (Figueras & Gratacos, 2014). Abnormality of Doppler flow in the umbilical arteries is

clinically significant as it reflects placental compromise, where *placental insufficiency* is considered the principal cause of FGR (Cetin & Alvino, 2009; Figueras & Gardosi, 2011; Story *et al.* 2013). The Doppler cerebroplacental ratio may also be utilised, calculated using the umbilical artery pulsatility index (PI) divided by the middle cerebral artery PI (umbilical/cerebral ratio), and thereby providing a more sensitive marker of growth restriction (Figueras & Gratacos, 2014). In contrast, small for gestational age (SGA) is a term often used to describe infants with birth weight below the 10th percentile, and this is likely to include FGR infants, in addition to infants who are naturally small but healthy. Clinically, the evaluation of placental function using umbilical artery Doppler allows a distinction between SGA and FGR (Figueras & Gardosi, 2011). Many published papers use the term fetal growth restriction or intrauterine growth restriction where in fact SGA would be the more appropriate term. For the purpose of this review we have included any work that describes their cohort as FGR or IUGR.

The causes of FGR are diverse, broadly incorporating factors that may be fetal (chromosomal or congenital abnormalities, multiples, infection), maternal (malnutrition, vascular disease, lifestyle factors including smoking or drug use) or placental in origin (Resnik, 2002). Poor placental function is the greatest contributor to FGR, causing *placental insufficiency* (Pollack & Divon, 1992; Gagnon, 2003; Figueras & Gardosi, 2011). Placental insufficiency results in chronic fetal hypoxaemia, and reduced nutrient availability including altered amino acid transfer and fetal hypoglycaemia (Soothill *et al.* 1987; McMillen *et al.* 2001; Cetin & Alvino, 2009). In turn, chronic fetal hypoxaemia and reduced nutrient availability directly cause decreased fetal growth rate. The growth-restricted fetus responds to chronic hypoxia by slowing its growth rate, and redistributing cardiac output to favour essential organs (brain, heart and adrenals) (Kamitomo *et al.* 1993; Miller *et al.* 2009; Damodaram *et al.* 2012; Poudel *et al.* 2015). This redistribution of fetal cardiac output tends to protect brain growth relative to other organs, resulting in asymmetric fetal growth, or so-called *brain sparing* (McMillen *et al.* 2001; Resnik, 2002; Geva *et al.* 2006*b*). However, brain sparing does not ensure normal brain development. Here, we will describe the neuropathological consequences that are observed in human FGR, and examine the experimental animal literature in an attempt to reveal the complex cellular responses and mechanisms of brain injury secondary to placental insufficiency and chronic hypoxia.

The human brain in FGR: structure and function

Placental insufficiency and FGR have neuropathological consequences for the developing brain. The spectrum of brain abnormalities associated with FGR is heterogeneous, reflecting spread in the timing and severity of *in utero* compromise, whether the FGR infant is born preterm or at term, and whether other co-existing complications are present (see Abstract figure). Two broad factors appear critical to neurodevelopmental outcome – the severity of placental dysfunction together with the gestational age at onset; and the gestational age at delivery (Baschat, 2011). Thus, the management of FGR represents a careful balance between antenatal *in utero* compromise that is likely to contribute to brain injury, and the risks associated with preterm delivery and postnatal intensive care (Baschat, 2011). The contribution of antenatal compromise *versus* postnatal complications, or potential interactions between the two, towards the development of neurodevelopmental sequelae is not yet known.

Current dogma of FGR describes the condition as either early-onset or late-onset, reflecting heterogeneity of underlying causes and clinical features. Early-onset FGR is typically diagnosed by the second trimester, is strongly associated with severe placental dysfunction and chronic fetal hypoxia, is present with preeclampsia in up to 50% of cases, and tends to describe the more severe cases of FGR (Baschat, 2014; Figueras & Gratacos, 2014). Late-onset FGR is the more common form, present in 70–80% of FGR, and typically becoming apparent in the third trimester of pregnancy. In late-onset FGR the umbilical artery Doppler may be normal, reflecting milder placental dysfunction, but advancing fetal deterioration is evidenced by changing umbilical/cerebral ratio (Baschat, 2014; Figueras & Gratacos, 2014). In both early- and late-onset FGR, progressive fetal hypoxia caused by placental dysfunction induces cardiovascular redistribution, and when this is sufficiently severe or prolonged, asymmetric fetal growth and brain sparing occur. The haemodynamic adaptation of brain sparing is considered a mechanism to protect brain development when oxygen availability is low. Unfortunately, however, normal brain development does not necessarily follow cardiac output redistribution to favour the brain (Fig. 1). Late-onset FGR infants born preterm or at term and with evidence of brain sparing have abnormal neurobehaviour in the neonatal period and at 2 years of age (Tolsa *et al.* 2004; Eixarch *et al.* 2008; Oros *et al.* 2010). Studies of neurodevelopment in early-onset FGR offspring also reveal adverse motor, cognitive and behaviour outcomes; however, these may be somewhat confounded by preterm birth (Baschat, 2014). FGR infants with altered umbilical artery Doppler demonstrate significantly poorer motor and cognitive outcomes at 2 years of age, and at school age, compared with appropriately grown age-matched preterm or term offspring (Vossbeck *et al.* 2001; Morsing *et al.* 2011). Scherjon and colleagues showed that fetal brain sparing with elevated umbilical/cerebral ratio was not associated with adverse neurodevelopmental outcome at 3 years of age, but at 5 years of age there was a negative association

with mean intelligence quotient (IQ) score such that infants with brain sparing had an IQ score 9-points lower than expected (Scherjon *et al.* 1998, 2000). Motor ability, cognition and behaviour scores remain lower in older children and young adolescents who demonstrated reversed end-diastolic velocity *in utero* and were born preterm (Schreuder *et al.* 2002). Both early- and late-onset FGR are a significant risk factor for the development of cerebral palsy (McIntyre *et al.* 2013; Baschat, 2014; Blair & Nelson, 2014).

