Pre-eclampsia and neurodevelopmental outcomes: potential pathogenic roles for inflammation and oxidative stress?

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Abbreviations:

ADHD – Attention-deficit/hyperactivity disorder
ASD – Autism spectrum disorder
CP – Cerebral palsy
CRP – C-reactive protein
DMN – Default mode network
DTI – Diffusion tensor imaging
ETC – Electron transport chain
FA – Fractional anisotropy
FC – Functional connectivity
GPx – Glutathione peroxidase
HDP – Hypertensive disorder(s) of pregnancy
HUVECs – Human umbilical vein endothelial cells
ISSHP – International Society for Studying Hypertension in Pregnancy
IUGR – Intrauterine Growth Restriction
LPS – Lipopolysaccharide
MDA – Malondialdehyde
MDI – Mental developmental index
MIA – Maternal immune activation
mPFC – Medial prefrontal cortex
MRI – Magnetic resonance imaging
mROS – Mitochondrial reactive Oxygen Species
mtDAMPs – Mitochondrial damage-associated molecular patterns
mtDNA – Mitochondrial DNA
PE – Pre-eclampsia
PE-F1 – First generation offspring exposed prenatally to pre-eclampsia
PPV – Positive predictive value
ROS – Reactive Oxygen Species
rsFC – Resting state functional connectivity
rs-fMRI – Resting-state functional magnetic resonance imaging
RUPP – Reduced uterine perfusion pressure
SGA – Small for Gestational Age
SLF – Superior longitudinal fasciculus
SOD – Superoxide dismutase

Abstract:

Pre-eclampsia (PE) is a common and serious hypertensive disorder of pregnancy that occurs in approximately 3-5% of first-time pregnancies and is a well-known leading cause of maternal and neonatal mortality and morbidity. In recent years, there has been accumulating evidence that *in utero* exposure to PE acts as an environmental risk factor for various neurodevelopmental disorders, particularly autism spectrum disorder and ADHD. At present, the mechanism(s) mediating this relationship are uncertain. In this review, we outline the most recent evidence implicating a causal role for PE exposure in the aetiology of various neurodevelopmental disorders and provide a novel interpretation of neuroanatomical alterations in PE-exposed offspring and how these relate to their sub-optimal neurodevelopmental trajectory. We then postulate that inflammation and oxidative stress, two prominent features of the pathophysiology of PE, are likely to play a major role in mediating this association. The increased inflammation in the maternal circulation, placenta and fetal circulation in PE expose the offspring to both prenatal maternal immune activation – a risk factor for neurodevelopmental disorders, which has been well-characterised in animal models – and directly higher concentrations of pro-inflammatory cytokines, which adversely affect neuronal development. Similarly, the exaggerated oxidative stress in the mother, placenta and fetus induces the placenta to secrete factors deleterious to neurons, and exposes the fetal brain to directly elevated oxidative stress and thus adversely affects neurodevelopmental processes. Finally, we describe the interplay between inflammation and oxidative stress in PE, and how both systems interact to potentially alter neurodevelopmental trajectory in exposed offspring.

Keywords:

Pre-eclampsia, Neurodevelopmental Disorder, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Inflammation, Oxidative Stress.

1.0 Introduction

Pre-eclampsia (PE) is a common hypertensive disorder of pregnancy (HDP), characterised by new-onset hypertension on or after 20 weeks' gestation as well as any one of proteinuria, organ dysfunction or uteroplacental dysfunction [1]. PE affects approximately 3-5% of primiparous women worldwide [2–4] and is a leading cause of maternal mortality [5, 6]. Women who have had a pregnancy complicated by PE are also at an increased risk of long-term cardiovascular, renal and metabolic morbidity and mortality [7–10].

Crucially, PE exposure is also a leading cause of perinatal mortality and morbidity. Infants exposed to PE (PE-F1) have an increased risk of neonatal death, neonatal thrombocytopenia, neutropenia, bronchopulmonary dysplasia [11] and hypotension [12], and PE may account for between 1 in 10 and 1 in 4 perinatal deaths [13]. Two meta-analyses reported that children and adolescents exposed to PE *in utero* have higher systolic and diastolic blood pressure and BMI than controls, without major differences in blood glucose or lipid profiles [14, 15]. A study from the Helsinki Birth Cohort Study of children born in Helsinki between 1934 and 1944 followed the offspring for 60 – 70 years after birth and reported that adults who had been exposed to PE *in utero* had a two-fold increased risk of stroke [16].

The largest study concerning long-term morbidity in PE-F1s was conducted by Wu et al., in which the authors used birth records for all singleton live births in Denmark 1978-2004 (N=1,545,443) and matched these with hospitalization records for several diseases until the end of 2004 (0 – 27 years follow-up) [17]. In this study, PE-F1s in every age group had a higher risk of hospitalization, with incidence risk ratios ranging from 1.13 to 1.26. PE-F1s born at term were at increased risk of hospitalization for digestive system diseases, asthma, pneumonia, infectious and parasitic diseases and epilepsy than term controls, while PE-F1s born pre-term (< 37 weeks) had a higher risk of hospitalization for digestive system diseases, skin diseases and genital malformations than term controls.

So, while the effects of PE on the mother are well established, more recently there has been considerable accumulating research characterising the effects of PE exposure on a range of outcomes in the child. Additionally, there has been recent interest in elucidating the mechanisms of this association, particularly using preclinical models of PE [18]. In the following section we review the growing evidence that fetal exposure to PE increases the risk of a range of adverse neurodevelopmental outcomes in the offspring.

2.0 Evidence of an Association between PE exposure and Neurodevelopmental Outcome.

Here we review the evidence for an association between fetal exposure to PE and risk for autism spectrum disorder, attention-deficit/hyperactivity disorder, cerebral palsy, schizophrenia and epilepsy, and alterations in cognitive function in the offspring. We also discuss current limitations and knowledge gaps to understanding these associations. Although PE may also confer an increased risk on exposed offspring for various other brain disorders and deficits throughout the lifespan, the current review will focus on neurodevelopmental disorders.

2.1 Autism Spectrum and Attention Deficit/ Hyperactivity Disorders

Autism spectrum disorder (ASD) is a group of related neurodevelopmental disorders characterised by social communication deficits and stereotypic behaviours, which affects an estimated 1 – 1.5% of

children [19, 20]; while attention-deficit/hyperactivity disorder (ADHD) is characterised by inattention, hyperactivity and impulsivity, with an estimated prevalence of 1.4 -3% [21]. The role of pre- and perinatal risk factors in the aetiology of these two highly prevalent neurodevelopmental disorders is increasingly well-recognised, and the evidence for an association between PE and offspring neurodevelopmental trajectory is strongest for ASD and ADHD.

Several cohort studies, most commonly retrospective population-based studies, have identified PE exposure as an independent risk factor for ASD [22–26] and ADHD [26–29]. The evidence from case-control studies, however, is less conclusive. While many have reported a positive association between PE exposure and ASD [30–32] or ADHD [33–35], others reported no such association [36–43], while another reported a borderline-significant association with ADHD [44]. This discrepancy may be due to the fact that case-control studies have less control than cohort studies over confounding variables (see section 2.5); their larger proclivity for bias; or smaller sample sizes, as PE incidence was too low in some studies to see an effect – the case-control studies above which reported positive findings typically had much larger samples than those that did not. Other studies which did not specify the type of HDP that offspring were exposed to also noted a similar positive association with ASD [45–48] and ADHD [49, 50].

Recent meta-analyses provide the most convincing evidence that there is a strong association between PE exposure and ASD or ADHD. Four meta-analyses published between 2017 – 2018 all concluded that PE-F1s have a significantly increased relative risk or odds ratio for ASD, ranging from 1.32 to 1.50 [51–54], while one of these [52] reported an odds ratio of 1.28 for ADHD. Interestingly, a recent population-based retrospective cohort study found that offspring exposed to PE both via their mother and intergenerationally via their maternal grandmother are more likely again to be diagnosed with ASD or ADHD than those exposed via only their mother, suggesting an intergenerational association between PE exposure and these disorders [55]. Overall, the emerging literature suggests that PE exposure increases offspring risk of ASD and ADHD.

2.2 Other Common Neurodevelopmental Disorders: Cerebral Palsy, Schizophrenia and Epilepsy

The term cerebral palsy (CP) is used to describe motor disabilities with cerebral origin that are acquired in prenatal or early postnatal life, with a wide range of aetiology and symptomology [56]. Among studies that do not dichotomize the sample into pre-term- and full-term-born infants, there is no clear relationship between PE exposure and risk for CP: while many studies report a higher risk of CP among PE-F1s [57–61], others report do not [62–64]. Failing to make this distinction may be problematic because pre-term birth is itself a well-recognised risk factor for CP [60, 65]. However, among children born at or after 37 weeks' gestation, there is evidence of a positive association between PE exposure and CP [66–69]. Intriguingly, the opposite is commonly seen among PE-F1s born pre-term, in that PE exposure appears to have a protective effect against CP [17, 70–72]. Illustrating this elusive relationship, one large retrospective population-based cohort study (N = 1,764,509) reported a negative association between PE exposure and CP risk for infants born at 23 – 31 weeks' gestation, no association when born at 32 – 36 weeks, and a positive association when born on or after 37 weeks [69].

Schizophrenia is a complex neurodevelopmental disorder, which comprises psychosis, apathy, social withdrawal and cognitive impairment and has an equally complex aetiology associated with various genetic and environmental risk factors [73]. Interestingly, placentae from pregnancies complicated by PE express higher levels of genes associated with the genomic risk of schizophrenia [74]. PE exposure, however, has long been controversial as a risk factor for schizophrenia and the evidence is mixed. Two large retrospective cohort studies observed a

positive association between PE exposure and schizophrenia [75, 76], while a third reported no increased risk [77], although outcome measures in the latter study included non-schizophrenia psychotic disorders. The evidence is mixed from case-control studies: although some report an increased schizophrenia risk among PE-F1s [78, 79], most do not [80–84]. Meta-analyses from 2002 and 2018 reported significant odds ratios of 1.36 and 1.37, respectively, among PE-F1s for schizophrenia [85, 86], while a more recent and conclusive meta-analysis reported an odds ratio of 1.32, although this did not reach statistical significance ($p = 0.059$) [87]. Overall, the data suggest that PE exposure may be linked to offspring schizophrenia risk, although this is still uncertain.

Epilepsy is a neurological disease characterised by a propensity or predisposition for generating epileptic seizures [88]. Obstetric and perinatal complications, including eclampsia, have been implicated as risk factors for idiopathic childhood epilepsy [89], yet surprisingly few studies have investigated pre-eclampsia as a perinatal risk factor for the disease. Those that have, however, generally report an increased risk of epilepsy among PE-F1s [26, 58, 90]. If the sample is divided into term- and preterm-born offspring, the association is seen specifically for those born at term [27, 91], which suggests that, like CP, the effects of PE on epilepsy in the offspring may be gestational age-dependent.

In summary, the role of PE exposure in the aetiology of other common neurodevelopmental disorders is less certain than it is for ASD and ADHD. It appears, however, to have a gestational age-dependent effect on CP risk; its effect on schizophrenia risk is contentious; and despite the paucity of literature, appears to be positively associated with epilepsy.

2.3 Cognitive Function

Cognitive function is an individual's capacity to adequately think , learn and remember and is typically measured by one's performance across the domains of perception, reasoning, intuition and creativity [92]. A number of studies have reported poorer cognitive function among PE-F1s compared to controls (for systematic review, see Tuovinen et al., 2014 [93]). In infancy, the Bayley scales is commonly used to determine mental developmental index (MDI), encompassing the infant's current level of cognitive, language, social and personal skill development. Three studies have reported lower MDI scores among exposed offspring [94–96], while one study reported higher scores [97]. However, this latter study measured all pregnancy-induced hypertension, and not PE specifically, as its exposure; additionally, whereas the first three studies measured MDI at 24 months, this study was conducted at 18 months.

