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Programming the brain: common outcomes and gaps in knowledge from animal studies of IUGR

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Abstract

IUGR in humans is associated with impaired pre- and postnatal neurodevelopment, and subsequent postnatal cognition, resulting in lower IQ, poorer memory, visuomotor and executive function skills, as well as behavioural and attentional problems. Experimental models of IUGR are needed to allow direct testing of causality and interventions, and have benefits in reducing both confounding by comorbidities such as prematurity, and variation due to environment and genetics. This review describes and discusses experimental models of IUGR in which neurodevelopmental and cognitive outcomes of IUGR have been reported. We consider the timing of neurodevelopment relative to birth and to the period of restriction, as well as the effects of each experimental perturbation on the fetal environment and development, before discussing neurodevelopmental and cognitive outcomes for progeny as fetuses, neonates and into adolescent and adult life. Experimental IUGR induces broadly similar outcomes to human IUGR, with altered brain morphology, in particular grey matter loss and discordant trajectory of white matter development, and poorer cognition and memory reported in various studies. Nevertheless, there remain gaps in knowledge of neurodevelopment in experimental models. We end the review with recommendations for the design of future studies to further investigate the mechanisms underlying adverse neurodevelopmental consequences of IUGR, and to evaluate interventions that may subsequently improve outcomes of IUGR in humans.

Keywords: IUGR, animal models, neurodevelopment, cognition, brain

1. Introduction

Intrauterine growth restriction (IUGR) occurs in approximately 15% of births worldwide, and 7% of pregnancies in developed countries [1]. IUGR is characterised by a restrictive environment that prevents the fetus from meeting its genetic potential for growth [2], and often results in a neonate who is small relative to gestational age [SGA, born with a birth weight in the lowest 10th centile of the population, 3]. While IUGR can be induced by maternal undernutrition [4], in developed countries IUGR is predominantly associated with maternal, fetal and uterine factors [reviewed in 5], that lead to poor placental function. This includes reduced uterine artery, placental and umbilical blood-flows [5, 6], and decreased fetal oxygen and nutrient supply [7-10]. Fetal nutrient demand increases with growth as gestation progresses, and late in gestation demand approaches placental capacity even in normal pregnancy. Accordingly, placental blood flow and efficiency increases in later pregnancy [11, 12], such that there is a positive relationship between placental and birth weight in humans and sheep [11, 13], and placental size and efficiency increase with advancing pregnancy [11]. These progressive placental adaptations appear less successful in the pregnancies with an IUGR fetus, which have lower blood flow relative to fetal size developing in later pregnancy [11]. Because the level of placental dysfunction in IUGR increases as pregnancy progresses [14] substrate deficiency in human IUGR pregnancies is greatest during the third trimester, which corresponds with maximal in utero rates of neurodevelopment [15], with lifelong structural and functional consequences.

SGA status is often used as a proxy for IUGR in human studies due to limited data on fetal growth trajectories, but will also capture individuals born with a low birth weight who have not undergone the pathological exposure to a restrictive fetal environment [16]. Fetuses, neonates, children and adolescents who were subjected to IUGR and/or born SGA have reduced head circumference and reduced total and regional brain volumes compared to controls [17-23]. This is largely due to grey matter loss, as well as discordant white matter development and microstructural changes, suggesting

reduced myelination and axon injury [18-20, 22-28]. The impaired functional outcomes in IUGR and SGA infants, children and adults are highly correlated with these morphological outcomes [24, 25, 27-30]. Compared to infants born at a size appropriate for their gestational age (AGA), IUGR and SGA infants have more immature neurobehavioural scores [17, 24-26, 31, 32] and, as children, have lower IQ and poorer language, working and short-term memory, executive function and visuomotor skills [33-42]. There are also higher incidences of cerebral palsy, attention deficit hyperactivity symptoms and behavioural problems in offspring of IUGR pregnancies compared to AGA [27, 31, 33, 38, 43, 44]. In addition, low birth weight (<2500 g) interacts with a genetic risk for depression; in combination these are associated with a higher incidence of depressive symptoms [45], although this has not been examined in IUGR or SGA offspring. Cognitive and behavioural consequences ultimately contribute to poorer academic outcomes in IUGR and SGA children than in those who were born AGA [35, 38, 39, 42].

In addition to the limitations of human studies, where IUGR may not be clearly differentiated from other causes of low birth weight, there are a number of confounding factors limiting the capacity to fully characterise the consequences of IUGR and their underlying mechanisms in humans. Firstly, IUGR is rarely a discreet condition and comorbidities are common. The incidence of preterm birth is 11-20% in the SGA population [16, 46], compared to overall rates of 6-10% worldwide [3, 16, 46], and the incidence of SGA is 25% in very preterm children [16], compared to rates of 15% overall [47]. Because IUGR and preterm birth are each independently associated with adverse morphological, cognitive and motor outcomes [23, 24, 44, 48, 49], it can be difficult to separate the consequences of each. Secondly, human studies are confounded by environmental factors that are correlated with prenatal growth, postnatal growth and neurodevelopment. For example, lower family socioeconomic status and poorer maternal education are each associated with increased risk of IUGR or SGA pregnancy [16, 50-52], poorer postnatal growth in AGA and SGA children [53], and poorer cognitive and academic outcomes in healthy children [50, 54, 55]. Postnatal

neurodevelopmental outcomes such as IQ correlate positively with incidence and rate of catch up growth of head circumference [38, 56-59], a proxy measure of brain size that corresponds well to frontal lobe volume [60]. Catch up growth of head circumference occurs during the first 6-12 postnatal months [61], during a period of rapid postnatal brain development [62, 63], but is frequently incomplete, such that IUGR children fail to catch up to non-IUGR individuals [17]. In addition, preterm IUGR and very low birth weight children are at increased risk of failure of catch-up growth of head circumference [18, 23, 61, 64]. There is therefore confounding due to the effects of both postnatal environment and gestational age on postnatal growth, which adds to the difficulty in defining effects of prenatal exposures on neurodevelopment in human cohorts.

Animal models are therefore necessary to control for, or minimise, these confounding factors, and also allow direct testing of causality and greater investigation of underlying mechanisms. To enable translation of the findings from these preclinical models to defining mechanisms that may apply in humans, and to evaluate and identify effective interventions to improve long-term outcomes, it is important to consider the timing of neurodevelopment relative to both birth and the gestational age at onset of the restricted intrauterine growth. This review compares the different animal models used to study effects of prenatal growth restriction on neurodevelopment, describes the neurodevelopmental and cognitive outcomes of these, and the gaps in knowledge and suggests future directions for research in this field.