Brain structure

Deficits in brain structure and function are commonly observed in FGR offspring (Fig. 2). Despite the adaptation of brain sparing, a number of studies report that FGR infants have smaller head circumference than age-matched appropriately grown infants (Harel *et al.* 1985; Tolsa *et al.* 2004; Padilla *et al.* 2010). This is clinically important, since small head size during infancy is a strong predictor for poor neurodevelopmental outcome (Gale *et al.* 2006). Human FGR is associated with decreased total brain and cortical grey matter volumes (Tolsa *et al.* 2004) with significantly smaller brain volume first evident *in utero* (Businelli *et al.* 2015). Relative cortical grey matter volume is decreased by FGR, indicating that there is a specific vulnerability of grey matter to FGR, independent of overall brain volume reduction (Tolsa *et al.* 2004), and these structural abnormalities are paralleled by neonatal neurobehavioural deficits such as less well developed attention capacity. Postmortem studies of human infants with FGR confirm a decrease in the total number of cells within the brain (Samuelsen *et al.* 2007) and decreased myelin content (Chase *et al.* 1972). Head circumference often remains lower in 6-year-old children and adolescents that were SGA at birth (Hadders-Algra & Touwen, 1990; Pryor *et al.* 1995).

Soon after birth, FGR infants display significant differences in morphological neurostructure, evident as altered cortical gyrification, which is likely to be due to a thinner cortical thickness compared to appropriately grown infants (Dubois *et al.* 2008), and at 12 months of age FGR infants have reduced structural complexity of brain grey and white matter (Esteban *et al.* 2010). Preterm FGR infants with brain sparing and who underwent MRI at term-equivalent age further demonstrate a delay in myelination and reduced posterior white matter volume in the absence of white matter lesions (Ramenghi *et al.* 2011). A number of studies note decreased volume in the hippocampus and the cerebellum, contributing to the discussion that these areas are very vulnerable to chronic hypoxia during periods of accelerated growth (Lodygensky

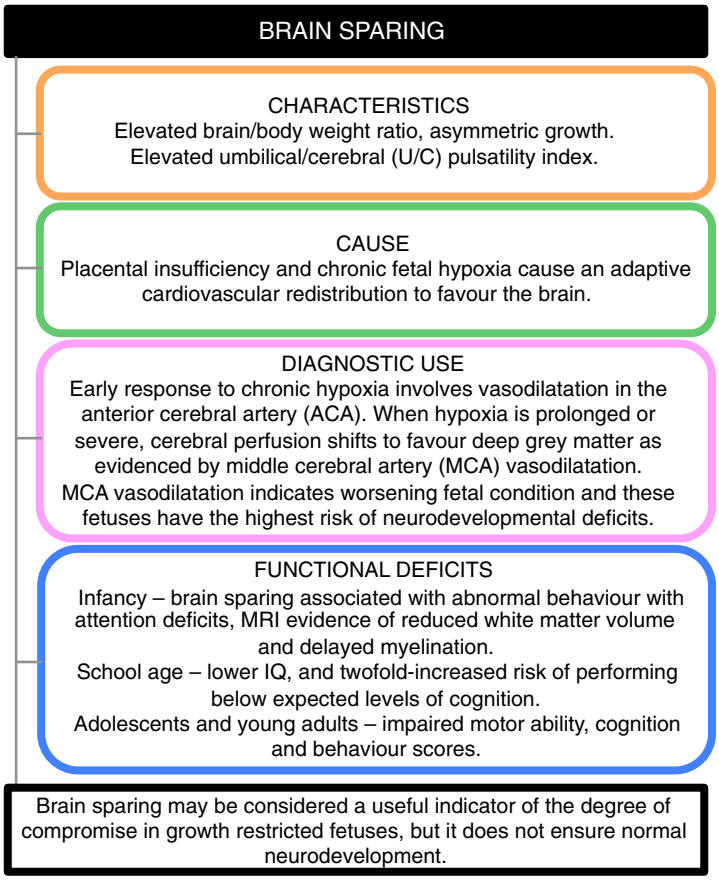


Figure 1. The characteristics, cause, diagnostic use and neuropathology associated with brain sparing in human infants and children
Brain sparing occurs as an adaptive cardiovascular response to fetal hypoxia and may protect against worse brain damage, but does not *spare the brain* from injury.

et al. 2008; Padilla *et al.* 2011, 2014). One particularly useful imaging advancement is the use of diffusion tensor imaging (DTI) assessment of fractional anisotropy (FA), which provides microstructural information on the organisation and integrity of white matter tracts. In healthy, myelinated white matter, FA values are high and radial diffusivity (RD) is low, since water molecules preferentially diffuse in the direction of the tracts rather than perpendicular to fibre tracts (Huppi *et al.* 1998). In neonatal white matter, the FA increases and the RD decreases with age, as fibre organisation, axonal coherence and myelination progress (van de Looij *et al.* 2015). In FGR infants, DTI imaging of the white matter at 12 months of age suggests a complex set of altered white matter organisation, with clustered areas of decreased FA in the corpus callosum, but increased FA in fronto-occipital, internal and external capsule white matter tracts (Padilla *et al.* 2014). Recently, developments in whole brain connectome analysis show reduced global and local network efficiency using graph model measures (Batalle *et al.* 2012) and reduced connectivity in long range cortico-basal ganglia connections predominantly in the prefrontal and limbic networks in preterm children born FGR, compared with preterm children with appropriate birth weight. These structural brain network measures also correlate with neurobehavioral impairments such as hyperactivity or cognitive deficits, in the executive function domain at school age (Fischi-Gomez *et al.* 2014). Notably, suboptimal brain development *in utero* has profound long-term consequences, with deficits in total brain volume and white matter integrity underlying reduced IQ and cognitive impairment particularly in preterm infants with additional FGR (Chiang *et al.* 2009; Guellec *et al.* 2011). Interestingly, in the large French cohort study EPIPAGE, the rate of neurocognitive deficits in moderately preterm infants with FGR is around 40%, and is identical to the incidence of neurocognitive deficits in extremely preterm infants (Guellec *et al.* 2011), indicating that there is a common period of vulnerability in brain development, both for intra-uterine and extra-uterine adverse conditions.