Lower IQ has been noted among PE-F1s from 3 to 18 years old [98–101], although one large study observed no association [102]; however, IQ is a very narrow measure of intelligence and all of these studies used different tests to measure offspring IQ. The first study to investigate academic performance among PE-F1s reported poorer verbal reasoning only when compared to unexposed siblings [103], although this reduced the ability to control for confounding variables, such as gestational age, and reduced the sample to PE-F1s with siblings who could be compared to. A more recent cohort study from Iceland found that after controlling for covariates, PE-F1s perform worse than their unexposed peers at 9, 12 and 15 years old on mathematics but not language arts [104].Two older studies found that PE exposure is a risk factor for intellectual disability in childhood [105, 106]. This has been confirmed by a more

recent population-based cohort study [26] and is in line with reports that children exposed to PE are more likely to avail of special needs services and special education classes than their unexposed peers [101, 107].

The Helsinki Birth Cohort Study has reported that PE-F1s have poorer verbal reasoning skills and total intellectual ability at 20 years old [108]. Interestingly, when subjects were followed up at a mean of age of 69, they exhibited an increased rate of cognitive decline and higher rates of self-reported cognitive dysfunction, suggesting the deleterious effects of PE exposure persist into old age [109–111]. However, to the best of the authors' knowledge, no study so far has implicated prenatal PE exposure as a risk factor for any form of dementia. Taken together, these data suggest that PE may also be associated with impaired cognitive function in exposed offspring.

2.4 Validity and Types of PE Exposure

Detailed medical birth registries are kept by Denmark, Iceland, Finland, Norway and Sweden and the manner in which these registries are kept is remarkably similar, to the point that their data can even be combined to generate larger cohorts [112]. Many of the studies presented in sections 2.1 – 2.3 which provide some of the most convincing evidence for a causal role of PE in the aetiology of neurodevelopmental disorders, are population-based studies using these Nordic registries [17, 24, 60, 69, 75, 76, 78, 91, 98, 104, 26, 29, 31, 39, 41, 44, 46, 55], so the validity of these registries is an important factor for determining the true relationship between PE and offspring neurodevelopmental disorders. The specificity and positive predictive value (PPV) for Nordic registries varies depending on diagnosis, but is generally very high, although sensitivity can be quite low [113–115]. The PPV for PE in these registries is very high, ranging from 74 – 93%, while specificity is typically ~99% [116–120]; sensitivity of PE diagnosis, however, is only 43 – 69% [117–119], which means that the registries may be missing as many as half of the true PE cases. Increasing the sensitivity of the Nordic registries would mean that a higher proportion of true PE cases are reported in the PE groups, but how this would affect the results from the above-mentioned studies is uncertain. Other cohort studies, such as the Helsinki Birth Cohort Study [77, 108–111] and the Avon Longitudinal Study of Parents and Children [28, 81], as well as many smaller studies set in regional hospitals or clinics, defined PE according to gestational blood pressure and protein urine measurements, or a diagnosis made by a qualified clinician.

Although the International Society for the Study of Hypertension in Pregnancy (ISSHP) does not recommend classifying PE as 'mild' or 'severe' for clinical purposes, the distinction may be useful for research purposes [1, 121]. Surprisingly few studies compare the effects of mild vs. severe PE in their final analysis. Apart from one study measuring IQ [98], all of these studies reported a stronger effect on the offspring's risk of ASD, CP and epilepsy if PE was severe [17, 27, 32, 58]. Wu et al. found that the increased risk for epilepsy among PE-exposed term-born infants was greater when exposed to severe PE; while the protective effect of PE against CP in preterm-born offspring was seen only for severe PE [17]. It is therefore possible that there is a dose-response effect regarding fetal exposure to PE. However, as severe PE is much less common than mild PE, one limitation of making this distinction is to drastically reduce the sample size for the severe PE group, potentially affecting statistical power. Additionally, a few studies grouped eclampsia into the exposure group [25, 104] which is likely to confound the results, as eclamptic seizures are essentially a separate disease exposure for the fetus.

Another distinction that can be made is whether PE is early- (typically <34 weeks' gestation) or late-onset [121]. As with PE severity, however, very few studies subdivide the PE exposure group in this way. The few studies which do this report an increased risk for CP if exposed to early-, but not late-onset PE, and a greater increased risk for epilepsy if exposed to late- rather than early-onset PE [27, 57, 67]. In early-onset PE, there is a greater risk for intra-uterine growth restriction (IUGR) and preterm birth, and a higher involvement of placental pathology [122]. Additionally, in early-onset PE, the fetus is exposed to PE pathophysiology for a longer duration, and during a period in which neurodevelopmental processes are at an earlier and potentially more sensitive stage. Therefore, it would be a valuable contribution to our understanding of the relationship between PE and fetal neurodevelopment if more future studies dichotomize the PE exposure as early- or late-onset.

2.5 Confounding by Parity and Comorbid Obstetric Complications

Women who suffer from PE in their first pregnancy are less likely to have additional pregnancies, so PE incidence is correspondingly lower in the multiparous population [4, 123]. Importantly, high parity is itself a risk factor for neurodevelopmental disorders [36, 53, 78]. This means it is possible that the effect of PE on offspring neurodevelopment may be smaller than it would otherwise be if pre-eclamptic women progressed to multiparity at the same rate as normotensive women. However, most of the studies in this review control for parity as a potentially confounding variable in their multivariate analysis, while one study [62] restricted their sample to primiparous women only.

PE is also a leading cause of other obstetric complications, most notably pre-term birth, small for gestational age (SGA) birthweight and IUGR, and, importantly, these conditions are recognized as perinatal risk factors for neurodevelopmental disorders [22, 25, 44, 46, 53, 60, 75, 124, 125]. The studies described here generally control well for these and other factors as potentially confounding variables in their analyses, and the associations reported in this review, where possible, are based on adjusted risk figures from multivariate analysis models reported in these studies. PE is particularly associated with preterm births, so a few studies have stratified their sample by gestational age. This has revealed, for example, that PE reduces risk for CP in preterm-born infants compared to unexposed preterm controls, but increases the risk in term infants [68, 69] and that PE may only increase epilepsy risk in children born at term [17]. Similarly, PE may only increase risk for CP among term infants if they are SGA [126]. Although most cohort studies compare the PE group to an unexposed population and then control for confounding variables, some instead compare to unexposed siblings [29, 55, 103]. While this approach has the advantage of controlling for several maternal, paternal, genetic and sociodemographic factors, it can be difficult to control for the lower incidence of preterm birth, SGA and IUGR in unexposed siblings.

Exactly how much of the relationship between PE and offspring neurodevelopmental disorders is attributable to these factors can be difficult to determine. A number of studies restricted their analysis to preterm, SGA or IUGR-exposed populations [71, 72, 100, 127, 128] and in many cases still report an effect of PE on offspring neurodevelopment. One study reported that 50% of the relationship between PE and intellectual disability in the offspring was mediated by SGA; similarly, a recent study used Sobel testing to determine how much of the relationship between PE and cumulative mental disorders in the offspring is mediated by preterm birth or SGA, and in both cases found that the mediation effect was a similar size to the direct effect of

PE [129]. Thus it appears that these comorbid obstetric complications account for some, but not all, of the association between PE and offspring neurodevelopmental trajectory, and that the remaining effect may be attributable to some feature(s) intrinsic to the pathophysiology of PE.

In summary, PE is associated with sub-optimal neurodevelopmental outcome in exposed offspring, but some questions about this relationship remain unanswered – these are, primarily: how strong is the relationship between PE and disorders others than ASD and ADHD in exposed offspring; what proportion of PE is missed by Nordic registries and how may this affect the results from studies using these registries; does the effect of PE on fetal neurodevelopment become more drastic with an increase in PE severity; do early- and late-onset PE affect fetal neurodevelopment differently; and to what extent is the relationship mediated by confounding variables such as comorbid birth complications? Before discussing potential pathogenic mechanisms, we will next describe neuroimaging studies in PE-F1s and relate their results to the evidence provided above in section 2.

3.0 Evidence for neuroanatomical alterations in the brains of offspring exposed to Pre-eclampsia

Few neuroimaging studies have been carried out on PE-F1s, although one group has recently reported neuroanatomical alterations which are congruent with the studies described above [130]. The authors selected 10 children aged 7 – 10 years old who had been exposed to PE, and 10 age-matched controls, using three types of magnetic resonance imaging (MRI) paradigms to investigate regional grey matter volumes, white matter structural connectivity and functional connectivity differences between the groups.

3.1 Regional Grey Matter Volume

Although the authors reported no difference in total brain volume, PE-F1s exhibited larger regional corrected volumes of the amygdala, temporal lobe, brainstem and cerebellum. There was, however, a significant difference in birth weight between the groups, which may have confounded the results [130]. Enlarged amygdalae are seen in children with ASD [131, 132] and some cases of temporal lobe epilepsy [133] . Similarly, increased temporal lobe [134] and brainstem [135] volumes have been reported in children with ASD. Unlike the above finding of increased cerebellar volume, however, a smaller cerebellum is seen in patients with ASD [136], ADHD [137, 138] and schizophrenia [139].

3.2 Structural Connectivity

Diffusion tensor imaging (DTI) characterizes the diffusion of water molecules in tissues and can be used to map white matter tracts in the brain [140]. This is achieved by measuring fractional anisotropy (FA) as a proxy for white matter microstructural integrity, and axial and radial diffusion to determine the directionality of axons in the white matter tract. Using DTI, the authors reported that PE-F1s have increased white matter volume and fractional anisotropy in the caudate nucleus, increased white matter volume of the superior longitudinal fasciculus (SLF) and increased axial diffusion of the cingulate gyrus [141].

The caudate nucleus is part of the striatum and is involved in learning and memory, motor output and goal-directed behaviour [142]. Autistic children exhibit hyperconnectivity of the

striatum [143] and accelerated growth of caudate grey matter, which correlates with severity of restricted-repetitive behaviours [144]. They also display abnormal processing of social and non-social rewards associated with striatal activity, which may partially underlie their restricted interests [145]. Higher inflow/outflow and structural connectivity of the caudate nucleus have also been reported in Tourette's syndrome and frontal lobe epilepsy [146, 147].

The SLF is a frontoparietal white matter tract with a crucial role in language processing [148]. Language deficits are a prominent feature of ASD [149–151]. However, the literature on connectivity of the SLF in ASD is inconclusive – whereas one study reported increased FA in part of the SLF [152], others found decreased FA [153] or no FA change at all [154]. Similarly, language problems are common in schizophrenia [155], and schizophrenics display reduced FA of the SLF [156], particularly those with auditory hallucinations [157].

The cingulum bundle is a large white matter tract which forms a core part of the limbic system and its roles include episodic memory, pain and emotional processing [158]. In ASD there is increased mean diffusivity of the cingulum [159] and hypoactivity of the associated cingulate gyrus, which correlates with the severity of autistic symptoms [160]. ADHD and schizophrenia are characterised by dysfunctional emotional processing [161, 162] and, importantly, both disorders are associated with reduced FA of the cingulum [163–166]**.**

3.3 Functional Connectivity

Resting-state functional MRI (rs-fMRI) can be used to measure the degree of functional connectivity (FC) between two brain regions based on the temporal synchronization of their activity [167]. Using rs-fMRI, the authors observed higher connectivity in PE-F1s between the left amygdala and bilateral frontal pole, the right amygdala and left frontal pole and the medial prefrontal cortex (mPFC) and precuneus; and decreased connectivity between the mPFC and the left occipital fusiform gyrus [168].

The amygdala is a deep-brain nucleus involved in emotional learning and memory and fear processing [169], and the frontal pole is the most anterior part of the prefrontal cortex, concerned with goal-engineering processes [170]. In the neurotypical brain, rsFC between the amygdala and frontal pole increases after acute psychosocial stress [171]. Interestingly, increased amygdala-frontal pole rsFC positively correlates with symptom severity in adolescents with generalized anxiety disorder [172] and emotional liability in children with ADHD [173].

The mPFC and precuneus are part of the default mode network (DMN), a group of functionally related brain structures that are highly active at rest and suppressed during most tasks [174]. Increased rsFC between these regions is unusual considering DMN hypoconnectivity is seen at rest in schizophrenia [175], ADHD [176] and ASD with low verbal and cognitive performance [177], wherein the latter study DMN dysconnectivity was negatively correlated with IQ. However, it would be interesting to study DMN FC in PE-F1s during cognitive tasks, as task-related de-activation of the DMN is reduced in ASD and schizophrenia, and this reduction is associated with poorer task performance [178–180].