2. Timing of neurodevelopment in animal models of experimental IUGR

Rats, guinea pigs, rabbits and sheep are the non-human species most commonly used to examine the effects of IUGR on neurodevelopmental outcomes. However, the timing of neurodevelopmental events and gestation lengths vary between these species, and from those in humans (Figure 1). These inherent differences make comparisons between models difficult, and extrapolating findings

from one species to another largely invalid. For example, rats are one of the most frequently utilised model species, but many neurodevelopmental events that occur during gestation in humans occur postnatally in this species [Figure 1, 15]. Brain growth rate accelerates in the last trimester in humans, peaking around birth, but occurs comparatively later in the rat, peaking around postnatal days 7-8 [15]. Similarly, fetal neurogenesis and white matter development begin later in gestation in rats than humans [65]. Central myelination occurs entirely postnatally in the rat [15], but begins in the human brain-stem at 29 weeks gestation [Figure 1, 66]. As in humans, central myelination commences in late gestation in rabbits and guinea pigs and is sensitive to hypoxic damage *in utero* [Figure 1, 67, 68, 69]. However, myelination in peripheral as well as central and higher brain regions commences before birth in the sheep. Myelination of the majority of higher brain regions in humans commences postnatally, so sheep neurodevelopment is comparatively more advanced at birth than it is in humans [Figure 1, 15, 70]. Neurodevelopment in pigs shares some similarities to human, including occurrence of prenatal neurogenesis and both peri- and postnatal myelination, , although humans have more advanced development relative to percentage of gestation [reviewed in 71]. Some cognitive and neurodevelopmental consequences have been studied in pigs with spontaneous, naturally occurring growth restriction either due to large litter size or variable growth within a litter. These share similarities with outcomes reported in human IUGR, including brain sparing at birth [72], morphological changes including decreased grey matter [73], and altered cognition [73-75]. In depth discussion of this model is omitted from this paper however, as changes in the fetal environment has not yet been well characterised.

3. Methods and timing of experimental IUGR in animal models

A variety of paradigms of experimental IUGR have been utilised in studies of neurodevelopmental and cognitive outcomes. Experimental IUGR is generally induced by restricting fetal nutrient availability via global or nutrient-specific undernutrition of the mother, or by surgical or

pharmaceutical induction of placental insufficiency to restrict placental capacity to transfer nutrients from mother to fetus (Figure 2). Fetal and neonatal body and brain weights are reduced in the majority of these preclinical models, as is seen in human IUGR (Table 1, 2), although each model affects neurodevelopment, and in turn cognitive outcomes to varying degrees. While there are additional animal models of perturbed prenatal development in which neurodevelopment and/or cognitive outcomes have been investigated, for example those investigating effects of periconceptional and early gestational undernutrition in the sheep [76-78], these models do not restrict fetal growth in late gestation or reduce size at birth as occur in human IUGR and are therefore not discussed further in this review. Similarly, this review is limited to those models of IUGR in which neurodevelopmental and/or cognitive outcomes have been reported. This section describes key features of these models, including effects on fetal nutrient supply and metabolism, and development and timing relative to neurodevelopment. Specific neurodevelopmental and cognitive outcomes induced by IUGR in each model are described in following sections.

3.1. Maternal undernutrition

Models of IUGR based on maternal undernutrition (UN) differ from human IUGR associated with poor placentation, in that restriction is largely of nutrients without substantial restriction of oxygen. There is also considerable variability in the length, degree and timing of nutritional restriction between studies [79-88], with some studies restricting throughout gestation or the entire length of pregnancy studied [79, 82, 86, 89], whilst others may only restrict during part of gestation [80, 83, 84, 88], or extend maternal nutrient restriction into lactation [85, 87]. The patterns of restriction in these models also differ from that in human IUGR due to placental insufficiency, which progressively worsens during pregnancy [Figure 2, 14]. Differing types of nutrient restriction have been utilised, particularly in rats, with some restricting dietary protein, while others impose global nutrient restriction [79, 86, 88, 90-92]. Variation between studies in the severity and nature of the

nutrient restriction accounts in part for variable reductions in birth weight (Table 2). These range from 4 to 34% in progeny of globally nutrient-restricted rats [79, 87, 88, 93-96], whilst more severe restriction is seen in models of maternal protein restriction, with 7 to 52% reduction in birth weight in progeny [91, 92, 97-101]. The reported decrease in birth weight following the levels of maternal nutrient restriction used in neurodevelopmental studies in sheep and rabbits is milder ranging from 9.5% to 17.5% [83, 89, 102, 103]. Effects on fetal nutrient supply and metabolism also differ between the various models of IUGR (Table 1). For example, fetal blood glucose does not appear to be reduced by maternal protein restriction in rats [104, 105], but is reduced in other models of IUGR, such as utero-placental ligation in the guinea pig and in both utero-placental embolisation and carunclectomy-induced placental restriction in sheep [11, 106-111].

One particular limitation of models of maternal nutrient restriction in rodents is that the restriction is imposed only during earlier stages of neurodevelopment than are affected by IUGR in humans. For example, if maternal undernutrition is imposed in rats only during gestation, this does not impact the period of myelination, which occurs postnatally in rats, but commences prior to birth in humans [Figure 1, 66]. This can be addressed by continuing maternal undernutrition postnatally throughout lactation in the rat, but many studies do not do this.

3.2. Placental restriction induced during mid to late pregnancy

IUGR can be induced by restricted placental growth and/or function (PR). In small animals this is induced by restriction of uteroplacental blood flow during late pregnancy, which in the rat involves uterine artery ligation (ie. uteroplacental vessel ligation, UPL), usually at day 17 of the 21-22 day pregnancy [112-115]. In the rabbit, the period of restriction similarly comprises a relatively short proportion of gestation, with 40-50% of uteroplacental vessels ligated at day 25 of the 31 day rabbit pregnancy, and pups surgically delivered five days later [Fig 2, 102, 116, 117, 118]. Placental insufficiency is induced at an earlier stage of gestation in the guinea pig, with the uterine artery of

one horn ligated at mid-gestation [at day 30-35 days of the 68 day pregnancy, Fig 2, 106, 119-121]. IUGR can be induced during pregnancy in sheep by uteroplacental embolisation (UPE), where occlusion of the uteroplacental blood vessels is induced via repeated infusion of microspheres into the placental vascular bed, titrated to maintain a defined level of hypoxia [108, 110, 122, 123]. In the majority of studies, reduced placental blood flow is not maintained until term (Figure 2), with the duration of embolisation ranging from 6-30 days, and generally commencing on day 110-120 of gestation [108-110, 122, 123, 124 , 125].

All of these experimental models reduce fetal and neonatal growth, placental growth and fetal substrate supply (Table 1, 2), and induce clear signs of neurodevelopmental disruption in progeny (Tables 3 and 4) that persists into adulthood in small animal models (Table 5). To date, there are no reports of outcomes in adulthood in large animal models, such as the UPE sheep. Compounding this, the varying timing of restriction induced by UPL or UPE, and species-specific differences in temporal aspects of neurodevelopment, results in perturbations at different stages of neurodevelopment in each model (Figure 2). For example, IUGR induced by UPL in late gestation in rats occurs at a neurodevelopmental stage similar to mid-gestation in the human [15]. In contrast, late pregnancy placental restriction in the UPL guinea pig and rabbit, and UPE sheep, affects neurodevelopmental at stages similar to those occurring during late gestation in the human, including neurogenesis and white matter development [Figure 2, 67, 69, 70, 126].

One major drawback to all these models of IUGR induced in mid to late pregnancy is the need for surgical intervention during pregnancy, which may have additional consequences for fetal development. Even sham surgeries are associated with reduced fetal weight compared to controls in rats [127], due to mechanisms potentially including maternal stress. The UPL and UPE models are also predominantly models of late-pregnancy restriction, imposed acutely on previously unrestricted pregnancies. Pharmaceutical interventions may provide another, less acute avenue to

introduce placental restriction, although this has only been examined in rats to date. Placental restriction induced by intraperitoneal infusion of synthetic thromboxane A_2 (STA_2) analogues in the rat constricts placental blood vessels, which reduces birth and brain weight (Table 2). This in turn alters neurodevelopment in the fetus and neonate (Table 3, 4), and impairs neuromotor, cognitive and behavioural development at least to adolescence (Table 6). Pumps to infuse STA_2 are implanted at day 13 of gestation, thus the period of placental restriction is longer than uterine artery ligation models in rats, and with shorter and less invasive surgery, which reduces maternal compromise [128-131]. Further experimentation is needed to delineate the adult outcomes and underlying neurodevelopmental changes in this model of IUGR.