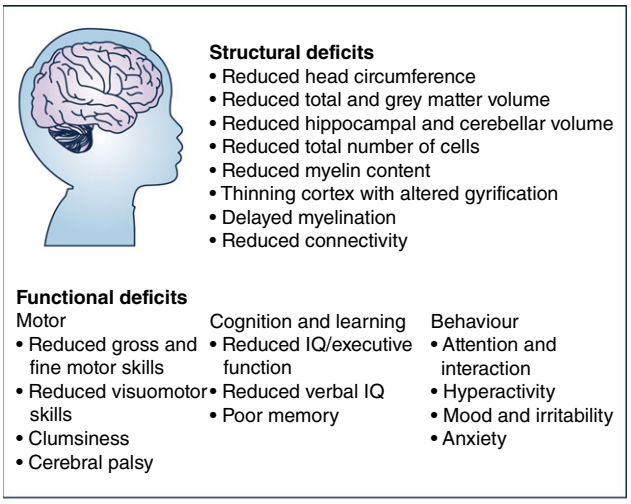


Figure 2. Deficits in brain structure and function commonly observed in FGR offspring
Listed at the top are structural deficits within the total brain, grey matter and white matter of FGR human infants. The bottom describes deficits in motor function, cognition and learning, and behaviour that have been observed in children that were FGR.

In addition to providing clinical information about the presence or degree of fetal brain sparing during conditions of fetal growth restriction, Doppler ultrasound can also give an insight into haemodynamic changes in cerebral perfusion associated with FGR. The middle cerebral artery (MCA) has been most often examined, and reduced Doppler pulsatility index in the MCA is commonly reported as evidence of brain vasodilatation (Hernandez-Andrade *et al.* 2012). However, recent studies in FGR fetuses suggest that vasodilatation of the MCA may only detect an advanced stage of brain blood flow redistribution, reflecting an association between progressive fetal demise and regional changes in cerebral perfusion (Figueroa-Diesel *et al.* 2007; Rossi *et al.* 2011). In FGR fetuses, vasodilatation is first evident in the anterior cerebral artery (ACA) before being observed in the MCA (Rossi *et al.* 2011; Hernandez-Andrade *et al.* 2012). This is indicative of preferential perfusion to the frontal region of the brain as an early response to chronic hypoxia. As chronic hypoxia continues, or becomes worse and the fetus deteriorates, perfusion changes to favour (in an attempt to protect) the basal ganglia at the expense of the frontal lobe, and reduced pulsatility index in the MCA become apparent (Hernandez-Andrade *et al.* 2012). Supporting this, decreasing MCA pulsatility index is correlated with worsening fetal hypoxaemia (Akalin-Sel *et al.* 1994), and an increased prevalence of brain injury (Spinillo *et al.* 2009). The presence of MCA vasodilatation is also associated with significantly increased risk for neonatal acidosis, indicative of fetal distress and poor fetal reserve in the face of intrapartum challenge (Cruz-Martinez *et al.* 2011). Vasodilatation in the MCA also predicts poor neonatal behaviour, and more than half of fetuses with abnormal Dopplers and growth restriction will subsequently have neurological deficits at 2 years of age (Eixarch *et al.* 2008). While abnormal MCA flow detects advanced haemodynamic changes in the FGR brain, ACA vasodilation, and therefore preferential blood flow to the frontal region, is also associated with deficits in neurodevelopmental behaviour soon after birth, and increased incidence of emotional and attention problems at 18 months of age (Roza *et al.* 2008; Cruz-Martinez *et al.* 2009). Combined, these data confirm that brain sparing

is a characteristic FGR response to chronic placental insufficiency and hypoxia, aimed at conserving energy and preserving normal cell processes in critical brain regions (Pearce, 2006). It is now evident that with advancing fetal hypoxia and compromise, the cerebral haemodynamic response involves two components – firstly an initial stage aimed at protecting the brain, followed by a second stage of decompensation that is associated with brain injury (Hernandez-Andrade *et al.* 2012). Certainly the observation of brain sparing is a very useful indicator of compromise in growth-restricted fetuses, and may act to moderate against greater injury to the developing brain. In general, however, it must be considered that the term *brain sparing* is a misnomer and the brain is not spared from injury (Fig. 1).