The fusiform gyrus, continuous between the temporal and occipital lobes, is important for face perception and object recognition [181]. Facial recognition deficits are present in both ASD [182] and schizophrenia [183]. Correspondingly, the fusiform gyrus is smaller in schizophrenia [184] and hypoactive during face recognition tasks in ASD [185, 186].

The main brain regions affected in this study were part of the "social brain", concerned with empathy, social cognition and social interaction [187]. Social cognition is impaired in both ASD and schizophrenia [188]. For example, children with ASD have reduced activity of social brain areas in response to emotional facial expressions [189]. In fact, the aberrant empathy and overall social brain deficits in schizophrenia have led to the "social brain hypothesis" of schizophrenia which postulates that the disease primarily manifests from social brain dysfunction [190].

Thus the regional volumetric brain changes, white matter structural connectivity and rsFC results from these three studies are congruous with the anatomical and functional brain changes seen in neurodevelopmental disorders. Although these results come from only one small pilot cohort, they suggest that PE-F1s have brain structural and functional alterations which may underlie their increased risk of neurodevelopmental disorders.

4.0 Potential Pathogenic Mediators of Pre-eclampsia that May Alter Fetal Neurodevelopmental Outcomes.

4.1 Inflammation

Although maternal inflammation is a physiological component of pregnancy [191, 192], PE is characterised by an exaggerated maternal inflammatory response, which can have a deleterious effects on fetal neurodevelopmental trajectories (Figure 1).

4.1.1 Increased inflammatory response in Pre-eclampsia

Dysregulated immune activation is a well-recognized feature of PE (reviewed by [193]). Women with PE have higher circulating concentrations of the pro-inflammatory cytokines TNFα, IL-6, IL-8 and IL-16 and C-reactive protein (CRP) [192, 194–198]. They may also have lower levels of anti-inflammatory cytokines, TGFβ and IL-10, although this is less well characterized [197, 199]. Correspondingly, there is an imbalance of circulating immune cell populations. Pre-eclamptic women have greater numbers of neutrophils, increased neutrophil activation [200] and increased leukocytes [192] compared to normotensive pregnant women. There is also a reduction in regulatory T (T_{reg}) cell number [201], and immune cell populations are shifted towards an increased relative abundance of pro-inflammatory T-cells (Th1 > Th2 cells and Th17 > T_{reg} cells) [202]. Interestingly, monocytes from women with PE produce higher levels of TNFα, which inhibits proliferation of human trophoblasts [203].

Animal models of PE have elucidated a central role for inflammation in the pathophysiology of the disease. In the reduced uterine perfusion pressure (RUPP) pre-clinical model of pre-eclampsia, RUPP rats have increased levels of circulating TNFα and IL-6 [204, 205]; similarly, IL-6 infusion or transfer of Th-17 cells from RUPP rats to normal pregnant rats induces increased mean arterial pressure (MAP) and other features of PE [205, 206]. Conversely, the raised MAP and additional features of PE in RUPP rats can be ameliorated by injection of exogenous anti-inflammatory IL-4, IL-10 or T_{reg} cells, or by stimulating the proliferation of endogenous T_{reg} cells [207–210]. Additionally, injection of the bacterial endotoxin lipopolysaccharide (LPS) stimulates an immune response in rodents [211, 212], this pro-inflammatory state results in raised MAP and cardiovascular and renal deficits and is often used as a preclinical model of PE [213–215].

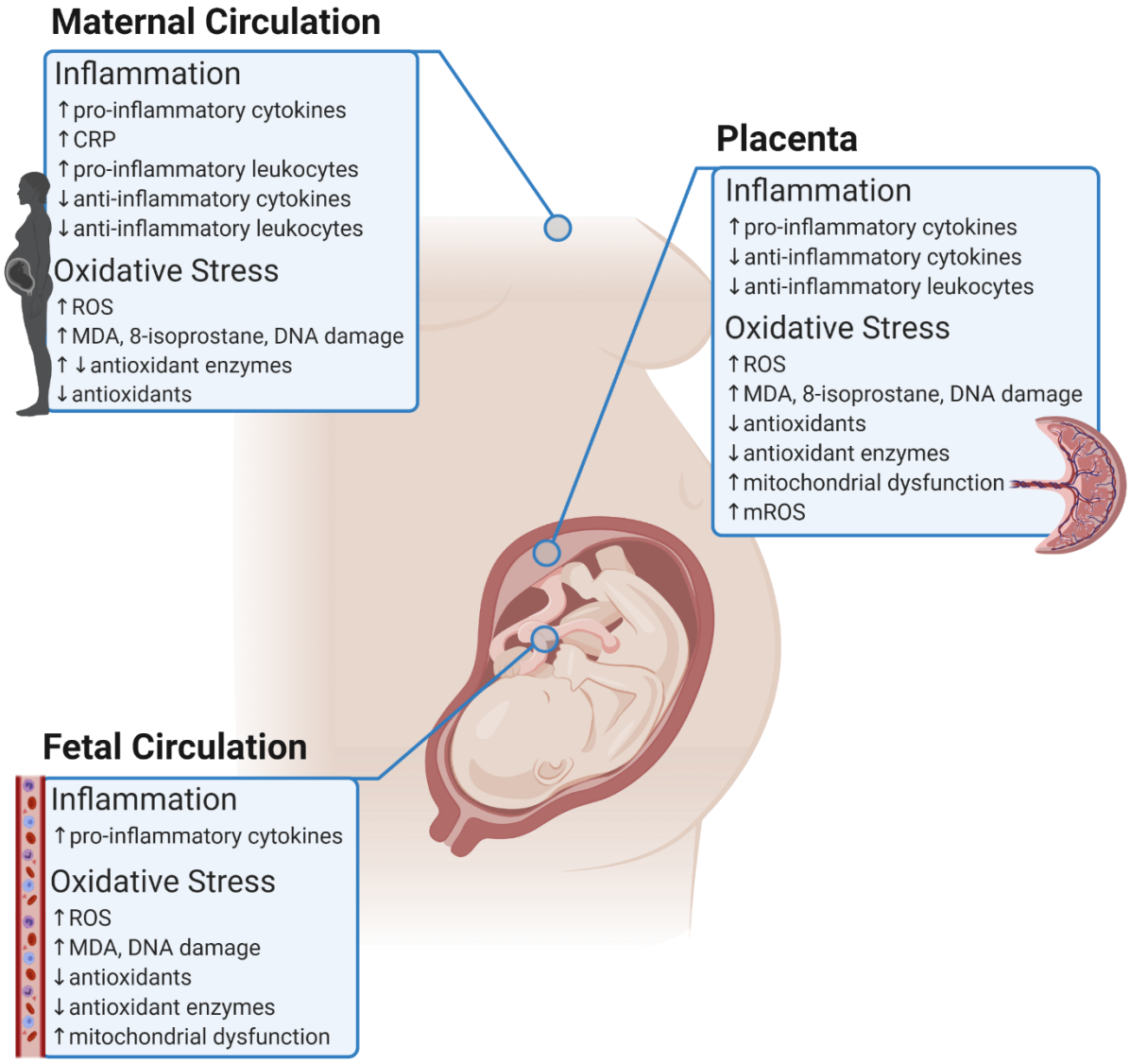

Figure 1: Overview of markers of inflammation and oxidative stress in PE. Various biomarkers of inflammation and oxidative stress have been reported in the maternal circulation, placenta and fetal circulation in pregnancies complicated by PE.

Pertinent to fetal development, pre-eclamptic placentae express or secrete significantly increased levels of pro-inflammatory cytokines TNFα, IL-1β, IL-6 and IL-16 [196, 216, 217] and lower levels of anti-inflammatory cytokines IL-4 and IL-10; it is also populated by fewer T_{reg} cells when compared with placentae from uncomplicated pregnancies [218–220]. Hypoxia/reoxygenation of human placental explants cultured *ex vivo* induces secretion of TNFα and IL-1β [221, 222]**.** There is also evidence that these inflammatory mediators reach the developing foetus. In placental vascular disease, which, like PE, is characterised by placental insufficiency, placentae express more IL-6 and IL-8 specifically on the fetal side [223]. Importantly, IL-6 has been shown to cross the placenta and reach the fetal circulation both *in vivo* and *ex vivo* [224, 225]**.** Umbilical cord blood of PE-F1s have higher concentrations of TNFα, IL-6 and IL-8 [226, 227] and while no human studies have investigated cytokine levels in the PE-F1 brain, IL-1β, IL-6 and IL-18 are found in high concentrations in the brain tissue of pups prenatally exposed to RUPP [228]. These latter findings demonstrate that PE-

F1s are not only prenatally exposed to maternal immune activation (MIA), but also directly to elevated concentrations of pro-inflammatory cytokines.

4.1.2 Implications of prenatal exposure to inflammation for fetal neurodevelopmental outcome

Maternal infection during pregnancy and the consequential induction of inflammation is a major environmental risk factor for ASD and schizophrenia [229, 230] and elevated maternal CRP during pregnancy is associated with a significantly increased risk of ASD [231]. At 7 years of age, children exposed to elevated TNFα during pregnancy have poorer performance on cognitive tests, although, interestingly, exposure to elevated levels of IL-8 improved performance, suggesting divergent roles of different pro-inflammatory cytokines [232]. Similarly, prenatal exposure to MIA can cause alterations in structural and functional brain connectivity. Elevated maternal IL-6 concentrations are associated with reduced neonatal FA in the central portion of the uncinate fasciculus, a frontolimbic tract implicated in neurodevelopmental disorders [233]; while elevated maternal IL-6 and CRP concentrations in the third trimester are associated with altered functional connectivity in the DMN, salience network and frontoparietal networks in exposed offspring [234].

Animal models of MIA provide mechanistic insights into this association. Mice prenatally exposed to the influenza virus develop schizophrenia-like behavioural deficits [235], caused not by the virus itself, but by the MIA it induces, since viral particles are not detected in the foetus, and the same behavioural deficits can be elicited by the viral mimetic compound poly(I:C) [236]. Prenatal poly(I:C)-induced behavioural deficits have been replicated in rats and can be attenuated by treatment with anti-psychotic drugs [237, 238]. Prenatal poly(I:C) exposure in mice also leads to dopamine and serotonin imbalances, mimicking the neurochemical alterations seen in schizophrenia [239, 240]. Prenatal exposure to LPS can have different effects on offspring depending on the timing of exposure: early exposure (GD12) in rats alters reward-seeking behaviour, whereas late exposure (GD16) causes motor deficits, without affecting the number of midbrain dopaminergic neurons postnatally [241].

One potential mechanism for this association is the influence of MIA on offspring microglia. Mouse offspring exposed to MIA have behavioural deficits accompanied by increased activation of microglia, reduced microglial expression of BDNF and an altered microglial methylome and transcriptome [242–244]. Interestingly, the areas of increased methylation are associated with inflammatory pathways, such as IL-4, IL-6, and IL-8 signalling [243]. This is particularly pertinent to neurodevelopment, considering the central role microglia play in regulating cortical neurogenesis and early postnatal synaptic pruning [245, 246]. As such, microglial alterations have been implicated in the pathogenesis of neurodevelopmental disorders such as ASD [247].

Neurodevelopmental alterations may also result from high concentrations of cytokines in the fetal brain. Rats exposed to LPS have higher levels of IL-1β in the placenta and TNFα, IL-1β and IL-6 in the amniotic fluid [248, 249]. Cytokines are known to cross the blood-brain barrier (BBB) [250], and, consequently, elevated concentrations of TNFα, IL-1β and IL-6 are found in the brains of MIA-exposed rats and mice [251, 252]. This aligns with observations of neuroinflammation in individuals with ASD and schizophrenia [253, 254]. One example of a pro-inflammatory cytokine with deleterious effects on neurodevelopment is IL-1β, which inhibits proliferation of neural progenitor cells and neurite growth of superior cervical ganglion

neurons via the IL-1R1 receptor [255, 256]. *In vivo*, IL-1β has been shown to activate microglia (which in turn secrete more IL-1β) and initiate BBB breakdown, increasing the brain's permeability to additional peripherally circulating cytokines [257, 258].