3.3. Placental restriction throughout pregnancy

The carunclectomy model of placental restriction (CX) in sheep is induced by removal of the majority of uterine caruncles (placental attachment sites) prior to pregnancy, which reduces placental size, in spite of compensatory hypertrophic growth of remaining placentomes [132]. Reduced placental size in turn impairs placental blood flow, and the efficiency and delivery of nutrients to the fetus (Table 1). Neonates from CX pregnancies are smaller than controls at birth with reductions of 20-30% in birth weight [133, 134], and smaller decreases (5%) in skull width, indicative of brain sparing [133, 135-137]. The advantages of this model are that, similar to human IUGR, the fetuses are hypoxic, and restriction is chronic and increases throughout the course of pregnancy [Figure 2, 11]. Moreover, no surgical intervention is required during pregnancy. Additionally, CX sheep offspring have similar postnatal endocrine and growth outcomes to the IUGR human, including insulin resistance [133, 138], increased visceral adiposity [135], and neonatal catch-up growth [135-141].

4. Neurodevelopmental and cognitive consequences of experimental IUGR

4.1. Fetal neurodevelopment

Fetal neurodevelopment has been examined more frequently in the UPL guinea pig and UPE sheep models than rat models of IUGR, but not at all in the UPL rabbit or CX sheep. In both the UPL guinea pig and UPE sheep there are morphological signs of disrupted development (see below), increased apoptosis and decreased expression of neurotropins, such as brain-derived neurotrophic factor [Table 2, 108, 109, 120, 142, 143]. In the late gestation guinea pig fetus, UPL decreases overall and neuronal volume of the whole brain, cerebrum and hippocampus (Table 3), consistent with the human IUGR fetus [19, 21, 22, 25, 28]. The impaired development of the hippocampus, myelination and white matter development in the UPL guinea pig have been investigated in detail, with both delays and decreases in myelination reported (Table 3). Region-specific changes in concentration and metabolism of neurotransmitters and catecholamines in the brain also occur in the UPL guinea pig. UPL elevates serotonin concentration in the frontal and temporal cortex, increases noradrenaline in the caudate nucleus, and alters dopamine and noradrenaline metabolism in a number of regions [144]. Similar patterns of volume loss and neurodevelopmental damage, including decreases in cortical myelination, and decreases in mitotic division and increased post-mitotic cell death in the cerebellum, but not hippocampus, have been reported for the UPE sheep (Tables 3 and 4). Specific attention has been paid to examining damage in the hippocampus, and to a lesser extent cerebellum in the UPE sheep. Similar damage is seen in both regions in UPE sheep, including white matter lesions, gliosis, loss of neurons, and decreased gross volume [109, 125, 145]. These models thus demonstrate causal effects of restricted placental function on fetal neurodevelopment by specifically manipulating this variable without genetic or environmental confounders associated with IUGR in human cohorts.

4.2. Neonatal neurodevelopment and cognitive outcomes

The majority of rat and rabbit studies have examined outcomes in neonates, whereas neonatal outcomes have not been examined in any great detail in the guinea pig, or at all in sheep models of

IUGR. In all rat IUGR models, and in the UPL rabbit, neonatal brain volume is decreased overall and within specific brain regions (Table 4). In addition to loss of volume, neuron number is also further impacted by decreased neuronal density in a number of brain regions, at least in progeny of rat pregnancies subject to maternal undernutrition or UPL (Table 4).Studies in the STA_2 rat suggest this may be due to delayed neuronal migration [146], which may be due to the decreased expression of neural cell adhesion molecule and brain derived neurotrophic factor, which guide neuronal differentiation and migration, observed in these animals [147]. Studies in the UPL rat have continued into early postnatal life to examine the onset of myelination. In early postnatal life, structural damage, decreased myelin volume, and region specific changes to numbers of pre-oligodendrocytes and oligodendrocytes, are evident in the UPL rat, indicating discordant brain development (Table 4). The UPL rat also has a loss of white matter volume in the corpus callosum at birth and during the first two weeks of postnatal life, as is the case in human IUGR neonates [23], whilst in the UPL rabbit there is decreased white matter volume in the hippocampus at birth (Table 4). While cognitive studies are not possible at this young age, neonatal neurobehaviour, including reflex development, is impaired in IUGR rats induced by either maternal global UN or STA_2 rat, and UPL rabbit models of IUGR (Table 6), consistent with observations in human IUGR neonates and toddlers [17, 26, 31, 32].

4.3. Adolescent and adult neurodevelopment and cognitive outcomes

Outcomes in the adolescent or adult have not been examined in the majority of experimental models of IUGR. Importantly, and consistent with persistent functional consequences of IUGR, SGA and low birth weight in humans [30, 39, 42, 148], existing studies do suggest long-term structural damage following experimental IUGR. These include damage which occurs during exposure to restriction and persist from fetal life, such as decreased neuronal density [117], which can be contributed by grey matter loss *in utero* resulting in decreased neuron numbers in later life. This

also includes further changes that develop after birth, including decreased myelination [112, 117, 149]. Studies in adolescent and adult animals (Table 5) also provide evidence of causation for long-term effects of a restricted environment *in utero*, by providing a common postnatal environment including diet and environmental stimuli in which all progeny are assessed. The adult UPL rat and UPL rabbit both have decreased neuronal density and myelination in multiple brain regions (Table 5). Maternal global or protein feed restriction in rats induces limited changes in brain volume in the adult (Table 6), in contrast to the volume losses and decreased levels of myelination seen in adolescent and young adult humans affected by IUGR and SGA [18, 27]. It is not clear whether these comparatively limited effects of maternal undernutrition on brain structure are a consequence of relatively mild restriction in this model, or are a characteristic of this species, since volumes of specific brain regions have not been reported for other experimental rat models of IUGR. There are also few gross structural consequences of IUGR in the adult CX sheep, in which grey and white matter areas remain unchanged in the prefrontal cortex (Hunter et al., unpublished data). The addition of structural studies in other experimental models of IUGR and detailed histological studies to assess more subtle changes will assist in comparisons of lasting neurodevelopmental consequences between these experimental models of IUGR and with human IUGR.

The majority of studies examining postnatal cognition have been conducted using rat models of IUGR. Maternal global or protein feed restriction in rats impairs reversal learning (a measure of executive function, in which rules or discriminations to solve a task are initially learned and then reversed), in pups and adult progeny, but in the majority of models there are no signs of spatial learning or memory impairments (Table 6). The opposite is true in the sheep (Table 6), in which initial learning but not memory is impaired during simple maze tasks in UPE lambs [sexes combined, 122], and during diamond maze tasks in male CX lambs and young adult sheep [150], but reversal learning is not impaired.