FGR is widely considered a risk factor for perinatal brain injury including intraventricular haemorrhage (IVH), albeit clinical studies document varied results with elevated, reduced, or unchanged rates of IVH in FGR infants compared to appropriately grown counterparts (Bernstein *et al.* 2000; Gilbert & Danielsen, 2003; von Beckerath *et al.* 2013; Malhotra *et al.* 2015). Placental insufficiency with abnormal umbilical artery Doppler was linked to the presence of IVH (Marsoosi *et al.* 2012). When considering that brain sparing is a characteristic response to placental insufficiency and chronic hypoxia, it is not surprising that alterations in blood flow to the brain may be both indicative of the clinical severity of FGR, and associated with neurodevelopmental impairments (Hernandez-Andrade *et al.* 2012). The adaptive response of brain sparing necessitates remodelling of the fetal brain circulation, structurally (altered number of blood vessels) and functionally, where chronic hypoxia induces vasodilatation of the cerebral circulation that can be detected via Doppler ultrasound as a decreased pulsatility index in the cerebral arteries (Roza *et al.* 2008; Hernandez-Andrade *et al.* 2012). This brain circulatory adaptation differs according to the severity of chronic hypoxia, and the gestational age of the fetus, reflecting the stage of cerebral circulatory development (Hernandez-Andrade *et al.* 2012). In SGA preterm infants, a significantly lower rate of IVH has been observed compared to AGA infants, and the authors hypothesised that intrauterine stress may be protective (Procianoy *et al.* 1980). Conversely, Bernstein *et al.* (2000) showed a non-significant trend towards increasing rates of IVH in FGR infants born between 25 and 30 weeks' gestation. When a large cohort of babies were separated into weekly birth intervals, it was found that IVH rates were significantly lower in FGR *versus* non-FGR infants born at 28 weeks, suggesting a protective effect of growth restriction, but that IVH rates became significantly elevated in late-preterm FGR births $>$ 34 weeks (Gilbert & Danielsen, 2003). This result has been confirmed by a more recent study (Ortigosa Rocha *et al.* 2010) showing that IVH was more common in late-preterm FGR infants compared to appropriately grown infants. This finding is of concern since late preterm births, $>$ 34 week and $<$ 37 weeks, account for the vast majority of preterm births, and the incidence of late-preterm births is increasing (Loftin *et al.* 2010).

Brain function

The adverse effects of FGR on brain structure have a variety of consequences for function. FGR infants born preterm and assessed at term equivalent age demonstrate functional deficits in neurobehavioural score for attention and responsivity, compared to appropriately grown preterm infants, with cerebral cortex grey matter volume correlated to attention–interaction score (Tolsa *et al.* 2004). At 7 months of age, FGR infants perform more poorly on a visual recognition memory task than age-matched appropriately grown infants (Gotlieb *et al.* 1988). Preterm FGR infants followed-up at 1, 2 and 3 years of age showed deficits in developmental and behavioural outcomes, compared to preterm age-matched appropriately grown infants, but it is interesting to note that preterm FGR infants were not different from birth weight matched controls (that is, infants who were born at an earlier gestation but were not growth restricted) (Sung *et al.* 1993). Leitner and co-workers undertook a longitudinal study from birth to middle school age (age 9–10 years) in children born with late-onset FGR with evidence of brain sparing. This study showed that FGR children have a complex set of neurodevelopmental deficits compared to age-matched appropriately grown children (Leitner *et al.* 2007). While suboptimal cognitive performance (IQ $<$ 85) was apparent in 15% of FGR children, they were also more likely to have specific learning disabilities such as reduced memory performance and visuomotor functions, attention and behavioural deficits (Leitner *et al.* 2007). Where brain sparing (elevated umbilical/cerebral ratio) was apparent, IQ at 5 years of age was 9 points lower (87 *versus* 96) compared to children with a normal umbilical/cerebral ratio (Scherjon *et al.* 2000). Multiple follow-up studies of FGR infants into school-age childhood find deficits in gross and fine motor skills, cognition, memory and academic ability, as well as neuropsychological dysfunctions encompassing poor attention, hyperactivity and altered mood (Low *et al.* 1992; Kok *et al.* 1998; Geva *et al.* 2006*a*,*b*; Fischi-Gomez *et al.* 2014).

It is apparent from the literature that determining the neurodevelopmental consequences of FGR is complicated by the severity of FGR, early or late onset, and the gestational age at delivery (Baschat, 2014). Early-onset severe FGR is considered high risk for deficits in outcome, and indeed at school age, severe FGR children perform worse on assessment tasks for cognition, motor function, behaviour and educational achievements than children

who had mild to moderate FGR, or preterm appropriately grown children (Schreuder *et al.* 2002). The combination of early-onset FGR, fetal cardiovascular compromise and preterm delivery is linked with the most significant neurodevelopmental deficits (Baschat, 2014). Preterm birth is likely to be an exacerbating factor when describing the neurological outcomes associated with FGR, and Yanney & Marlow (2004) suggest that preterm birth overrides the effects of FGR *per se*. This is supported by a large prospective French study that examined neurological outcomes in school-age children that were born AGA or SGA at 24–28 weeks or 29–32 weeks gestation, and found cognitive deficits, inattention–hyperactivity, and school difficulties in AGA and SGA infants born at 24–28 weeks gestation, and similarly in those SGA infants born in the 29–32 week group, but much less in infants born appropriate for gestational age at 29–32 weeks. Interestingly, even mild-SGA infants (10th–19th centile) born at 29–32 weeks also showed mild cognitive and behavioural difficulties (Guellec *et al.* 2011). Finally, it has also been shown that serious neurodevelopmental consequences are more prevalent in SGA infants who demonstrate perinatal acidosis (Soothill *et al.* 1995), suggesting that a secondary acute (birth) compromise has profound additive adverse effects in fetuses that have experienced chronic antenatal hypoxia. Recent studies find that impaired fetal growth increases the risk for low intellectual performance across all stages of gestation. Indeed this has been confirmed by comparing monozygotic twin pairs at school age or in adulthood, where the growth-restricted twin is at increased risk for low intellectual performance with reduced verbal IQ compared to the appropriately grown twin (Bergvall *et al.* 2006; Edmonds *et al.* 2010). In addition, a further study in twins has quantified the effects of low birth weight, showing that a 500 g increase in (term) birth weight results in a 2% increase in total brain volume, grey matter volume and white matter volume, and a 2-point increase in IQ (Raznahan *et al.* 2012).