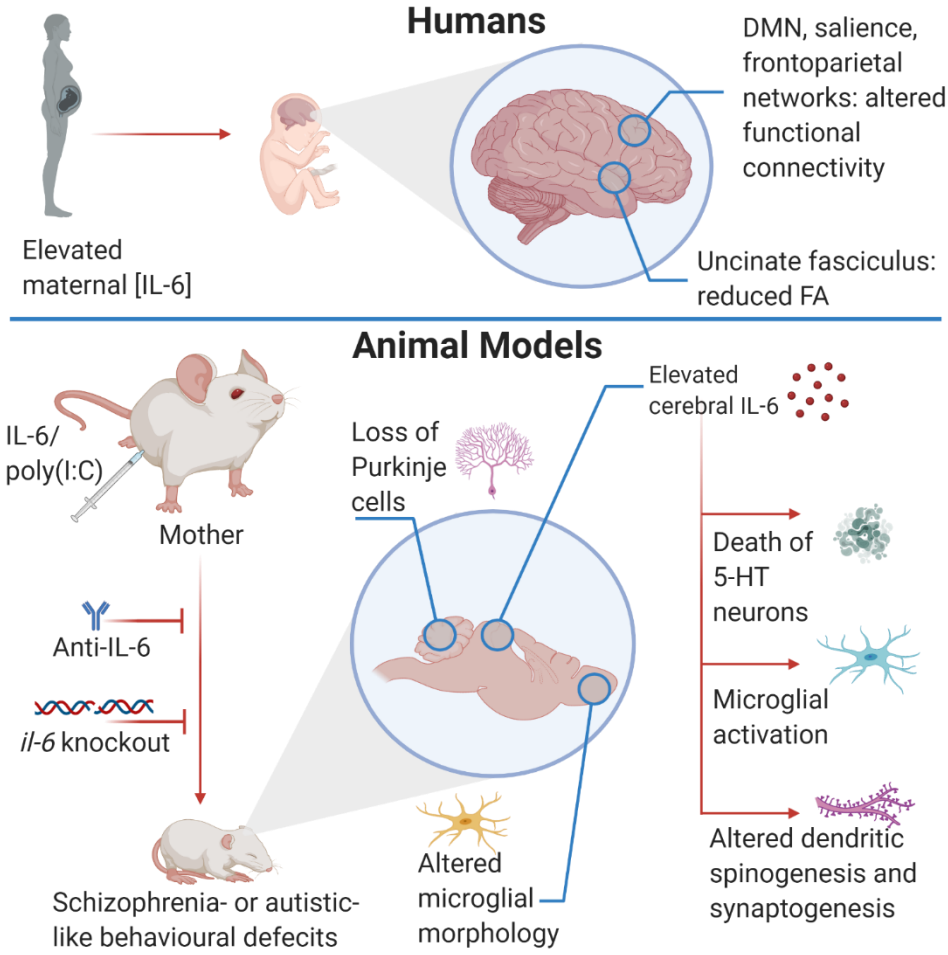

Figure. 2 The role of IL-6 in mediating adverse neurodevelopmental outcome of offspring exposed to MIA. Elevated maternal IL-6, as seen in PE, leads to neurodevelopmental deficits in humans and animal models of MIA. High [IL-6] from the placenta reaches the fetal brain, where it can have various deleterious consequences for developing neurons. The effects of prenatal IL-6 exposure on offspring brain and behaviour have been attenuated in animal models by anti-IL-6 antibody or il-6 knockout.

Perhaps the strongest candidate for a pathogenic mediator linking MIA and poor fetal neurodevelopmental outcome is IL-6 (Figure 2). The schizophrenia-like behaviours in mice prenatally exposed to poly(I:C) were shown to be IL-6-dependent [259]. In these experiments, maternal IL-6 or poly(I:C) administration induced similar behavioural deficits; however, poly(I:C) failed to affect offspring behaviour in *il-6*$^{-/-}$ mice or mice co-administered with an anti-IL-6 antibody [259]. Similarly, mice prenatally exposed to poly(I:C) have a transient increase in *il-6* expression in the brain, in addition to autistic-like behaviours and a loss of cerebellar Purkinje neurons, which are attenuated by maternal knockout of *il-6* or conditional knockout of *il-6* specifically in the placenta [260]. Chronic maternal administration of IL-6 also causes altered microglial morphology in exposed offspring, which is prevented by maternal IL-6 blockade [261]. These studies point to a primary role for IL-6 in facilitating structural and neurochemical brain changes in MIA-exposed offspring; furthermore, cerebral IL-6, similar to IL-1β, is increased in MIA and RUPP models, with detrimental effects on

neurodevelopment. IL-6 inhibits the survival of serotonergic neurons and, like IL-1β, increases microglial activity resulting in increased IL-6 secretion [262, 263]. In mice, elevated concentration of IL-6 in the brain leads to multiple behavioural deficits; increased excitatory synaptogenesis and reduced inhibitory synaptogenesis; and alterations in dendritic spine length and morphology [264]. Intriguingly, another study showed that serum from pre-eclamptic women increased neurite number, length and branching in primary cortical neurons, and found a trend towards higher IL-6 in the PE sera compared to controls, suggesting a potential mechanistic role for IL-6 in this study [48].

4.2 Oxidative Stress

Oxidative stress is the relative increase in intracellular reactive oxygen species (ROS) production and corresponding relative reduction in antioxidant levels. Elevated levels of ROS are a normal feature of gestation and play important physiological roles in the establishment of a healthy pregnancy, including regulation of endometrial changes, fertilization, implantation and placental and embryonic growth [265, 266]. Excessively high levels of ROS, however, have been associated with the pathophysiology of various pregnancy disorders, including PE, gestational diabetes mellitus and spontaneous abortion [267], and this may also contribute to the sub-optimal neurodevelopmental trajectory of PE-F1s.

4.2.1 Evidence for increased oxidative stress in Pre-eclampsia

Compared to those of normotensive pregnant women, circulating blood and erythrocyte samples from women with PE reveal increased ROS production [268–270]; higher levels of the oxidative stress markers malondialdehyde (MDA), 8-isoprostane and leukocyte DNA damage [271–274]; lower levels of the antioxidants glutathione, lycopene, vitamin C and vitamin E [268, 271, 275, 276]; and altered activity of the antioxidant enzymes superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) [268, 269, 271, 277]. Although ROS are produced by both endothelial and circulating blood cells during pregnancy, the dominant source in PE is the placenta. Pre-eclamptic placentae exhibit increased ROS production [278, 279]; elevated levels of MDA, 8-isoprostane and oxidative DNA damage [280–282]; low levels of glutathione [283]; and reduced expression and activity of SOD, GPx, thioredoxin and thioredoxin reductase [271, 279, 283–285]. Correspondingly, rats exposed to RUPP have higher placental MDA and 8-isoprostane levels and reduced SOD activity, and RUPP-induced hypertension is attenuated by the antioxidant tempol [286]. Collectively, these studies suggest that exaggerated oxidative stress is a prominent feature of PE.

Mitochondria are the primary source of ROS, and mitochondrial electron transport chain (ETC) deficits have been shown to increase ROS production [265, 287]. Notably, mitochondrial dysfunction in the placenta has been implicated as the major source of oxidative stress in PE. Mitochondria in pre-eclamptic placentae show extensive degeneration and apoptosis and have an altered metabolome [288] and mitochondrial protein expression profile, including downregulation of ETC complex V (ATP synthase) expression [289] and reduced expression and activity of ETC complex III (cytochrome c reductase) [290]. Correspondingly, mitochondria exhibit increased lipid peroxidation and MDA levels, which are markers of oxidative stress [291, 292]. Interestingly, mitochondria are not only a source of ROS, but also a target – dysfunctional mitochondria release ROS which can induce dysfunction and

consequent ROS release from neighbouring mitochondria, amplifying cellular oxidative stress [293].

In a large clinical trial, supplementation with the dietary antioxidants vitamin C and vitamin E failed to reduce the risk of PE [294]. One potential explanation for this is that the antioxidants failed to target the source of the problem – *mitochondrial* ROS (mROS). This hypothesis has led to a recent increase in the development of mitochondrial-targeted antioxidants as a potential therapeutic strategy with encouraging data emerging from pre-clinical models: RUPP exposure in pregnant rats leads to reduced ETC activity and respiratory rate and increased mROS production in placental mitochondria, and RUPP-induced hypertension was attenuated by the mitochondria-specific antioxidants MitoQ or MitoTEMPO [295]; RUPP-induced hypertension and increased sFlt1 levels were ameliorated by the nutraceutical mitochondrial antioxidant L-ergothioneine, effects that were mediated in part by specifically reducing mROS production [296]. There is further evidence of the potential therapeutic benefit of specifically targeting mitochondria in other models of hypertension, including angiotensin-II-induced hypertension in mice, which was significantly reduced following administration of mitoTEMPO, but, importantly, not by tempol, which lacks mitochondrial specificity [297]. Interestingly, the antioxidant trace element selenium is reduced in women with PE [298] and clinical trials implementing selenium supplementation have successfully reduced the risk of developing PE [299]. This may be because, unlike vitamins C and E, selenium exerts an antioxidant effect directly on placental mitochondria [300, 301].

Oxidative stress in PE is present not only in the maternal, but also fetal circulation. PE-F1 umbilical vein blood is characterised by increased ROS, MDA and leukocyte DNA damage, GPx hypoactivity and decreased levels of vitamin C and selenium [274, 276, 298]. Additionally, there is significant mitochondrial dysfunction in human umbilical vein endothelial cells (HUVECs) [302]. Collectively these data show that while women with PE have multiple features that are indicative of exaggerated oxidative stress, these changes can also be seen in neonatal PE-F1s (Figure 1).

4.2.2 The implications of prenatal exposure to oxidative stress for fetal neurodevelopmental programming

Firstly, placental oxidative stress, as seen in PE, may affect fetal neurodevelopment indirectly by inducing the placenta to secrete various factors into the fetal circulation capable of affecting the developing nervous system. This is illustrated by a series of elegant experiments, whereby the authors exposed the placental cell line BeWo or placental explants to hypoxia in order to induce oxidative stress. BeWo- or placenta-conditioned media contained increased concentrations of TNFα, which, when added to human embryonic stem cells, caused DNA damage and apoptosis – the latter effect blocked by an anti- TNFα antibody [222]. Conditioned medium from both BeWo cells and placental explants exposed to oxidative stress was next added to primary cortical neurons resulting in reduced dendritic growth and increased relative abundance of astrocytes. In a rat model of gestational hypoxia, exposed rats exhibited placental oxidative stress and offspring brains displayed similar neuronal deficits as seen *in vitro*. In both cases, these neuronal deficits were prevented by therapeutic targeting of the placenta with MitoQ [303]. Finally, using conditioned media from placental explants from women with PE, these authors established that when added to primary cortical neurons, there was reduced dendritic growth, decreased GluN1 expression and increased $GABA_{A\alpha1}$ expression in an astrocyte-dependent manner, effects that were diminished by *ex vivo* treatment of explants with

MitoQ [304]. Therefore, oxidative stress stimulates the release of factors from the placenta which are harmful to neurons.