4.4. Gaps in knowledge and future directions

Taken in combination there are clear gaps in knowledge when comparing outcomes between animal models, and to human IUGR. Firstly, the different ages studied make it difficult to make comparisons between species, in part due to the differing neurodevelopmental trajectories (Figure 1). Models and studies differ in the timing of exposure to restriction, whilst the variable timing at which outcomes are evaluated determine what outcomes it is possible to observe. For example, in the majority of rat studies, brains are studied at postnatal day 0 and 1. Thus examination of white matter development is impossible, as central myelination has not yet commenced at this age in the rat [15]. Earlier timing of neurodevelopment in other species, such as the guinea pig (Table 3) and rabbit (Table 4), mean that these species are useful in determining effects of experimental IUGR on fetal and neonatal neurodevelopment and reflexes. Sheep undergo neurodevelopment even earlier and may prove particularly useful for fetal studies in experimental IUGR. The lamb has previously been used to investigate white matter injury following asphyxia and preterm birth [151-155], and effects of perinatal exposure to corticosteroids [156-159] due to the onset of myelination in late pregnancy. There is therefore a considerable body of literature in this species examining possible mechanisms by which IUGR may influence outcomes, such as via hypoxia. Comparable neurodevelopmental data in the human is not currently available. To date, studies of the IUGR human fetus and neonate have largely examined grey matter volume, whereas the greatest effects of IUGR on neurodevelopment in toddlers and adolescents are on white matter [20, 26, 27].

The techniques used to study neurodevelopment and cognition in each experimental species also differ, which further complicates comparisons between species. Animal models are the only means by which mechanisms of damage associated with IUGR can be examined at the tissue or molecular level, as human studies rely on rare donations of tissue from miscarried fetuses, and thus are obtained at varying stages of prenatal development, and often exposed to pathological conditions

[19]. Assessment of neurodevelopmental outcomes in the rat and guinea pig frequently analyse microstructural, histological and gene expression outcomes [79, 85, 121, 128, 142, 160-162], but have not yet directly studied functional outcomes into adult life. In UPL rabbits, MRI and imaging techniques have been utilised [117, 163]; methods that are also used to assess brain morphology following IUGR in humans [18, 26, 29, 164]. Nevertheless, as is the case in humans, MRI studies do not permit for examination of causality. Studies that incorporate these imaging techniques concurrently with histological studies and measures of learning outcomes could prove a valuable way to relate structure (eg. myelination) with functional outcomes in future. It simply is not clear at present how the fetal and neonatal structural outcomes observed in rats, rabbits, sheep and guinea pigs translate to functional outcomes, nor what mechanisms underlie the structural and functional outcomes of IUGR.

Comparison of cognitive outcomes is also difficult between models, due to study at different ages and with varying tests. Neonatal neurobehavioural outcomes, such as development of reflexes, have been studied in the IUGR rat following maternal global or protein feed restriction or STA_2 administration [79, 87, 129, 165] and in the UPL rabbit [67, 68], but similar studies are not possible in guinea pigs and sheep, which are born more developed and with these reflexes already established [166]. Impairments of later memory and visuomotor skills have been observed in the majority of animal models of IUGR (Table 6), although some differences exist in outcomes between species and studies. Initial and reversal learning and memory are impaired in maze testing in progeny of maternal global feed restricted and UPL rats [79, 97, 113, 115, 167]. In contrast, although UPE and CX in sheep impair initial learning of maze routes in progeny [122, 150], reversal tasks are solved more quickly by CX than control progeny [150]. It is not clear whether this reflects differences in the type and timing of restriction, or behavioural differences between species. For example, in T and Y-maze tasks sheep rapidly acquire bias towards entering one arm preferentially and become averse to entering the other maze arm in reversal tasks [122, 168, 169].

In contrast, rats find novelty far more attractive, and are therefore more likely to explore maze arms they have not previously been able to access [170].

Understanding and comparison of cognitive outcomes of IUGR may also be limited by availability of validated tools for cognitive testing in many species, with few tools able to be utilised in both experimental and human IUGR. The majority of human studies report IQ, memory and other cognitive measures taken via written, oral or manual dexterity tests [33-42], which are obviously not possible in animal models. Perhaps more importantly, the vast majority of human motor and cognitive assessments were designed to detect relatively frank disability, and may well miss more subtle but still physiologically-relevant neurodevelopmental impairments. No group differences in mean neurodevelopmental scores exist between preterm IUGR and preterm AGA infants at twelve months corrected age [64], although the incidence of abnormal scores is increased in IUGR compared to AGA infants [31, 32]. Limited capacities in infancy limit the ability to measure subtle changes in development and cognition, particularly prior to language development. Tools such as the Assessment of Preterm Infants Behaviour therefore assess measures such as motor tone, attention and self-regulation in neonates [171] rather than cognition. There is a sharp trajectory of cognitive development after age six into adolescence, during which humans develop more complex cognitive abilities, especially executive functions. This enables use of a wider battery of testing tools in children than infants, which detect lower scores in IUGR children for a number of IQ subscales from the age of six onwards [172]. Few human IUGR studies have examined neurodevelopmental or cognitive outcomes past childhood and into adulthood, however. Maze testing is a useful measure of learning and memory and has been utilised in IUGR rats and sheep [95, 122, 150, 167], but to date only one study has utilised this in human IUGR with toddlers completing a maze task directly comparable to those tests used in animal studies [36]. Object recognition tests have been utilised in UPL rats and rabbits, allowing discrimination between different kinds of memory, specifically recognition and spatial memory [113, 115, 117]. Although

maze [150, 169, 173-175], and executive function tasks [168, 174] have been utilised in studies of sheep behaviour, not all of these tools have been yet applied to IUGR models. Use of a greater variety of tests in animal models of IUGR, to evaluate outcomes including executive function, dexterity, learning and non-spatial forms of memory, are necessary to enable better comparisons of functional deficits between human and experimental IUGR.

In all of these experimental models of IUGR, there is currently a lack of detailed longitudinal studies of cognitive changes throughout the lifespan in parallel with studies of structural neurodevelopment. Such studies are needed both to allow comparisons of outcomes with those of human IUGR, and to evaluate long-term consequences of interventions. Such longitudinal studies in large animal models may be precluded by husbandry costs and the lifespan, and be more feasible in small animal models due to their rapid neurodevelopment. Although longitudinal assessment of brain structure and reflex development has been performed in the UPL rabbit using MRI acquisition [116, 163], concurrent functional assessments are not yet available. To date, there have been few longitudinal studies of cognitive outcomes in any species, and due to the cost of maintaining animal cohorts, the same animals are generally tested at multiple ages. Experimenters therefore also need to account for effects of prior learning during analysis of data, as species such as sheep are capable of remembering both visual cues [176] and strategies required to solve maze tasks [150] for periods ranging from a month to a year after initial learning.

Finally, it is vital that more studies examine cognition in intact post-pubertal adults of each sex. In the rat, maternal UN has sex-specific effects on cognition [84], and these may in part be due to interactions with sex steroids. Sex hormones, particularly testosterone, affect behavioural stress responses in sheep [177, 178], whereas in rats both oestrogen and testosterone appear to independently affect both stress response and spatial learning [179-182]. Therefore studies utilising one sex or pre-pubertal animals are unlikely to produce data applicable to human adults.