A number of studies have analysed results based on the child's sex, where sex differences may influence neurodevelopmental outcomes for FGR infants. Parkinson and colleagues reported that poor school achievement and behavioural problems were more frequently observed in boys with early-onset growth restriction (Parkinson *et al.* 1981). This is supported by another study showing that FGR boys born very preterm (24–29 weeks) were at the greatest risk of cognitive impairment examined at school age, compared to FGR preterm girls and appropriately grown preterm offspring (Morsing *et al.* 2011). In girls, severe growth restriction is a strong indicator for impaired neurocognition, whereas mild- to moderate-growth restriction is not (Streimish *et al.* 2012). The pattern of adverse behaviours may also differ according to the child's sex; girls at school age that had been FGR at birth were more likely to be irritable and cry than non-FGR girls, whereas FGR boys tended to display anxiety, clumsiness and an inability to concentrate in class (Parkinson *et al.* 1981).

Animal experimental induction of FGR

FGR has been experimentally induced in rats, guinea pigs, rabbits and sheep, and the general physiology and advantages and disadvantages for each model have been reviewed previously (McMillen *et al.* 2001; Morrison, 2008; Basilious *et al.* 2015; Swanson & David, 2015) (Table 1). These animal models have been used experimentally to characterise altered brain development, and other organ and systemic pathologies associated with fetal growth restriction. While no single animal model can encompass the multifactorial causes and consequences of FGR, each animal model brings insight into the brain's developmental adaptations, cellular and microstructural responses to chronic hypoxia and hypoglycaemia, and potential causal pathways that contribute to brain injury (Table 1 and Fig. 3). These same animal models provide valuable and informative tools to examine the short- and longer-term benefits of potential neuroprotective therapies for use in FGR.

The most commonly used methods to induce FGR in fetal sheep are removal of the endometrial caruncles in the ewe prior to mating (Alexander, 1964; Robinson *et al.* 1979), by injecting microspheres in the placental circulation (Gagnon *et al.* 1994; Mallard *et al.* 1998; Louey *et al.* 2000) and by ligation of one of the umbilical arteries (Emmanouilides *et al.* 1968; Supramaniam *et al.* 2006). While carunclectomy results in placental insufficiency throughout gestation, the other methods reflect late onset FGR. In pregnant rodents, guinea pigs and rabbits, FGR is often induced by uterine artery ligation at different gestational ages (Wigglesworth, 1974; van Marthens *et al.* 1975). In precocial species such as the guinea pig, FGR uterine artery ligation is typically performed at mid-gestation (Lafeber *et al.* 1984), while in altricial species, such as the rat, FGR is induced at the end of pregnancy to mimic early third-trimester onset FGR in humans (Basilious *et al.* 2015). It is, however, useful to consider that the timing of brain development and maturation varies markedly across the experimental animal models studied. For example, sheep display a relatively mature brain at the time of birth compared to humans, while the rat brain is more immature at birth (Dobbing & Sands, 1979). Principally, the FGR animal models described here cause variable periods of chronic fetal hypoxia and hypoglycaemia to reflect human placental insufficiency, and in turn cause subsequent asymmetric FGR. Maternal nutrient restriction, maternal corticosteroid exposure and FGR are also important causes of compromised brain growth and growing areas of

Table 1. Summary of animal experimental models of FGR and their neuropathology

General description	Brain structure and microstructure in FGR offspring	References
Guinea pig; unilateral uterine artery ligation; onset 0.45 gestation (30 of 67 days gestation)		
FGR classified as <2 SDs below controls Fetal body weight reduced by 22–50% Brain sparing present Reduced crown-rump length Reduced forebrain and cerebellar weight	Ventriculomegaly and reduced basal ganglia volume Reduced hippocampal volume and number of CA1 pyramidal neurons Reduced cerebellar volume (molecular layer, internal granular layer, and white matter) with delayed development Reduced number of cerebellar Purkinje neurons Altered dendritic morphology of hippocampal neurons with reduced dendritic length, outgrowth and branch number Altered myelination profile with reduced total myelin, more unmyelinated axons and thinner myelin sheaths Reduced white matter volume at 60 days' gestation, normalised by young adulthood Transient delay in oligodendrocyte maturation and myelination, restored postnatally Astrocyte proliferation around blood vessels Sensorimotor deficits	Nitsos & Rees, 1990; Dieni & Rees, 2003; Rehn *et al.* 2004; Mallard *et al.* 2000; Tolcos *et al.* (2011)
Rabbit; ligation of 40–50% of uteroplacental vessels; onset 0.8 gestation (25 of 31 days gestation)		
Birth weight reduced by 26–40%	Reduced total brain volume Immature white matter organisation (less organised) that persists into early adulthood Diffusion MRI demonstrates decreased FA in hippocampus and subventricular white matter Reduced fibre tract connectivity, with altered connectivity correlated to neurobehavioural and cognitive deficits	Eixarch *et al.* 2012; Illa *et al.* 2013
Rats; uterine artery ligation; onset 0.86 gestation (19 of 22 days gestation)		
Body weight reduced at birth (10–20%), and persists until postnatal day 21 Gradient in the degree of FGR, depending on site of the fetus *in utero* Brain sparing present	Neuronal degeneration, apoptosis and sparse structure of the cerebral cortex, observed antenatally persistent to adulthood Reduced organisation of stratified cortical layer structure, reduced number of synapses Reduced hippocampal neuron number at birth Altered hippocampal astrocyte and immature oligodendrocyte number that was region and sex-specific Lesions observed in the cingular white matter and internal capsule, with neuroinflammation and astrogliosis Reduced number of mature oligodendrocytes, but not oligodendrocyte precursor cells, at postnatal day 14 Apoptosis of pre-oligodendrocytes, oligodendrocyte loss and reduced density of myelinated fibres persistent to day 21	Tashima *et al.* 2001; Reid *et al.* 2003; Olivier *et al.* 2005, 2007; Liu *et al.* 2011; Delcour *et al.* 2012; Fung *et al.* 2012; Reid *et al.* 2012; Basilious *et al.* 2015