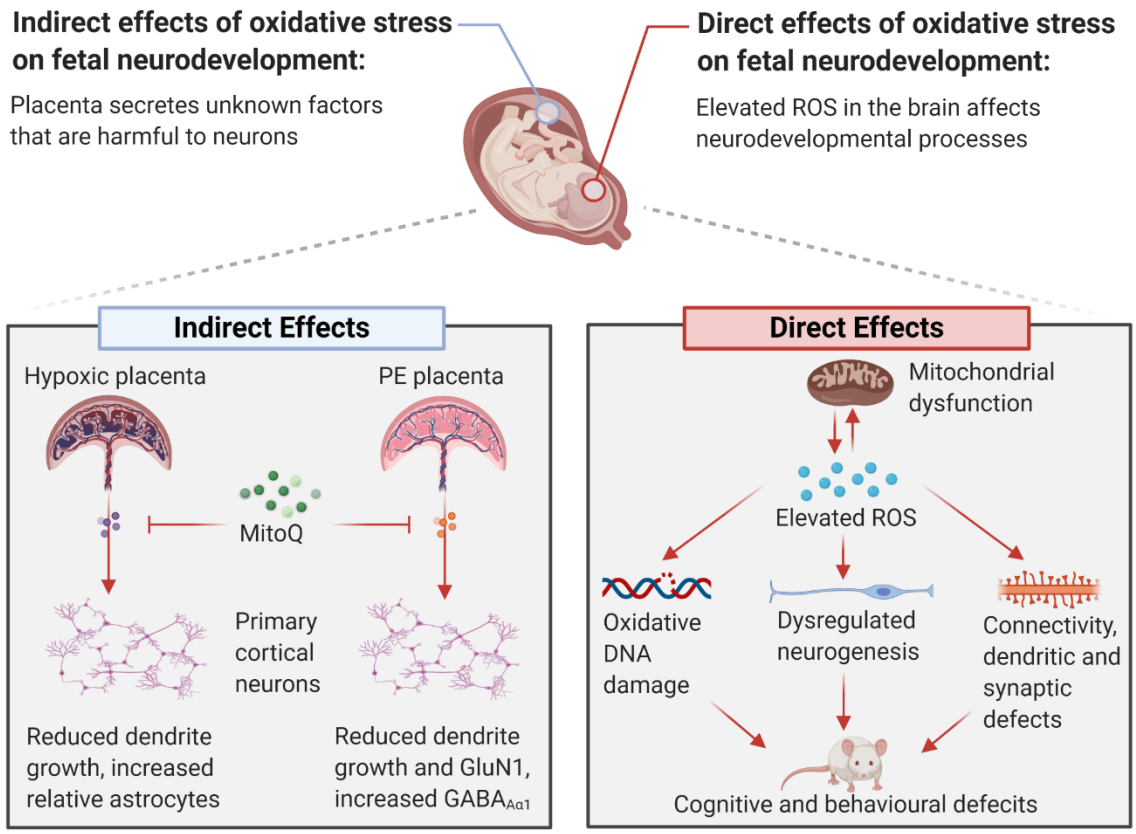

Figure 3: The influence of placental and fetal brain oxidative stress on fetal neurodevelopment. The exaggerated oxidative stress reported in PE may adversely impact fetal neurodevelopment both indirectly, via the release of factors from the placenta that are harmful to neurons; and directly, via the influence of ROS on neurodevelopmental processes.

Secondly, the high oxidative status of PE-F1s is particularly pertinent due the direct impact of ROS on neuronal development. Highly regulated concentrations of ROS modulate many neurodevelopmental processes, including neural progenitor cell proliferation and differentiation, apoptosis, dendritic growth and axonal guidance [305–309]. The brain, however, is particularly vulnerable to the deleterious effects of hyperphysiological oxidative stress and this has been illustrated by a number of animal studies. Mice with genetic impairments in the repair of oxidative DNA damage, for example, have memory deficits which can be recovered by antioxidant treatment [310]. Offspring of rats exposed to the L-NAME (Nωnitro-L-arginine methyl ester) preclinical model of PE have reduced neurogenesis at birth, decreased numbers of oligodendrocytes in the cortex, delayed development of sensorimotor reflexes and reactions and impaired spatial learning [300-302] and it has recently been shown that rats prenatally exposed to this model also exhibit raised levels of oxidative stress markers in the cortex and cerebellum [303]. Similarly, in a mouse model of DiGeorge/22q11 deletion syndrome, a developmental disorder which includes widespread neurodevelopmental deficits, layer 2/3 cortical neurons had mitochondrial damage and oxidative stress concurrent with defects in connectivity, synapse integrity and dendritic growth and branching, which manifested as cognitive behavioural deficits in the mice. These mitochondrial, dendritic and behavioural alterations were ameliorated by antioxidant treatment [311]. Finally, in a rat model

of MIA, male, but not female, offspring exhibit oxidative stress in the hippocampus and corresponding spatial learning deficits, which were rescued by maternal treatment with antioxidants, suggesting that some of the effects of MIA on offspring behaviour in males are mediated by oxidative stress [312]. In line with these observations, high levels of markers of oxidative stress are reported in those with ASD, ADHD, epilepsy and schizophrenia [313–316]. This has been most extensively investigated in ASD, where there is prominent mitochondrial dysfunction and oxidative stress in the brain [317–319]. Overall, these data suggest that the oxidative stress reported in PE-F1s may contribute to their sub-optimal neurodevelopmental trajectory via the direct effects of exaggerated ROS concentrations on neurodevelopmental processes (Figure 3).

4.2.3 The interplay between oxidative stress and inflammation

Oxidative stress and inflammation are inextricably linked and cannot be viewed as independent systems in the context of PE. Placental oxidative stress is one of the earliest events in PE and this causes the placenta to secrete various factors into the maternal circulation, ultimately leading to the hyperinflammatory and oxidative state that characterises the disease [320]. Markers of both oxidative stress and inflammation can be detected in advance of the onset of clinical symptoms and circulating levels of IL-6 are highly correlated with protein carbonylation, an oxidative stress marker, in PE [272, 273, 321, 322].

Oxidative stress activates redox-sensitive transcription factors, particularly NF-κB, upregulating cytokine gene expression [323, 324]. In the human placenta, hypoxia/reoxygenation activates p38, NF-κB and MAPK signalling pathways, increasing expression of downstream TNFα and IL-1β, an effect that is blocked by vitamins C or E [325]. Similarly, mitochondrial dysfunction in trophoblasts stimulates IL-6 secretion, which is blocked by vitamin E or the antioxidant, deferoxamine [326]. Activation of T-cell receptors induces intracellular ROS and downstream IL-2 and IL-4 production, which can be prevented by inhibition of ETC complex I [327]. Complex IV inhibition alters leukocyte response to LPS, increasing IL-6 and decreasing TNFα production; also, in healthy adults, leukocyte complex IV activity is correlated with IL-6 levels [328].

Another mechanism by which oxidative stress can promote inflammation in PE is the production of mitochondrial damage-associated molecular patterns (mtDAMPs) [329]. Oxidative stress induces the release of mtDNA and N-formyl peptides, both of which act as mtDAMPs and bind TLR-9 or FPR-1 receptors, respectively, on neutrophils to activate and drive them towards a pro-inflammatory phenotype [330]. This may have implications for PE, due to increased circulating levels of mtDNA and increased TLR-9 expression and activity in dendritic cells and placenta [200, 331–333]. Similarly, PE serum induces mROS and TLR-9 expression in HUVECs, an effect which is attenuated by MitoTEMPO [334]. Thus, oxidative stress in PE, via activation of redox-sensitive transcription factors and mtDAMPs, induces the release of cytokines both from the placenta and from immune cells.

The reverse is also true, in that inflammation promotes oxidative stress, by stimulating mitochondrial and non-mitochondrial (primarily via NADPH oxidase activity) ROS production [267]. Injection of IL-17 or Th17 cells from RUPP rats into normal pregnant rats induces placental oxidative stress [206, 335]; conversely, RUPP-induced placental oxidative stress is diminished by injection of IL-10, TNFα blocker or T_{reg} cells [207, 209, 336]. Endogenous natural killer (NK) cells also contribute to RUPP-induced placental oxidative stress, while NK

cell depletion mitigates these effects [337]. When stimulated by N-formyl peptides, neutrophils from pre-eclamptic women release higher levels of ROS than those from normotensive controls resulting in increased endothelial cell damage, suggesting that, in PE, there is a heightened sensitivity to inflammation-induced oxidative stress [338].

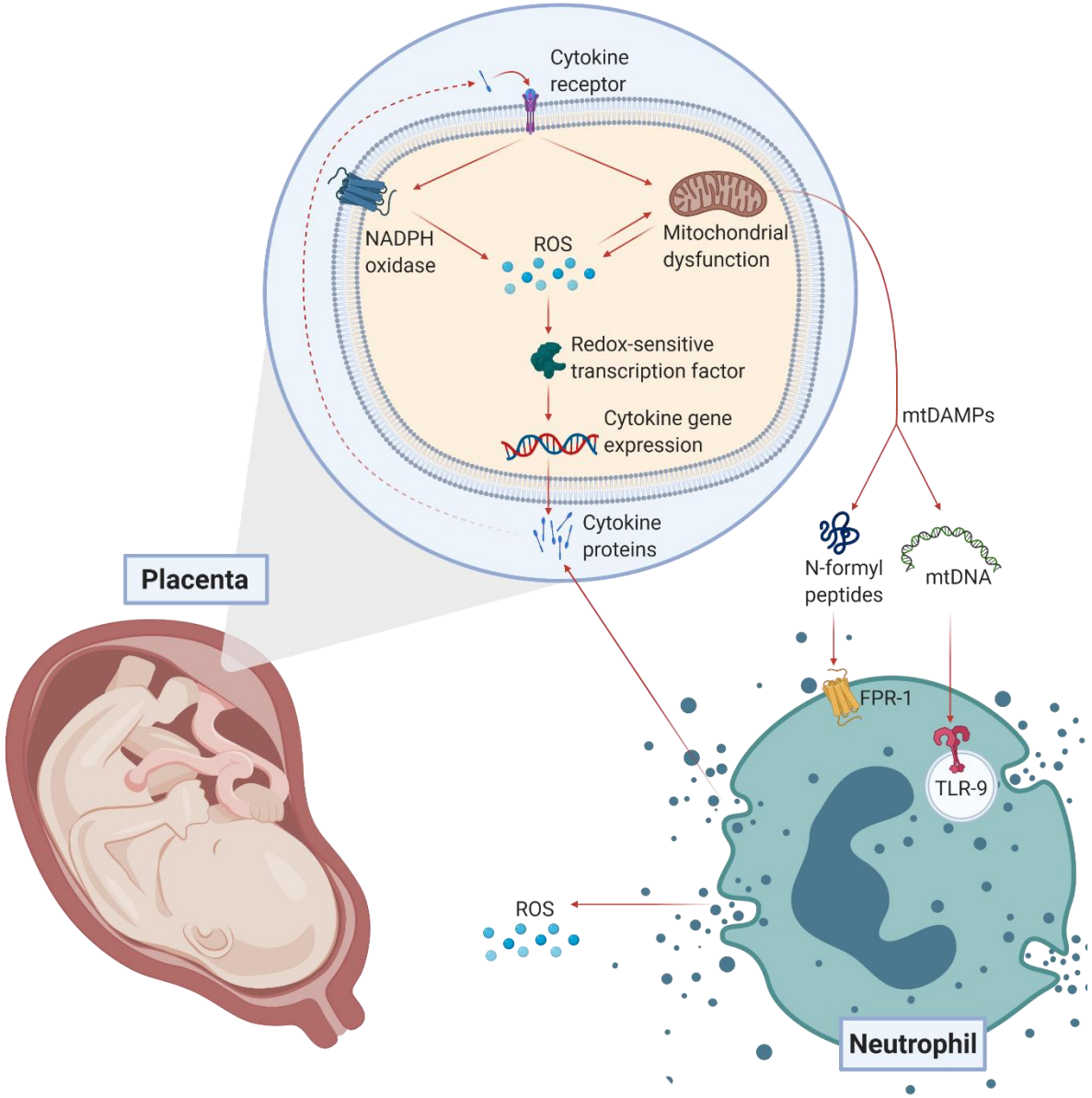

Figure 4: The interplay between oxidative stress and inflammation in the context of PE. Exaggerated oxidative stress and maternal immune activation are well-characterised features of PE and both systems interact such that increases in one induce a corresponding increase in the other. This is particularly well-characterised in the placenta and circulating immune cells such as neutrophils, resulting in the constant maintenance of an adverse *in utero* microenvironment, which is likely to have deleterious consequences for fetal neurodevelopment.

Thus, the roles of inflammation and oxidative stress are convergent and interconnected. Upregulation of one leads to increases in the other, in a self-perpetuating cycle that culminates in a highly oxidative and inflammatory microenvironment for the developing foetus (Figure 4). This adverse *in utero* environment persists throughout gestation and may have deleterious consequences for fetal neurodevelopmental outcome.

5.0 Conclusion:

The association between PE and offspring neurodevelopmental outcome is becoming increasingly well recognized. Recent evidence has established *in utero* exposure to PE as a risk factor for ASD and ADHD and may also confer an increased risk upon offspring for poor cognitive function, CP, epilepsy, schizophrenia and neuroanatomical alterations similar to those seen in these disorders. Currently, however, the associative mechanisms are yet to be fully elucidated, and this review proposes inflammation and oxidative stress as potential leading candidates. Although inflammation and oxidative stress have been discussed independently in this review for the purpose of clarity, it is important to recognize that these systems are intricately interconnected and increases in one lead, via positive feedback, to augmentation of the other.