Additionally, stress induced by human contact and isolation during the course of testing may impact outcomes differently dependent on species. Sheep find proximity to observers aversive [183-186], and minimising stress is critical to avoid confounding during cognitive testing. Further complicating this issue, prenatal exposures also have sex-specific effects on stress responses. For example in adult sheep progeny of maternal globally-feed restricted pregnancies, UN males have a greater locomotion response than control males in response to sudden movement (reactivity test) [84]. Both UN and control females share this rapid locomotion response, but this persists for a shorter duration in UN than control females [84]. Low birth weight (in term-born children and thus likely to reflect restricted growth *in utero*) also has sex-specific effects on the cortisol response to stress in pre-pubertal human children [187]. As adults, low birth weight women have greater systolic blood pressure during stress tasks than controls, and also greater heart rate during the luteal but not follicular phase of the menstrual cycle [188]. Responses to the same stress tasks do not differ between control and low birth weight men [188]. Stress affects cognitive outcomes including memory [189], and both stress response and effects of IUGR appear to be sex-specific and reactive to levels of sex steroids. It is therefore important to include gonadally-intact animals of both sexes and evaluate outcomes before and after puberty to fully characterise the effects of IUGR on cognition [84].

5. Conclusions and recommendations

Animal models of IUGR have enabled examination of causal links between IUGR and morphological and cognitive outcomes, and minimisation of environmental and genetic confounders and variation. There are merits and drawbacks to each currently utilised experimental model of IUGR. Nevertheless, in the majority of models, experimental IUGR produces progeny with broadly similar outcomes to human IUGR, including altered brain morphology, particularly grey matter loss and discordant trajectory of white matter development, and poorer cognition and memory. These preclinical studies have been limited, however, by lack of concurrent and detailed

443 characterisation of mechanisms and functional outcomes, and a paucity of longitudinal studies
444 including pre- and post-pubertal animals of both sexes.

445

446 In order to further investigate the mechanisms underlying adverse neurodevelopmental and
447 functional consequences of IUGR, and to evaluate interventions that will subsequently improve
448 outcomes of IUGR in humans, we recommend that preclinical studies need to incorporate the
449 following design considerations:

450 1. The method of restriction should induce similar changes in the intrauterine environment to
451 those seen in human IUGR, including decreased nutrient and oxygen availability.

452 2. The timing of growth restriction relative to neurodevelopment should be similar to that seen
453 in human IUGR.

454 3. Neurodevelopmental and cognitive outcomes should resemble those reported following
455 human IUGR, including incidence of brain sparing in more severe cases of restriction,
456 reduction of brain volume at birth, particularly grey matter volume, delayed and discordant
457 white matter development, and impaired learning, memory, visuomotor and executive
458 function skills.

459 4. Species-appropriate cognitive tests that minimise confounding by factors including stress
460 should be used.

461 5. Outcomes should be evaluated across the life course and in gonadally-intact animals of both
462 sexes.

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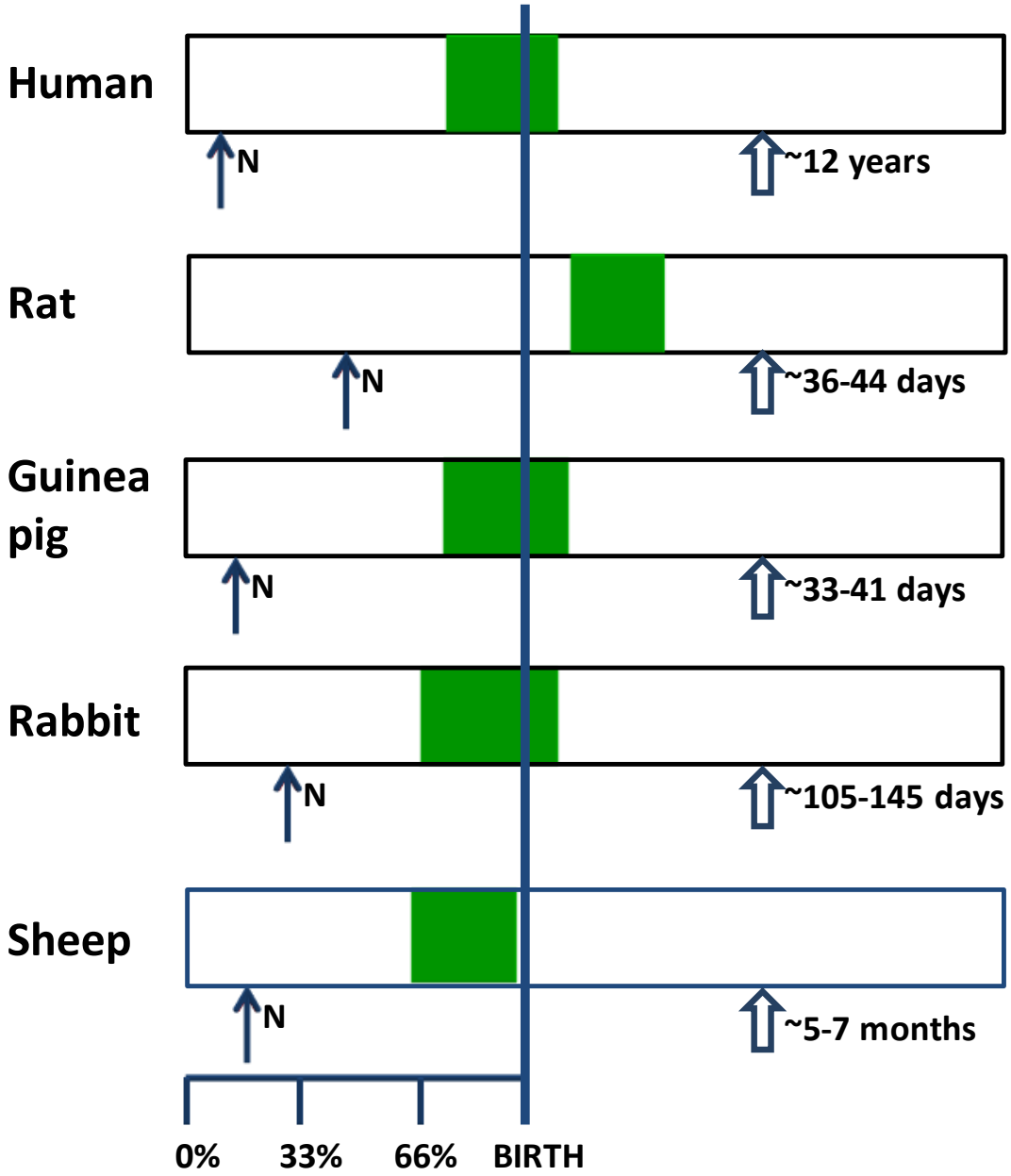