(*Continued*)

Table 1. Continued

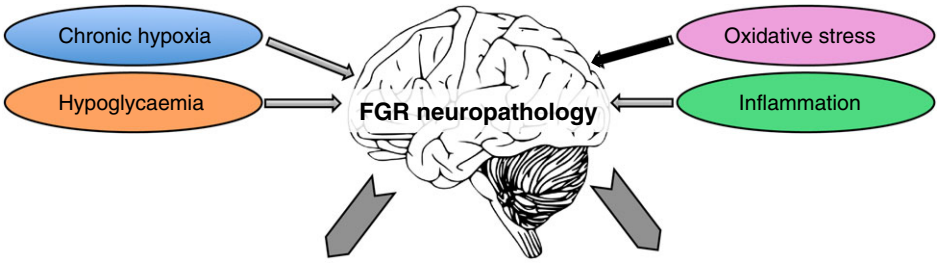
General description	Brain structure and microstructure in FGR offspring	References
	Deficits in white matter utrastructure, with disorganised fibre tracts, swollen axons and hypomyelination Astrogliosis present at postnatal day 14, but not observed in adulthood Transient hypervascularisation within the white matter, present at birth and normalised by postnatal day 14 Locomotor deficits in mature male FGR rats, but not females Locomotor hyperactivity and deficits in short- and long-term object memory in adult rats, correlated with birth weight Strength and coordination deficits present at postnatal day 14 and persisting into adulthood to a lesser degree	
Rats; chronic hypoxia; 10% O_2 from day 5 to 19 of gestation		
Body weight reduced by 15% at postnatal day 3	Increased neuroinflammation (number of activated microglia) in periventricular white matter Increased cell death in periventricular white matter Astrogliosis in cingulate white matter Reduced density of myelinated fibres in cingulate and lateral white matter	Pham *et al.* 2015
Sheep; placental embolisation with microspheres; onset 0.8 gestation (120 of 145 days gestation)		
Chronic intermittent hypoxaemia (O_2↓30–50%) Body weight reduced 20% near-term Brain sparing present	Reduced density of myelinated fibres with thinner myelin sheaths in cortical white matter Reduced cerebellar volume (molecular layer and external granular layer) Reduced number of cerebellar Purkinje neurons Astrogliosis in the cerebral cortex and cortical white matter Blood vessels appeared dilated	Mallard *et al.* 1998
Sheep; single umbilical artery ligation (SUAL); onset 0.7 gestation (105 of 145 days gestation)		
Chronic fetal hypoxaemia (O_2↓20–25%) Birth weight reduced by 25% Brain sparing present	Disorganisation of white matter tracts with reduced density of myelinated fibres Neuronal degeneration in hippocampal CA3 cells No change in the number of immature/ mature oligodendrocytes in most white matter regions Axonal injury and evidence of lipid peroxidation (oxidative stress) in white matter tracts	Miller *et al.* 2014
Sheep; carunclectomy; prior to mating		
Birth weight reduced by 30% Chronic fetal hypoxaemia (O_2↓30–45%) Brain sparing present	Reduced growth of cortical neuropil, and reduced synapse density Reduced number of cerebellar Purkinje cell dendritic spines and area of arborisation	Bisignano & Rees 1988; Rees *et al.* 1998

investigation (Woodall *et al.* 1996; Antonow-Schlorke *et al.* 2011; Cottrell *et al.* 2012; Somm *et al.* 2012, 2014; Soo *et al.* 2012; Swanson & David, 2015).

Effect of experimental FGR on brain development

Morphological alterations in grey matter are commonly seen in FGR animal models including reduced volume of motor and visual cortices, hippocampus, basal ganglia and cerebellum (Rees *et al.* 1988; Mallard *et al.* 1998, 2000; Rehn *et al.* 2004). Ventriculomegaly is also noted in the guinea pig model of FGR (Rehn *et al.* 2004). Neuronal loss is observed within the FGR brain across a number of regions, including the hippocampus (Fung *et al.* 2012; Miller *et al.* 2014), and surviving neurons demonstrate selective changes in the morphology of hippocampal cell dendrites (Dieni & Rees, 2003). Indeed the hippocampus appears particularly susceptible to injury in growth-restricted offspring, with reduced volume and total number of neurons, and with surviving neurons demonstrating abnormal axonal and dendritic morphology, as well as altered connectivity (Mallard *et al.* 2000; Dieni & Rees, 2003; Delcour *et al.* 2012; Illa *et al.* 2013; Miller *et al.* 2014; Basilious *et al.* 2015). These cellular disturbances in the hippocampus are, however, complex with results obtained in rats showing that FGR induces neuronal, astrocytic and immature oligodendrocyte deficits in a region- and sex-specific manner (Fung *et al.* 2012). Neuronal cells of the cerebral cortex are also vulnerable, with significant cell loss, and disturbance in proliferation and migration of existing neurons that is first evident antenatally and persists for at least 10 weeks postnatally in FGR rats (Tashima *et al.* 2001; Liu *et al.* 2011). Deficits in neuronal connectivity are also apparent, with term-equivalent FGR fetal sheep demonstrating a 17% decrease in synaptic density within the cerebral cortex (Bisignano & Rees, 1988). Furthermore, cell proliferation zones show decreased expression of anti-apoptotic proteins (Bcl-2), while p53 (pro-apoptotic) immunoreactivity is increased (Uysal *et al.* 2008).