Both inflammation and oxidative stress are prominent features of PE pathophysiology, creating a sub-optimal *in utero* environment. Persistent exposure to this inflammatory and oxidative milieu, as well as fetal inflammation and oxidative stress, are likely to affect neurodevelopmental programming in exposed offspring via the mechanisms provided in section 4 of this review. On these premises, targeting maternal immune activation, particularly IL-6, and maternal oxidative stress, particularly mROS in the placenta, are predicted to improve the neurodevelopmental outcome of exposed offspring. Although, to the best of our knowledge, no study to date has attempted both interventions simultaneously, several animal studies, as discussed above, have significantly improved offspring neurodevelopmental outcome using one therapeutic approach or the other. These studies are encouraging and suggest that similar interventions in humans may ameliorate the increased risk of neurodevelopmental disorders seen in PE-F1s.

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Competing Interests

The authors declare that they have no competing interests.

References:

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1. Brown MA, Magee LA, Kenny LC, et al (2018) The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 13:291–310
2. Ananth C V., Keyes KM, Wapner RJ (2013) Pre-eclampsia rates in the United States, 1980-2010: Age-period-cohort analysis. BMJ 347:. https://doi.org/10.1136/bmj.f6564
3. Abalos E, Cuesta C, Grosso AL, et al (2013) Global and regional estimates of

preeclampsia and eclampsia: A systematic review. Eur. J. Obstet. Gynecol. Reprod. Biol. 170:1–7
4. Hernández-Díaz S, Toh S, Cnattingius S (2009) Risk of pre-eclampsia in first and subsequent pregnancies: Prospective cohort study. BMJ 339:34. https://doi.org/10.1136/bmj.b2255
5. Saleem S, McClure EM, Goudar SS, et al (2014) Une étude prospective de la mortalité maternelle, foetale et néonatale dans les pays à revenus faible et intermédiaire. Bull World Health Organ 92:605–612. https://doi.org/10.2471/BLT.13.127464
6. Say L, Chou D, Gemmill A, et al (2014) Global causes of maternal death: A WHO systematic analysis. Lancet Glob Heal 2:e323–e333. https://doi.org/10.1016/S2214-109X(14)70227-X
7. Barrett PM, McCarthy FP, Kublickiene K, et al (2020) Adverse Pregnancy Outcomes and Long-term Maternal Kidney Disease: A Systematic Review and Meta-analysis. JAMA Netw open 3:e1920964. https://doi.org/10.1001/jamanetworkopen.2019.20964
8. Leon LJ, McCarthy FP, Direk K, et al (2019) Preeclampsia and cardiovascular disease in a large UK pregnancy cohort of linked electronic health records a CALIBER study. Circulation 140:1050–1060. https://doi.org/10.1161/CIRCULATIONAHA.118.038080
9. Feig DS, Shah BR, Lipscombe LL, et al (2013) Preeclampsia as a Risk Factor for Diabetes: A Population-Based Cohort Study. PLoS Med 10:e1001425. https://doi.org/10.1371/journal.pmed.1001425
10. Funai EF, Friedlander Y, Paltiel O, et al (2005) Long-term mortality after preeclampsia. Epidemiology 16:206–215. https://doi.org/10.1097/01.ede.0000152912.02042.cd
11. Backes CH, Markham K, Moorehead P, et al (2011) Maternal Preeclampsia and Neonatal Outcomes. J Pregnancy 2011:. https://doi.org/10.1155/2011/214365
12. Teng RJ, Wu TJ, Sharma R, et al (2006) Early neonatal hypotension in premature infants born to preeclamptic mothers. J. Perinatol. 26:471–475
13. Hodgins S (2015) Pre-eclampsia as underlying cause for perinatal deaths: Time for action. Glob. Heal. Sci. Pract. 3:525–527
14. Andraweera PH, Lassi ZS (2019) Cardiovascular Risk Factors in Offspring of Preeclamptic Pregnancies—Systematic Review and Meta-Analysis. J Pediatr 208:104-113.e6. https://doi.org/10.1016/j.jpeds.2018.12.008
15. Davis EF, Lazdam M, Lewandowski AJ, et al (2012) Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: A systematic review. Pediatrics 129
16. Kajantie E, Eriksson JG, Osmond C, et al (2009) Pre-eclampsia is associated with increased risk of stroke in the adult offspring the helsinki birth cohort study. Stroke 40:1176–1180. https://doi.org/10.1161/STROKEAHA.108.538025
17. Wu CS, Nohr EA, Bech BH, et al (2009) Health of children born to mothers who had preeclampsia: a population-based cohort study. Am J Obstet Gynecol 201:269.e1-269.e10. https://doi.org/10.1016/j.ajog.2009.06.060
18. Gumusoglu SB, Chilukuri ASS, Santillan DA, et al (2020) Neurodevelopmental Outcomes of Prenatal Preeclampsia Exposure. Trends Neurosci. 43:253–268
19. Lyall K, Croen L, Daniels J, et al (2017) The Changing Epidemiology of Autism Spectrum Disorders. Annu Rev Public Health 38:81–102. https://doi.org/10.1146/annurev-publhealth-031816-044318
20. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J (2018) Autism spectrum disorder. Lancet 392:508–520
21. Thapar A, Cooper M (2016) Attention deficit hyperactivity disorder. Lancet 387:1240–1250

22. Burstyn I, Sithole F, Zwaigenbaum L (2010) Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. Chronic Dis Can 30:125–134
23. Getahun D, Fassett MJ, Peltier MR, et al (2017) Association of Perinatal Risk Factors with Autism Spectrum Disorder. Am J Perinatol 34:295–304
24. Maher GM, O'Keeffe GW, Dalman C, et al (2020) Association between preeclampsia and autism spectrum disorder: a population-based study. J Child Psychol Psychiatry Allied Discip 61:131–139. https://doi.org/10.1111/jcpp.13127
25. Mann JR, McDermott S, Bao H, et al (2010) Pre-eclampsia, birth weight, and autism spectrum disorders. J Autism Dev Disord 40:548–54. https://doi.org/10.1007/s10803-009-0903-4
26. Sun BZ, Moster D, Harmon QE, Wilcox AJ (2020) Association of Preeclampsia in Term Births With Neurodevelopmental Disorders in Offspring. JAMA Psychiatry e200306. https://doi.org/10.1001/jamapsychiatry.2020.0306
27. Mann JR, McDermott S (2011) Maternal pre-eclampsia is associated with childhood epilepsy in South Carolina children insured by Medicaid. Epilepsy Behav 20:506–511. https://doi.org/10.1016/j.yebeh.2011.01.006
28. Dachew BA, Scott JG, Mamun A, Alati R (2019) Pre-eclampsia and the risk of attention-deficit/hyperactivity disorder in offspring: Findings from the ALSPAC birth cohort study. Psychiatry Res 272:392–397. https://doi.org/10.1016/j.psychres.2018.12.123
29. Maher GM, Dalman C, O'Keeffe GW, et al (2020) Association between preeclampsia and attention-deficit hyperactivity disorder: a population-based and sibling-matched cohort study. Acta Psychiatr Scand. https://doi.org/10.1111/acps.13162
30. Buchmayer S, Johansson S, Johansson A, et al (2009) Can association between preterm birth and autism be explained by maternal or neonatal morbidity? Pediatrics 124:. https://doi.org/10.1542/peds.2008-3582
31. Polo-Kantola P, Lampi KM, Hinkka-Yli-Salomäki S, et al (2014) Obstetric risk factors and autism spectrum disorders in Finland. J Pediatr 164:358–365. https://doi.org/10.1016/j.jpeds.2013.09.044
32. Walker CK, Krakowiak P, Baker A, et al (2015) Preeclampsia, placental insufficiency, and autism spectrum disorder or developmental delay. JAMA Pediatr 169:154–62. https://doi.org/10.1001/jamapediatrics.2014.2645
33. Getahun D, Rhoads GG, Demissie K, et al (2013) In utero exposure to ischemic-hypoxic conditions and attention-deficit/ hyperactivity disorder. Pediatrics 131:. https://doi.org/10.1542/peds.2012-1298
34. Golmirzaei J, Namazi S, Amiri S, et al (2013) Evaluation of Attention-Deficit Hyperactivity Disorder Risk Factors. Int J Pediatr 2013:953103. https://doi.org/10.1155/2013/953103
35. Silva D, Colvin L, Hagemann E, Bower C (2014) Environmental risk factors by gender associated with attention-deficit/ hyperactivity disorder. Pediatrics 133:. https://doi.org/10.1542/peds.2013-1434
36. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W (2009) Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics 123:1293–1300. https://doi.org/10.1542/peds.2008-0927
37. Deykin EY, Macmahon B (1980) Pregnancy, Delivery, and Neonatal Complications Among Autistic Children. Am J Dis Child 134:860–864. https://doi.org/10.1001/archpedi.1980.02130210044012
38. Glasson EJ, Bower C, Petterson B, et al (2004) Perinatal factors and the development of autism: A population study. Arch Gen Psychiatry 61:618–627.

https://doi.org/10.1001/archpsyc.61.6.618
39. Larsson HJ, Eaton WW, Madsen KM, et al (2005) Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol 161:916–925. https://doi.org/10.1093/aje/kwi123
40. Mrozek-Budzyn D, Majewska R, Kieltyka A (2013) Prenatal, perinatal and neonatal risk factors for autism - Study in Poland. Cent Eur J Med 8:424–430. https://doi.org/10.2478/s11536-013-0174-5
41. Gustafsson P, Kallen K (2011) Perinatal, maternal, and fetal characteristics of children diagnosed with attention-deficit-hyperactivity disorder: results from a population-based study utilizing the Swedish Medical Birth Register. Dev Med Child Neurol 53:263–268. https://doi.org/10.1111/j.1469-8749.2010.03820.x
42. Amiri S, Malek A, Sadegfard M, Abdi S (2012) Pregnancy-related Maternal Risk Factors of Attention-Deficit Hyperactivity Disorder: A Case-Control Study. ISRN Pediatr 2012:. https://doi.org/10.5402/2012/458064
43. Ketzer CR, Gallois C, Martinez AL, et al (2012) Is there an association between perinatal complications and ttention-deficit/hyperactivity disorder-inattentive type in children and adolescents? . Brazilian J. Psychiatry 34:321–328
44. Halmøy A, Klungsøyr K, Skjærven R, Haavik J (2012) Pre- and perinatal risk factors in adults with attention-deficit/ hyperactivity disorder. Biol Psychiatry 71:474–481. https://doi.org/10.1016/j.biopsych.2011.11.013
45. Langridge AT, Glasson EJ, Nassar N, et al (2013) Maternal conditions and perinatal characteristics associated with autism spectrum disorder and intellectual disability. PLoS One 8:e50963. https://doi.org/10.1371/journal.pone.0050963
46. Hultman CM, Sparén P, Cnattingius S (2002) Perinatal risk factors for infantile autism. Epidemiology 13:417–423. https://doi.org/10.1097/00001648-200207000-00009
47. Dodds L, Fell DB, Shea S, et al (2011) The role of prenatal, obstetric and neonatal factors in the development of autism. J Autism Dev Disord 41:891–902. https://doi.org/10.1007/s10803-010-1114-8
48. Curran EA, O'Keeffe GW, Looney AM, et al (2018) Exposure to Hypertensive Disorders of Pregnancy Increases the Risk of Autism Spectrum Disorder in Affected Offspring. Mol Neurobiol 55:5557–5564. https://doi.org/10.1007/s12035-017-0794-x
49. Böhm S, Curran EA, Kenny LC, et al (2019) The Effect of Hypertensive Disorders of Pregnancy on the Risk of ADHD in the Offspring. J Atten Disord 23:692–701. https://doi.org/10.1177/1087054717690230
50. Pohlabeln H, Rach S, De Henauw S, et al (2017) Further evidence for the role of pregnancy-induced hypertension and other early life influences in the development of ADHD: results from the IDEFICS study. Eur Child Adolesc Psychiatry 26:957–967. https://doi.org/10.1007/s00787-017-0966-2
51. Dachew BA, Mamun A, Maravilla JC, Alati R (2018) Pre-eclampsia and the risk of autism-spectrum disorder in offspring: meta-analysis. Br J Psychiatry 212:142–147. https://doi.org/10.1192/bjp.2017.27
52. Maher GM, O'Keeffe GW, Kearney PM, et al (2018) Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis. JAMA psychiatry 75:809–819. https://doi.org/10.1001/jamapsychiatry.2018.0854
53. Wang C, Geng H, Liu W, Zhang G (2017) Prenatal, perinatal, and postnatal factors associated with autism. Medicine (Baltimore) 96:e6696. https://doi.org/10.1097/MD.0000000000006696
54. Xu RT, Chang QX, Wang QQ, et al (2018) Association between hypertensive disorders of pregnancy and risk of autism in offspring: A systematic review and