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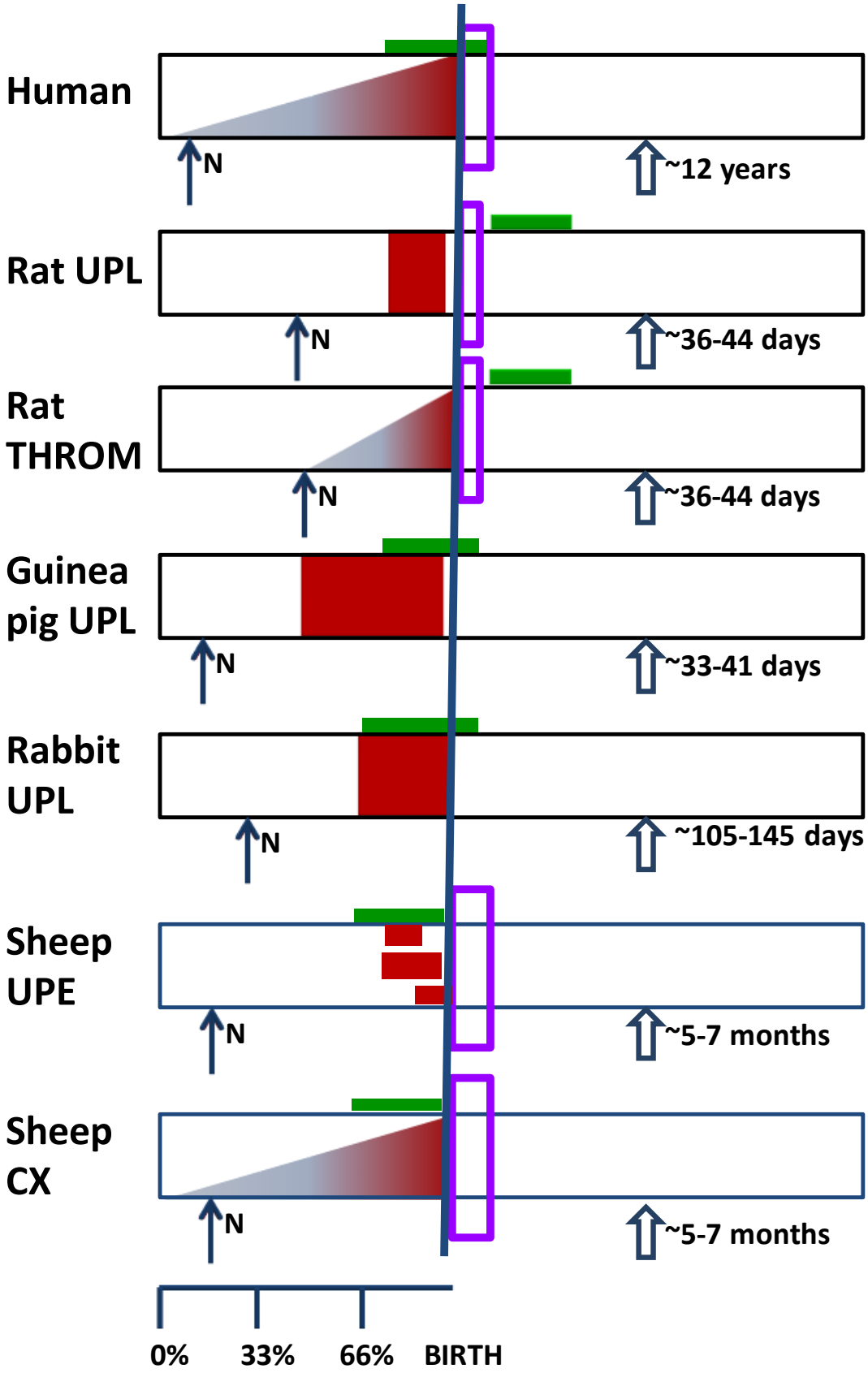
465 Figure 1 – Timing of neurodevelopment in humans and in species utilised in animal models of
466 IUGR. N = onset of neurogenesis, green panel = onset of myelination, hollow arrow indicates onset
467 of puberty. Data on onset of neurogenesis and onset of myelination were taken directly from the
468 literature for rats and sheep [15, 65, 70].Timing of neurogenesis and myelination of the guinea pig
469 and rabbit was extrapolated using the most recent models predicting developmental timing across
470 species from available information from mapped developmental events and based on data on white
471 matter development after the apparent onset of myelination in these species [67, 68, 119, 166, 190].
472 Data on onset of puberty were taken from data using species-appropriate measures in human [191],

rat [192], guinea pig [193, 194], rabbit [195, 196] and sheep [197, 198]. Diagram does not show maturation of myelination, which continues into adolescence in the majority of species for which data is available [e.g. rats and humans, 15].



477

478 **Figure 2 – Timing of placental restriction (PR) in human IUGR and animal models of IUGR.**

479 UPL = uteroplacental vessel ligation, THROM = thromboxane A_2 analogue (STA_2) administration,

UPE = uteroplacental vessel bed embolisation, CX = carunclectomy, N = onset of neurogenesis, hollow arrow = onset of puberty, green bar = period of majority of myelination, solid red bar = period of acute restriction, with multiple bars indicating different periods of restriction used in the same IUGR model, red gradient = chronic restriction with gradually increasing strength, purple box = period of catch up growth in species in which it has been reported (no data are available for rabbit or guinea pig following UPL). Periods of restriction depicted in this figure were chosen as most representative of the timing described in the literature: rat UPL [112, 115], guinea pig UPL [119-121], rabbit UPL [116-118], sheep UPE [109, 123, 125] and sheep CX [107, 132, 133]. Maternal global feed or protein restriction have been applied for multiple periods in rats, encompassing whole or part of gestation and may end at delivery or continue throughout lactation [79-88] – due to the variety of timing used in these studies they are not shown above.

Table 1 – Fetal growth outcomes in animal models of IUGR.
↓ decreased compared to healthy controls, ↑ increased compared to healthy controls, = unchanged/not different to controls, + present in this model. Days of pregnancy are designed by embryonic day, eg. E10.

	Rat maternal feed restriction	**Rat maternal protein restriction**	**Sheep maternal feed restriction**	**Rat maternal thromboxane**	**Rat uteroplacental vessel ligation**	**Guinea pig uteroplacental vessel ligation**	**Rabbit uteroplacental vessel ligation**	**Sheep uteroplacental embolisation**	**Sheep caruncleclectomy**
Fetal weight	**↓13%** [199]	**↓5-35%** [86, 104, 200] **↑7-25%** [201]	**=** [80] [82] **↓11%** [82]	**↓**[128]	**↓8-31%** [112 , 202-204] **= E19, ↓E21** [160]	**↓22-63%** [106, 119, 121, 142-144, 161, 162, 205-207]	**↓20-36%** [102, 208, 209]	**↓20-42%** [108, 109, 111]	**↓15-43%** [11, 107, 210, 211]
Placental weight		**↓9.5-35%** [104, 200] **=** [86] **↑↓ during pregnancy** [201]	= [89] **↓size as pregnancy progresses** [82]		**↓20%** [202]	**↓21-40%** [106, 142-144, 161, 206]	= [102, 208] **↓44%** [212]	**↓35%** [109]	**↓36-64%** [11, 107, 132, 210, 211]
Fetal brain size		= [86] **↑12%** [201]	**↓E90, = E135** [82]	**=E16, E18** [128] **↓E20** [128]	**= E19, E22** [160, 203]	**↓10-20%** [142, 143, 161, 162, 205, 207] **=** [144, 206]	**↓10-22%** [102, 208, 209] **= E25** [208]	**=** [108, 111, 123] **↓8.5%** [109]	**↓14-17%** [11]
Brain sparing		**+** [86], **-** [201]	**=** [80, 82]		**+** [160]	+ [119, 142, 144, 161, 162, 205-207]	+ [102, 208]	+ [108, 109, 122, 123]	+ [11]
Hypoxia			**= d113-116** [80]			+ peripheral blood, severity varies in brain [144]	**+** [208]	**+** [108, 109, 111, 122, 125] + transient [123]	+ [11, 210, 213]
Fetal glucose		**↑E14, = E21** [104]	↓[82] **=** [80]		**↓E22** [203]	**↓E49-51** [106]		↓ [108, 109, 111]	↓ [107, 213]
Fetal insulin		**↑E14, = E21** [104]	**= E90, ↓E135** [82]		**= E22** [203]	**↓E49-51** [106]			↓[107]
Fetal amino acids		↑↓ [200]	**= protein** [82]						
Gestation length	**=** [79, 87]		**=** [89]					=/↓ [124] **↓3-16** [122, 125]	**=** [135, 139, 141] **↓2.2 days** [134]

Table 2 – Neonatal and long-term growth outcomes in animal models of IUGR.
↓ decreased compared to healthy controls, ↑ increased compared to healthy controls, = unchanged/not different to controls, + present in this model.