Reduced volume of the cerebellar white matter (Mallard *et al.* 2000) and subcortical white matter tracts (Mallard *et al.* 1998) including up to 20% reduction of myelin density in parts of the cerebral white matter are seen in FGR sheep (Miller *et al.* 2014). Further, axonal injury (β-APP immunoreactivity) and lipid peroxidation are increased in the white matter in FGR newborn sheep (Miller *et al.* 2014), and axonal swelling is observed postnatally in FGR rats (Olivier *et al.* 2007). Growth-restricted guinea pig fetuses also demonstrate a reduction in the total number of myelinated axons and, where axons were myelinated, the myelin sheath thickness was reduced (Nitsos & Rees, 1990). The delay in oligodendrocyte maturation and myelination *in utero* is transient and myelin is restored postnatally in the FGR guinea pig (Tolcos *et al.* 2011; Pham *et al.* 2015). As with observations in humans, the effects of FGR on white matter appears to be dependent on the severity of the initial growth restriction, as rats with severe FGR exhibit white matter damage that persisted to adulthood (Olivier) while moderate FGR is associated with diffuse white matter lesions, transient hypomyelination, microglial



Grey Matter Pathology
↓ Cortical grey matter volume
↓ Deep grey matter volume
Neuronal loss
Sparse & disorganised cortical structure
Axonal injury
Altered connectivity networks
↓ Number of synapses
Altered dendritic morphology

White Matter Pathology
↓ Myelin content
↓ Posterior white matter volume
Regional ↓ in fractional anisotropy (FA) indicating reduced fiber organisation
Delayed oligodendrocyte maturation
Hypomyelination, more unmyelinated axons with thinner myelin sheaths
Altered vascularisation
Neuroinflammation (↑ activated microglia)
Astrogliosis

Figure 3. A summary of human and animal experimental results showing the principal adverse mechanisms contributing to grey matter and white matter pathology in FGR
Chronic fetal hypoxia, hypoglycaemia, oxidative stress and inflammation are the likely causes of adverse neurodevelopment. Gross changes in brain volume are observed in both grey and white matter of the FGR brain, contributed by cell loss and sparsity of neuropil layers with altered axons, dendrites, synapses and myelination.

activation and astrogliosis (Olivier *et al.* 2007). The moderate deficits within the white matter may still have long-term effects, with myelination abnormalities resolving after birth, but behavioural deficits still found in 8-week-old FGR female rats (Reid *et al.* 2012). Interestingly, it was recently reported in the FGR rabbit model that regional fractional anisotropy changes, indicative of white matter disorganisation, were correlated with worse outcome in neurobehavioural tests (Eixarch *et al.* 2012) and FGR-induced brain reorganisation persisted up to 70 days of age in the rabbit (equivalent to pre-adolescence human age) (Batalle *et al.* 2014). Indeed, FGR rabbits at 70 days postnatal age demonstrate a number of persistent neurostructural abnormalities consistent with delayed white matter development and poor connectivity. FGR rabbits show changes in grey matter using DTI imaging indicative of altered dendritic architecture, and decreased FA in the hippocampus and subventricular white matter reflecting less organised fibre tracts. These MRI changes were correlated with neurobehavioural and cognitive impairments in FGR rabbits, principally indicative of compromised short-term memory and attention and anxiety behaviour (Illa *et al.* 2013).

FGR effects on cerebral metabolites, the vascular network and cerebral blood flow

Animal studies have not shown evidence that FGR results in reduced total blood flow to the brain (Clapp *et al.* 1984); rather, higher blood flow is seen to some brain areas (Poudel *et al.* 2015), while reduced regional blood flow is observed in other studies, including decreased blood flow to periventricular white matter (Miller *et al.* 2009). Neither cerebral oxidative metabolites nor glucose appears to be altered in FGR rats (Brown & Vannucci, 1978). On the other hand, more recent studies using mass spectrometry suggest that FGR in rabbits leads to metabolic alterations in the fetal brain, affecting neuronal viability, energy metabolism, amino acid levels, fatty acid profiles and oxidative stress mechanisms (van Vliet *et al.* 2013). There is also evidence to show that while central catecholaminergic pathways are not affected by FGR (Oyama *et al.* 1992), both serotonin metabolism and cholinergic functions may be altered (Represa *et al.* 1989; Thordstein & Hedner, 1992; Manjarrez-Gutierrez *et al.* 2010).