metaanalysis of observational studies. Oncotarget 9:1291–1301. https://doi.org/10.18632/oncotarget.23030
55. Maher GM, Dalman C, O'Keeffe GW, et al (2020) Association between Preeclampsia and Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder: An Intergenerational Analysis. Acta Psychiatr Scand acps.13180. https://doi.org/10.1111/acps.13180
56. Blair E, Watson L (2006) Epidemiology of cerebral palsy. Semin. Fetal Neonatal Med. 11:117–125
57. Mor O, Stavsky M, Yitshak-Sade M, et al (2016) Early onset preeclampsia and cerebral palsy: A double hit model? Am J Obstet Gynecol 214:105.e1-105.e9. https://doi.org/10.1016/j.ajog.2015.08.020
58. Nahum Sacks K, Friger M, Shoham-Vardi I, et al (2019) Long-term neuropsychiatric morbidity in children exposed prenatally to preeclampsia. Early Hum Dev 130:96–100. https://doi.org/10.1016/j.earlhumdev.2019.01.016
59. Öztürk A, Demirci F, Yavuz T, et al (2007) Antenatal and delivery risk factors and prevalence of cerebral palsy in Duzce (Turkey). Brain Dev 29:39–42. https://doi.org/10.1016/j.braindev.2006.05.011
60. Thorngren-Jerneck K, Herbst A (2006) Perinatal factors associated with cerebral palsy in children born in Sweden. Obstet Gynecol 108:1499–1505. https://doi.org/10.1097/01.AOG.0000247174.27979.6b
61. Stelmach T, Pisarev H, Talvik T (2005) Ante- and perinatal factors for cerebral palsy: Case-control study in Estonia. J Child Neurol 20:654–661. https://doi.org/10.1177/08830738050200080401
62. Love ER, Crum J, Bhattacharya S (2012) Independent effects of pregnancy induced hypertension on childhood development: A retrospective cohort study. Eur J Obstet Gynecol Reprod Biol 165:219–224. https://doi.org/10.1016/j.ejogrb.2012.08.015
63. Palmer L, Blairt E, Petterson B, Burton P (1995) Antenatal antecedents of moderate and severe cerebral palsy. Paediatr Perinat Epidemiol 9:171–184. https://doi.org/10.1111/j.1365-3016.1995.tb00132.x
64. Withagen MIJ, Wallenburg HCS, Steegers EAP, et al (2005) Morbidity and development in childhood of infants born after temporising treatment of early onset pre-eclampsia. BJOG An Int J Obstet Gynaecol 112:910–914. https://doi.org/10.1111/j.1471-0528.2005.00614.x
65. van Lieshout P, Candundo H, Martino R, et al (2017) Onset factors in cerebral palsy: A systematic review. Neurotoxicology 61:47–53. https://doi.org/10.1016/j.neuro.2016.03.021
66. Blair E, Watson L (2016) Cerebral palsy and perinatal mortality after pregnancy-induced hypertension across the gestational age spectrum: Observations of a reconstructed total population cohort. Dev Med Child Neurol 58:76–81. https://doi.org/10.1111/dmcn.13014
67. Mann JR, McDermott S, Griffith MI, et al (2011) Uncovering the complex relationship between pre-eclampsia, preterm birth and cerebral palsy. Paediatr Perinat Epidemiol 25:100–110. https://doi.org/10.1111/j.1365-3016.2010.01157.x
68. Greenwood C, Yudkin P, Sellers S, et al (2005) Why is there a modifying effect of gestational age on risk factors for cerebral palsy? Arch Dis Child Fetal Neonatal Ed 90:. https://doi.org/10.1136/adc.2004.052860
69. Trønnes H, Wilcox AJ, Lie RT, et al (2014) Risk of cerebral palsy in relation to pregnancy disorders and preterm birth: A national cohort study. Dev Med Child Neurol 56:779–785. https://doi.org/10.1111/dmcn.12430
70. Gray PH, O'Callaghan MJ, Mohay HA, et al (1998) Maternal hypertension and

neurodevelopmental outcome in very preterm infants. Arch Dis Child Fetal Neonatal Ed 79:F88–F93. https://doi.org/10.1136/fn.79.2.F88
71. Murphy DJ, Johnson AM, Sellers S, MacKenzie IZ (1995) Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. Lancet 346:1449–1454. https://doi.org/10.1016/S0140-6736(95)92471-X
72. Spinillo A, Capuzzo E, Cavallini A, et al (1998) Preeclampsia, preterm delivery and infant cerebral palsy. Eur J Obstet Gynecol Reprod Biol 77:151–155. https://doi.org/10.1016/S0301-2115(97)00246-7
73. Khan Z, Martin-Montañez E, Muly E (2013) Schizophrenia: Causes and Treatments. Curr Pharm Des 19:6451–6461. https://doi.org/10.2174/1381612811319360006
74. Ursini G, Punzi G, Chen Q, et al (2018) Convergence of placenta biology and genetic risk for schizophrenia article. Nat Med 24:792–801. https://doi.org/10.1038/s41591-018-0021-y
75. Eide MG, Moster D, Irgens LM, et al (2013) Degree of fetal growth restriction associated with schizophrenia risk in a national cohort. Psychol Med 43:2057–2066. https://doi.org/10.1017/S003329171200267X
76. Dalman C, Allebeck P, Cullberg J, et al (1999) Obstetric complications and the risk of schizophrenia: A longitudinal study of a National Birth Cohort. Arch Gen Psychiatry 56:234–240. https://doi.org/10.1001/archpsyc.56.3.234
77. Tuovinen S, Räikkönen K, Pesonen A-K, et al (2012) Hypertensive disorders in pregnancy and risk of severe mental disorders in the offspring in adulthood: the Helsinki Birth Cohort Study. J Psychiatr Res 46:303–10. https://doi.org/10.1016/j.jpsychires.2011.11.015
78. Byrne M, Agerbo E, Bennedsen B, et al (2007) Obstetric conditions and risk of first admission with schizophrenia: A Danish national register based study. Schizophr Res 97:51–59. https://doi.org/10.1016/j.schres.2007.07.018
79. O'Dwyer JM (1997) Schizophrenia in people with intellectual disability: The role of pregnancy and birth complications. J Intellect Disabil Res 41:238–251. https://doi.org/10.1111/j.1365-2788.1997.tb00703.x
80. Suvisaari JM, Taxell-Lassas V, Pankakoski M, et al (2013) Obstetric complications as risk factors for schizophrenia spectrum psychoses in offspring of mothers with psychotic disorder. Schizophr Bull 39:1056–1066. https://doi.org/10.1093/schbul/sbs109
81. Zammit S, Odd D, Horwood J, et al (2009) Investigating whether adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 years in the ALSPAC birth cohort. Psychol Med 39:1457–1467. https://doi.org/10.1017/S0033291708005126
82. Thomas H V., Dalman C, David AS, et al (2001) Obstetric complications and risk of schizophrenia: Effect of gender, age at diagnosis and maternal history of psychosis. Br J Psychiatry 179:409–414. https://doi.org/10.1192/bjp.179.5.409
83. Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA (2003) Do Hypertension and Diuretic Treatment in Pregnancy Increase the Risk of Schizophrenia in Offspring? Am J Psychiatry 160:464–468. https://doi.org/10.1176/appi.ajp.160.3.464
84. Kendell RE, McInneny K, Juszczak E, Bain M (2000) Obstetric complications and schizophrenia. Two case-control studies based on structured obstetric records. Br J Psychiatry 176:516–522. https://doi.org/10.1192/bjp.176.6.516
85. Dachew BA, Mamun A, Maravilla JC, Alati R (2018) Association between hypertensive disorders of pregnancy and the development of offspring mental and behavioural problems: A systematic review and meta-analysis. Psychiatry Res 260:458–467. https://doi.org/10.1016/j.psychres.2017.12.027

86. Cannon M, Jones PB, Murray RM (2002) Obstetric complications and schizophrenia: Historical and meta-analytic review. Am. J. Psychiatry 159:1080–1092
87. Davies C, Segre G, Estradé A, et al (2020) Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. The Lancet Psychiatry 7:399–410. https://doi.org/10.1016/s2215-0366(20)30057-2
88. Guerrini R (2006) Epilepsy in children. In: Lancet. Elsevier, pp 499–524
89. Whitehead E, Dodds L, Joseph KS, et al (2006) Relation of pregnancy and neonatal factors to subsequent development of childhood epilepsy: A population-based cohort study. Pediatrics 117:1298–1306. https://doi.org/10.1542/peds.2005-1660
90. Degen R (1978) Epilepsy in children - An etiological study based on their obstetrical records. J Neurol 217:145–158. https://doi.org/10.1007/BF00312956
91. Wu C Sen, Sun Y, Vestergaard M, et al (2008) Preeclampsia and risk for epilepsy in offspring. Pediatrics 122:1072–8. https://doi.org/10.1542/peds.2007-3666
92. Antony JM, Weaver I, Rueffer M, et al (2017) The essentials of a global index for cognitive function. Transl Neurosci 8:87–96. https://doi.org/10.1515/tnsci-2017-0014
93. Tuovinen S, Eriksson JG, Kajantie E, Räikkönen K (2014) Maternal hypertensive pregnancy disorders and cognitive functioning of the offspring: a systematic review. J Am Soc Hypertens 8:832–47.e1. https://doi.org/10.1016/j.jash.2014.09.005
94. Cheng SW, Chou HC, Tsou KI, et al (2004) Delivery before 32 weeks of gestation for maternal pre-eclampsia: Neonatal outcome and 2-year developmental outcome. Early Hum Dev 76:39–46. https://doi.org/10.1016/j.earlhumdev.2003.10.004
95. Schlapbach LJ, Ersch J, Adams M, et al (2010) Impact of chorioamnionitis and preeclampsia on neurodevelopmental outcome in preterm infants below 32 weeks gestational age. Acta Paediatr Int J Paediatr 99:1504–1509. https://doi.org/10.1111/j.1651-2227.2010.01861.x
96. Szymonowicz W, Yu VYH (1987) Severe pre-eclampsia and infants of very low birth weight. Arch Dis Child 62:712–716. https://doi.org/10.1136/adc.62.7.712
97. McCowan LME, Pryor J, Harding JE (2002) Perinatal predictors of neurodevelopmental outcome in small-for-gestational-age children at 18 months of age. Am J Obstet Gynecol 186:1069–1075. https://doi.org/10.1067/mob.2002.122292
98. Ehrenstein V, Rothman KJ, Pedersen L, et al (2009) Pregnancy-associated Hypertensive Disorders and Adult Cognitive Function Among Danish Conscripts. Am J Epidemiol 170:1025–1031. https://doi.org/10.1093/aje/kwp223
99. Heikura U, Hartikainen A-L, Nordström T, et al (2013) Maternal Hypertensive Disorders during Pregnancy and Mild Cognitive Limitations in the Offspring. Paediatr Perinat Epidemiol 27:188–198. https://doi.org/10.1111/ppe.12028
100. Many A, Fattal A, Leitner Y, et al (2003) Neurodevelopmental and cognitive assessment of children born growth restricted to mothers with and without preeclampsia. Hypertens Pregnancy 22:25–29. https://doi.org/10.1081/PRG-120016791
101. Van Wassenaer AG, Westera J, Van Schie PEM, et al (2011) Outcome at 4.5 years of children born after expectant management of early-onset hypertensive disorders of pregnancy. Am J Obstet Gynecol 204:510.e1-510.e9. https://doi.org/10.1016/j.ajog.2011.02.032
102. Seidman DS, Laor A, Gale R, et al (1991) Pre-eclampsia and offspring's blood pressure, cognitive ability and physical development at 17-years-of-age. BJOG An Int J Obstet Gynaecol 98:1009–1014. https://doi.org/10.1111/j.1471-0528.1991.tb15339.x
103. Barker DJP, Edwards JH (1967) Obstetric Complications and School Performance. Br Med J 3:695–698. https://doi.org/10.1136/bmj.3.5567.695
104. Sverrisson FA, Bateman BT, Aspelund T, et al (2018) Preeclampsia and academic