	Rat **maternal feed restriction**	**Rat** **maternal protein restriction**	**Sheep** **maternal feed restriction**	**Rat** **maternal thromboxane**	**Rat** **uteroplacental vessel ligation**	**Guinea pig** **uteroplacental vessel ligation**	**Rabbit** **uteroplacental vessel ligation**	**Sheep** **uteroplacental embolisation**	**Sheep** **caruncleclectomy**
NEONATE									
Birth weight	= [214] ↓**4-23%** [79, 87, 88, 93-96]	= [201, 215] ↓**7-52%** [91, 92, 97-101, 216]	↓**9.5-14%** [83, 89] = [84]	↓[128, 129, 131, 146]	↓**8-40%** [99, 112, 114, 115, 160, 203, 217, 218]	↓**36-42%** [145, 162]	↓**18-44%** [102, 116-118, 163, 212]	↓**42-48%** [122, 124, 125]	↓**17-28%** [132, 134-141]
Brain size	= [214] ↓**cerebrum, 11%** [79]	↓**11-66%** [90, 99, 101] = [201, 215]		↓[129]	= [160, 203] ↓**33%** [99] ↓**forebrain** [217]	↓**14%** [162] ↓**forebrain** [145]	↓**10-34%** [102, 116, 118, 212]		↓**5% skull width** [136-138, 141]
Brain sparing				+ [129]	- [160]	+ [162]	+ [102, 116] = [118]	+ [124]	+ [136]
Catch up growth	+ [85, 94-96] - [93, 199]	- [90, 100] + [92, 97]	= [89]	- [129] + [131]	- [112, 217] + [114, 115, 160, 203] =/- [218]			+ [124] - [122]	+ [135-141, 219]
ADULT									
Adult body weight	= [79, 95] ↓**8%** [85, 93, 94]	= [97, 215, 216] ↓**4-53%** [97-100]	= [83, 84]	= [131]	= [114, 115, 160] ↓**14-33%** [99, 112] = / ↓ [218]	↓**15%** [162]	= [117, 163]		= [139, 141] =/↓**sex specific** [219]
Adult brain size	= **forebrain** [79, 85] ↓**4%** [93]	= [215]				↓**12%** [162]	= [163]		= **skull width** [141]

Table 3: Fetal neurodevelopmental outcomes in animal models of IUGR. Gestational age is shown as embryonic day, eg E20 for day 20 of gestation. CA1, CA2, CA3, CA4 = cornu ammonis fields 1-4 respectively, DG = dentate gyrus, ↓ decreased compared to healthy controls, ↑ increased compared to healthy controls, = unchanged/not different to controls, + present in this model.

Outcomes	**Rat** **maternal thromboxane**	**Rat** **uteroplacental vessel ligation**	**Guinea pig** **uteroplacental vessel ligation**	**Sheep** **uteroplacental embolisation**
VOLUME				
Total	**↓26.9% E20** [128]		**↓ 9%** [205]	**↓ 9.5%** [109]
Cerebrum	**↓44.5% E20** [128]		**↓ 13.5%** [205] **=** [162]	**=** [109]
Hippocampus			**↓ 26%** [205]	
Cerebellum			**=** [162]	**=** [109]
Striatum			**↓ 13%** [205]	
Ventriculomegaly			**+** [205]	
NEURONAL DENSITY				
Cortex		**↓parietal cortex** [160]	↓ [69, 149]	
Hippocampus			**↓dentate gyrus** [69]	= [111]
Cerebellum				**↓ Purkinje neurons and molecular layer width** [108]
HIPPOCAMPAL DEVELOPMENT				
Synaptogenesis			**↓CA1, CA3, DG** [121]	
Synaptic maturation			**↓CA1, DG** [121]	
Dendrite length			**↓ apical and basal arbor, CA1, DG** [161]	
Dendrite number			**= apical, ↓basal intersections, CA1** [161]	
Dendritic branches			**= basal, ↓ apical, CA1** [161]	
Dendritic spines			**↑ CA1, DG** [161]	
Region measurements			**↓stratum oriens, mossy fibre layer** [142]	**=** [108, 111]

Outcomes	Rat maternal thromboxane	Rat uteroplacental vessel ligation	Guinea pig uteroplacental vessel ligation	Sheep uteroplacental embolisation
WHITE MATTER				
Volume			**↓ cerebrum, E60** [162] **↓cerebellum E60** [142, 162]	
Myelination			**↓cerebrum, cerebellum, CA1 hippocampus, dorsal fornix, dorsal fimbria, corpus callosum, periventricular white matter, parasagittal white matter** [119, 121, 143, 206] **=/↓ spine, age dependent** [119] **= subcortical white matter, d65** [143] **Delayed maturation of myelin** [162]	**↓cerebral cortex, striatum** [108] **Thinner sheaths, signs of degeneration** [108]
Damage				**+ lesions in cerebrum** [108] **+ lesions, gliosis, axonal degeneration** [109]
Oligodendrocytes			**↑ numbers in cerebellum** [162]	
ASTROGLIOSIS				
Cerebrum			**= E52** [119] **↑E60, E62** [119, 162] **= E65** [143]	**↑cortex** [108, 109]
Striatum				↑ [108]
Cerebellum			**=** [119] **↑ E60** [162]	
Hippocampus			**= E65** [143]	

Table 4 – Neonatal and pre-weaning neurodevelopmental outcomes in animal models of IUGR. ↑ increased compared to healthy controls, = unchanged/not different to controls, + present in this model. VMH = ventromedial hypothalamic nucleus, PVH = paraventricular hypothalamic nucleus, CC = corpus callosum, CA1, CA2, CA3, CA4 = cornu ammonis fields 1-4 respectively, DG = dentate gyrus. Age indicated in days from birth where appropriate, eg. d10 for day 10 postnatal age.

	Rat **maternal feed restriction**	**Rat** **maternal protein restriction**	**Rat** **maternal thromboxane**	**Rat** **uteroplacental vessel ligation**	**Guinea pig** **uteroplacental vessel ligation**	**Rabbit** **uteroplacental vessel ligation**	**Sheep** **uteroplacental embolisation**
VOLUME							
Brain	↓**11%** [79]	↓**11%** [90]	↓**17.3%** [128, 129]			↓**10-18%** [116, 212]	= [125]
Forebrain	↓**10-15%** [79, 85]		↓ [129]		↓**13-16%** [145, 162]	↓**19%** [212]	= [125]
Cortex			↓**31%** [128]			↓**20%** [217]	
Striatum						↓**12%** [212]	
Hippocampus	= [85]	= [91]		↓**CA1, males, d0** [220] = **CA2, CA3, d0** [220]		↓**22.5%** [212]	
Cerebellum			↓ [129]		↓**23%** [145, 162]		= **at birth** [125] ↓**22%, 8 weeks** [125]
Hypothalamus		↓**18%** [91]					
Dentate gyrus				↓**females, d0** [220]			
Corpus callosum				↓ [114]			
NEURONAL COUNT							
Cortex	↓ [79]		↓ **density, d0** = **density, d7** [129]			= [118]	= **density, 8 weeks** [125]
VMH and PVH		↑ **density** [90]					
Dentate gyrus	= [214]			↓**females, d0** [220]			
Hippocampus	= **CA1, CA3** [214] ↓**CA2, CA4** [214]			↓**CA1, CA3, males d0** [220]	↓**19% CA1** [145]		