Normal brain development and function require appropriate networks of blood vessels to supply high energy demands, and a highly integrated communication system between cells. The *neurovascular unit* comprises vascular endothelial cells ensheathed by a basal lamina membrane, in close association with surrounding astrocytes and pericytes. FGR fetal sheep and newborn lambs show evidence of altered cerebrovascular growth, with a relatively late onset period of chronic fetal hypoxaemia inducing increased capillary vessel size but no change to the number of vessels within the cortex (Rees *et al.* 1998), while FGR lambs demonstrate reduced vessel density within the brain's white matter, accompanied by decreased endothelial cell proliferation (Castillo-Melendez *et al.* 2015). Astrogliosis, characterised by enlarged astrocytes and with more processes is described in the fetus or neonatal growth-restricted rat, guinea pig and sheep (Nitsos & Rees, 1990; Rees *et al.* 1998; Olivier *et al.* 2007), and may or may not resolve after birth (Tolcos *et al.* 2011; Delcour *et al.* 2012). The attachment of astrocytes and pericytes to blood vessels is reduced in FGR lambs, which may impact the integrity of the blood–brain barrier (Castillo-Melendez *et al.* 2015). Functional differences are also observed, with reactivity of cerebral blood vessels altered in FGR, likely to be mediated by decreased endothelium-dependent relaxation (Herrera *et al.* 2014). It has also been shown that the cerebrovascular response to exogenous antenatal glucocorticoids, administered to mature the preterm lung, is quite different in human and sheep growth-restricted fetuses compared to their appropriately grown counterparts (Miller & Wallace, 2013).

The observation of astrogliosis in FGR is interesting, as it is a characteristic pathology in white matter injury (Back & Rosenberg, 2014), and may provide the basis for a brain injury biomarker in FGR. S100B is an astroglial protein that is released in response to glial injury, and human cord blood S100B concentrations are associated with the later diagnosis of cerebral palsy (Costantine *et al.* 2011). Umbilical cord blood levels of S100B are elevated in FGR newborns (Gazzolo *et al.* 2002). During pregnancy, S100B levels in maternal blood are elevated with a growth-restricted fetus that is then diagnosed with IVH after birth (Gazzolo *et al.* 2006). Furthermore, brain sparing (umbilical artery PI/middle cerebral artery PI ratio > 1) was apparent in all FGR fetuses with elevated maternal S100B, and cord blood S100B is negatively correlated with decreased PI in the middle cerebral artery, indicative of blood flow redistribution towards the cerebral circulation (Gazzolo *et al.* 2002).

Summary

It is clear that growth-restricted infants represent a high-risk population for antenatal, perinatal and postnatal complications. Moderate to severe FGR infants are at increased risk of stillbirth and likely to be born preterm, and FGR imposes additional risks for birth complications and neonatal morbidities than preterm infants who are not growth restricted. These risk factors are all exacerbated when evidence of brain sparing is apparent. Brain sparing results from the chronically hypoxic fetal environment imposed by placental insufficiency, and it is likely that this haemodynamic adaptation involves two stages, with the

first aimed at protecting the brain with increased oxygen supply, followed by a second stage of decompensation. Brain sparing is therefore considered a useful indicator of the degree of compromise in growth-restricted fetuses, but it does not ensure normal brain development (Fig. 1). Indeed it is clear that growth-restricted infants present a high-risk subgroup of infants with a complex and distinct set of microstructural brain abnormalities not observed in appropriately grown infants (Fig. 3).

In human FGR, decreased total brain volume is first apparent *in utero*, along with reduced total cell number, and a specific and independent vulnerability of the cortical grey matter to volume loss. Recent imaging advances demonstrate more complex microstructural changes in the FGR brain, which include altered fibre organisation and impaired connectivity networks such as the long range cortico-basal ganglia thalamic tracts. Consequently, neurological impairments are described in response to FGR, and may be immediately evident in the newborn with altered attention and alertness. Neurological impairments in school age children who were born with FGR have now been well characterised comprising gross and fine motor deficits, and specific learning disabilities encompassing cognitive, memory, and academic performance. Neurobehavioural dysfunctions are also widely described in FGR children, including poor attention, hyperactivity and irritability. It is, however, evident from the wide range of observations and outcomes that many studies describing structural or functional pathologies (or their absence) subsequent to FGR do not clearly control for the clinical phenotype – early- or late-onset FGR, severity, and gestational age at birth. It is apparent that early-onset severe FGR infants with evidence of brain sparing (MCA vasodilatation) and born preterm are the infants with the most pronounced neuropathologies.

Animal models to induce placental insufficiency, chronic hypoxia and FGR provide an opportunity to examine the microstructural, functional and biochemical consequences for the developing growth-restricted brain. The controlled experimental setting allows us to distinguish between the effects of early- or late-onset placental insufficiency, chronic hypoxia and/or hypoglycaemia. As with human findings, it is the most severely affected FGR offspring with brain sparing that demonstrate significant brain structural deficits. At the cellular level there is a fundamental but region-specific loss of neuronal cells, and altered developmental progression of oligodendrocytes and myelination, leading to deficits in white matter organisation and axonal injury. Indeed there appears an imbalance between the regulation of cellular proliferation and apoptosis within the developing brain of growth-restricted fetuses. The morphology of remaining neurons is also affected, with a number of studies reporting decreased dendritic outgrowth and reduced cellular connectivity. Given that brain sparing is a key adaptation in response to chronic hypoxia, it is not surprising that cerebral vascular development is altered in FGR offspring including reduced structural integrity of the neurovascular unit, which may in turn cause an altered susceptibility to intraventricular haemorrhage, with these effects also dependent on the severity and duration of hypoxia. Reactive astrogliosis is noted in a number of animal models of FGR, which is important since astrogliosis is a principal pathology in white matter injury. FGR animal models can be used to examine the mechanisms that contribute to neuropathologies identified in FGR, and accordingly have identified the direct effects of chronic hypoxia, and additional indirect effects such as oxidative stress, or inflammatory mediators. With advances in the identification of neuropathologies in growth-restricted fetuses and newborns, and particularly the complex microstructural changes in brain development, we must now look towards targeted therapies to restore normal brain development in response to placental insufficiency, chronic hypoxia and FGR.

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Additional information

Competing interests

The authors declare no conflicts of interest.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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