Cerebellum			**↓17% molecular layer, ↓22.5% granule layer** [145]	**= density, delayed migration, 8 weeks old** [125]
Cell proliferation	**↑↓hippocampus, hypothalamus, age and region specific** [199]	**=/↑ cingulate white matter, dependent on severity of restriction** [218]		
WHITE MATTER				
Volume			**↓cortex, cerebellum, hippocampal CA1 and stratum oriens** [145, 162]	**↓hippocampal stratums oriens width** [125]
Structural damage and lesions		**+** [112] **↑ axonal degeneration** [114]		**+ cerebrum, cerebellum** [125]
Apoptosis		**↑d0, d3** [112, 218, 221]		
MYELINATION				
Brain				↓ [116]
Cerebrum			**=** [162]	**=** [125]
Corpus callosum		**↓d7** [112, 218] **↓d14** [222]		
Pre-oligodendrocytes		**↓cingulum and CC d7** [112, 218]		
Oligodendrocytes		**↓ CC d14** [218, 222] **↑↓ cingulum, p7, dependent on severity** [218] **↑↓ CA1, sex specific** [220] **= immature oligodendrocytes, CA3, DG, d0** [220]		

ASTROGLIOSIS

Cerebrum			**+ parietal, frontal and temporal lobes** [125]
Hypothalamus	↓ [90]		
Hippocampus		**↑CA3, males, d0** [220]	
Dentate gyrus		**↑males, d0** [220]	
Corpus callosum		**↑d21** [222]	
Cingulum		**↑d7, d13, d14, d21, adults** [112, 114, 218]	
Internal capsule		**↑d7, d14** [112]	
External capsule		**=** [112]	

Table 5 – Adolescent and adult neurodevelopmental outcomes in animal models of IUGR. Gestational age is shown in days of gestation, eg d20 for day 20 of gestation. CA1, CA2, CA3, CA4 = cornu ammonis fields 1-4 respectively, DG = dentate gyrus, ↓ decreased compared to healthy controls, ↑ increased compared to healthy controls, = unchanged/no different to controls, + present in this model.

Outcomes	**Rat** **maternal protein restriction**	**Rat** **maternal thromboxane**	**Rat** **uteroplacental vessel ligation**	**Guinea pig** **uteroplacental vessel ligation**	**Rabbit** **uteroplacental vessel ligation**
VOLUME					
Brain	↓ [93]			↓[162]	= [163]
Cerebrum	= [79, 85] ↓ [93]				
Midbrain	↓ [93]				
Hippocampus	= [85, 93]				
Cerebellum	= [79, 85] ↓ [93]			↓[162]	
Corpus callosum			↓ [115]	↓**width** [162]	
NEURONAL DENSITY					
Cerebrum	= [79]				↓**insular, temporal and occipital cortex, indirect evidence** [117]
Hippocampus	= [85]	↑ **neuronal proliferation, adolescent females** [131]	= [113, 115] ↑**degenerating neurons, CA3** [113]		↓**indirect evidence** [117]
Dentate gyrus			= [101]		
Cerebellum	= [79]				↓ **indirect evidence via MRI** [117]
Fornix			↑ **degenerating neurons** [113]		
Entorhinal cortex			↓ [113, 115] ↑ **degenerating neurons** [113]		

Cingulate cortex	= [113]		
External capsule	↑ **degenerating neurons** [113]		
Prefrontal cortex	= [115]		↓ **indirect evidence** [117]
GABAergic interneurons	↑ **prefrontal cortex** [115]		
WHITE MATTER			
Axonal density			↓ **left hemispheric anxiety and memory pathways** [117]
Axonal degeneration	**+ cingulate and somatosensory cortices, internal capsule, pontocerebellar tract** [115]		
Microstructural reorganisation			+ [163]
MYELINATION			
Cerebrum		= [162]	↓ [117]
Corpus callosum	= [222] ↓ **d60** [40]		
Cingulum	↓ **d60** [112]		
Internal and external capsule	**= d60** [112]		
Astrogliosis			
Hippocampus	↑**CA1** [113, 115]		
Dentate gyrus	↑ [113, 115]		
Entorhinal cortex	↑ [113, 115]		
Cingulum	↑ [113, 115] = [94]		
Fornix	↑ [113]		
Motor cortex	= [115]		
Somatosensory cortex	↑ [115]		

Table 6 – Neurobehavioural and cognitive outcomes in animal models of IUGR. Postnatal age is shown days where appropriate, eg. d10 for 10 postnatal days of age. ↓ decreased compared to healthy controls, ↑ increased compared to healthy controls, = unchanged/not different to controls, + present in this model.

Outcome	Rat maternal feed restriction	Rat maternal protein restriction	Sheep maternal feed restriction	Rat maternal thromboxane	Rat uteroplacental vessel ligation	Rabbit uteroplacental vessel ligation	Sheep uteroplacental embolisation	Sheep carunclectomy
Neonatal neurobehaviour	**= reflexes** [79] **↓ righting reflex, d3-4 males, d3 females** [87] **↓cliff avoidance, d7 females, d8, both sexes** [87] **↓negative geotaxis, d7-8 males** [87]	**= reflexes d10-21** [165]		**↓surface righting, d2-9** **↓ negative geotaxis d 4-15** [129]		**↓righting reflexes, locomotion, head turning and smell test scores as d1 neonates** [116]		
Neuromotor		**↓ grip strength adult males** [165]		**↓ motor learning, males** [129]	**↓motor learning, adults** [222]			
Spatial learning	**= adult males** [95]	**= adults** [97, 165]			**= adult males** [167]		**↓initial simple maze tests (lambs)** [122] **= extended simple maze testing, obstacle course tasks, t-maze tasks (lambs)** [122]	**↓initial simple maze tests (male lambs and young adults)** [150]
Reversal learning	**↓ male pups** [79]	**↓ adult males, with ↑ perservarative errors** [97]	**↓ in maze tasks, adult males** [84] **= maze tasks, adult females** [84]					**↑ lambs, young adults** [150]
Fear and avoidance learning	**↑ male pups** [79] **= adult males** [95]			**↓** [129]				

MEMORY							
Recognition					↓ **adults** [113, 115, 223]	↓ **adults** [117]	
Spatial	= **adult males** [95]	= **adult males** [97]		↓ **adolescent females** [131]	↓ **adult males** [115, 167]		= **lambs and adults** [150]
Short term		= **adult males** [97]			= **adults males** [167]		
BEHAVIOUR							
Behavioural anxiety	= **male pups** [79] =/↑ **adult males** [93, 94]	↓ **adults** [98, 216]	↑ **reactivity to physical restraint and surprise, adults** [84]	↑ **adolescent females** = **adolescent males** [131]		↑ **adults** [117]	↑ **low birth weight female lambs** [150]
Spontaneous ambulation	= **adult males** [94, 95]	↑ **females** [165]	↑ **in isolation tasks, adults** [84]		↑ **adults** [113-115] ↓ **adult males** [160]	↓	
Hyperactivity		↑ **adult females** [165]			↑**adults** [113-115]		
Exploratory behaviour		↑**adult females** [216]			↑**adults** [113-115]	↓ **adults** [117, 163]	
Response to novelty			↓**novelty seeking, adults** [84]		= **adults** [113]		

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