performance in children: A nationwide study from Iceland. PLoS One 13:e0207884. https://doi.org/10.1371/journal.pone.0207884
105. Taylor DJ, Davidson J, Howie PW, et al (1985) Do pregnancy compllications contribute to neurodevelopmental disability? Lancet 325:713–716. https://doi.org/10.1016/S0140-6736(85)91261-9
106. Salonen JT, Heinonen OP (1984) Mental retardation and mother's hypertension during pregnancy. J Intellect Disabil Res 28:53–56. https://doi.org/10.1111/j.1365-2788.1984.tb01601.x
107. Griffith MI, Mann JR, McDermott S (2011) The risk of intellectual disability in children born to mothers with preeclampsia or eclampsia with partial mediation by low birth weight. Hypertens Pregnancy 30:108–115. https://doi.org/10.3109/10641955.2010.507837
108. Tuovinen S, Räikkönen K, Kajantie E, et al (2012) Hypertensive disorders in pregnancy and intellectual abilities in the offspring in young adulthood: The Helsinki Birth Cohort Study. Ann Med 44:394–403. https://doi.org/10.3109/07853890.2011.573497
109. Tuovinen S, Räikkönen K, Kajantie E, et al (2012) Hypertensive disorders in pregnancy and cognitive decline in the offspring up to old age. Neurology 79:1578–1582. https://doi.org/10.1212/WNL.0b013e31826e2606
110. Tuovinen S, Aalto-Viljakainen T, Eriksson JG, et al (2014) Maternal hypertensive disorders during pregnancy: Adaptive functioning and psychiatric and psychological problems of the older offspring. BJOG An Int J Obstet Gynaecol 121:1482–1491. https://doi.org/10.1111/1471-0528.12753
111. Tuovinen S, Eriksson JG, Kajantie E, et al (2013) Maternal hypertensive disorders in pregnancy and self-reported cognitive impairment of the offspring 70 years later: The Helsinki Birth Cohort Study. Am J Obstet Gynecol 208:200.e1-200.e9. https://doi.org/10.1016/j.ajog.2012.12.017
112. Maret-Ouda J, Tao W, Wahlin K, Lagergren J (2017) Nordic registry-based cohort studies: Possibilities and pitfalls when combining Nordic registry data. Scand. J. Public Health 45:14–19
113. Engeland A, Bjørge T, Daltveit AK, et al (2009) Validation of disease registration in pregnant women in the Medical Birth Registry of Norway. Acta Obstet Gynecol Scand 88:1083–1089. https://doi.org/10.1080/00016340903128454
114. Schmidt M, Schmidt SAJ, Sandegaard JL, et al (2015) The Danish National patient registry: A review of content, data quality, and research potential. Clin. Epidemiol. 7:449–490
115. Sund R (2012) Quality of the Finnish Hospital Discharge Register: A systematic review. Scand J Public Health 40:505–515. https://doi.org/10.1177/1403494812456637
116. Thomsen LCV, Klungsøyr K, Roten LT, et al (2013) Validity of the diagnosis of pre-eclampsia in the Medical Birth Registry of Norway. Acta Obstet Gynecol Scand 92:943–950. https://doi.org/10.1111/aogs.12159
117. Klungsøyr K, Harmon QE, Skard LB, et al (2014) Validity of Pre-Eclampsia Registration in the Medical Birth Registry of Norway for Women Participating in the Norwegian Mother and Child Cohort Study, 1999-2010. Paediatr Perinat Epidemiol 28:362–371. https://doi.org/10.1111/ppe.12138
118. Kristensen J, Langhoff-Roos J, Theil Skovgaard L, Børlum Kristensen F (1996) Validation of the Danish birth registration. J Clin Epidemiol 49:893–897. https://doi.org/10.1016/0895-4356(96)00018-2
119. Klemmensen ÅK, Olsen SF, Østerdal ML, Tabor A (2007) Validity of preeclampsia-

related diagnoses recorded in a national hospital registry and in a postpartum interview of the women. Am. J. Epidemiol. 166:117–124
120. Ludvigsson JF, Andersson E, Ekbom A, et al (2011) External review and validation of the Swedish national inpatient register. BMC Public Health 11:. https://doi.org/10.1186/1471-2458-11-450
121. Tranquilli AL, Brown MA, Zeeman GG, et al (2013) The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertens 3:44–47. https://doi.org/10.1016/j.preghy.2012.11.001
122. Redman CW (2017) Early and late onset preeclampsia: Two sides of the same coin. Pregnancy Hypertens An Int J Women's Cardiovasc Heal 7:58. https://doi.org/10.1016/j.preghy.2016.10.011
123. Seeho SK, Algert CS, Roberts CL, Ford JB (2016) Early-onset preeclampsia appears to discourage subsequent pregnancy but the risks may be overestimated. In: American Journal of Obstetrics and Gynecology. Mosby Inc., pp 785.e1-785.e8
124. Kronenberg ME, Raz S, Sander CJ (2006) Neurodevelopmental outcome in children born to mothers with hypertension in pregnancy: The significance of suboptimal intrauterine growth. Dev Med Child Neurol 48:200–206. https://doi.org/10.1017/S0012162206000430
125. Strang-Karlsson S, Räikkönen K, Pesonen AK, et al (2008) Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. Am J Psychiatry 165:1345–1353. https://doi.org/10.1176/appi.ajp.2008.08010085
126. Strand KM, Heimstad R, Iversen AC, et al (2013) Mediators of the association between pre-eclampsia and cerebral palsy: population based cohort study. BMJ 347:. https://doi.org/10.1136/bmj.f4089
127. Leitner Y, Harel S, Geva R, et al (2012) The neurocognitive outcome of IUGR children born to mothers with and without preeclampsia. J Matern Neonatal Med 25:2206–2208. https://doi.org/10.3109/14767058.2012.684164
128. Morsing E, Maršál K (2014) Pre-eclampsia-An additional risk factor for cognitive impairment at school age after intrauterine growth restriction and very preterm birth. Early Hum Dev 90:99–101. https://doi.org/10.1016/j.earlhumdev.2013.12.002
129. Lahti-Pulkkinen M, Girchenko P, Tuovinen S, et al (2020) Maternal Hypertensive Pregnancy Disorders and Mental Disorders in Children. Hypertension 75:1429–1438. https://doi.org/10.1161/HYPERTENSIONAHA.119.14140
130. Rätsep MT, Paolozza A, Hickman AF, et al (2016) Brain structural and vascular anatomy is altered in offspring of pre-eclamptic pregnancies: A pilot study. Am J Neuroradiol 37:939–945. https://doi.org/10.3174/ajnr.A4640
131. Kim JE, Lyoo IK, Estes AM, et al (2010) Laterobasal amygdalar enlargement in 6- to 7-year-old children with autism spectrum disorder. Arch Gen Psychiatry 67:1187–1197. https://doi.org/10.1001/archgenpsychiatry.2010.148
132. Nordahl CW, Scholz R, Yang X, et al (2012) Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: A longitudinal study. Arch Gen Psychiatry 69:53–61. https://doi.org/10.1001/archgenpsychiatry.2011.145
133. Lv RJ, Sun ZR, Cui T, et al (2014) Temporal lobe epilepsy with amygdala enlargement: A subtype of temporal lobe epilepsy. BMC Neurol 14:. https://doi.org/10.1186/s12883-014-0194-z
134. Schumann CM, Bloss CS, Barnes CC, et al (2010) Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. J Neurosci 30:4419–4427. https://doi.org/10.1523/JNEUROSCI.5714-09.2010

135. Bosco P, Giuliano A, Delafield-Butt J, et al (2019) Brainstem enlargement in preschool children with autism: Results from an intermethod agreement study of segmentation algorithms. Hum Brain Mapp 40:7–19. https://doi.org/10.1002/hbm.24351
136. Courchesne E, Karns CM, Davis HR, et al (2001) Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. Neurology 57:245–254. https://doi.org/10.1212/WNL.57.2.245
137. Valera EM, Faraone S V., Murray KE, Seidman LJ (2007) Meta-Analysis of Structural Imaging Findings in Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry 61:1361–1369. https://doi.org/10.1016/j.biopsych.2006.06.011
138. Hoogman M, Bralten J, Hibar DP, et al (2017) Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. The Lancet Psychiatry 4:310–319. https://doi.org/10.1016/S2215-0366(17)30049-4
139. Dietsche B, Kircher T, Falkenberg I (2017) Structural brain changes in schizophrenia at different stages of the illness: A selective review of longitudinal magnetic resonance imaging studies. Aust. N. Z. J. Psychiatry 51:500–508
140. Alexander AL, Lee JE, Lazar M, Field AS (2007) Diffusion Tensor Imaging of the Brain. Neurotherapeutics 4:316–329. https://doi.org/10.1016/j.nurt.2007.05.011
141. Figueiró-Filho EA, Croy BA, Reynolds JN, et al (2017) Diffusion tensor imaging of white matter in children born from preeclamptic gestations. Am J Neuroradiol 38:801–806. https://doi.org/10.3174/ajnr.A5064
142. Grahn JA, Parkinson JA, Owen AM (2009) The role of the basal ganglia in learning and memory: Neuropsychological studies. Behav. Brain Res. 199:53–60
143. Di Martino A, Kelly C, Grzadzinski R, et al (2011) Aberrant striatal functional connectivity in children with autism. Biol Psychiatry 69:847–856. https://doi.org/10.1016/j.biopsych.2010.10.029
144. Langen M, Bos D, Noordermeer SDS, et al (2014) Changes in the development of striatum are involved in repetitive behavior in autism. Biol Psychiatry 76:405–411. https://doi.org/10.1016/j.biopsych.2013.08.013
145. Clements CC, Zoltowski AR, Yankowitz LD, et al (2018) Evaluation of the social motivation hypothesis of autism a systematic review and meta-analysis. In: JAMA Psychiatry. American Medical Association, pp 797–808
146. Klugah-Brown B, Luo C, Peng R, et al (2019) Altered structural and causal connectivity in frontal lobe epilepsy. BMC Neurol 19:70. https://doi.org/10.1186/s12883-019-1300-z
147. Worbe Y, Marrakchi-Kacem L, Lecomte S, et al (2014) Altered structural connectivity of cortico-striato-pallido-thalamic networks in Gilles de la Tourette syndrome. Brain 138:472–482. https://doi.org/10.1093/brain/awu311
148. Kamali A, Flanders AE, Brody J, et al (2014) Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. Brain Struct Funct 219:269–281. https://doi.org/10.1007/s00429-012-0498-y
149. Lombardo M V., Pierce K, Eyler LT, et al (2015) Different functional neural substrates for good and poor language outcome in autism. Neuron 86:567–577. https://doi.org/10.1016/j.neuron.2015.03.023
150. Williams DL, Cherkassky VL, Mason RA, et al (2013) Brain function differences in language processing in children and adults with autism. Autism Res 6:288–302. https://doi.org/10.1002/aur.1291
151. Jones TB, Bandettini PA, Kenworthy L, et al (2010) Sources of group differences in functional connectivity: An investigation applied to autism spectrum disorder.

Neuroimage 49:401–414. https://doi.org/10.1016/j.neuroimage.2009.07.051
152. Fitzgerald J, Leemans A, Kehoe E, et al (2018) Abnormal fronto-parietal white matter organisation in the superior longitudinal fasciculus branches in autism spectrum disorders. Eur J Neurosci 47:652–661. https://doi.org/10.1111/ejn.13655
153. Jou RJ, Jackowski AP, Papademetris X, et al (2011) Diffusion tensor imaging in autism spectrum disorders: Preliminary evidence of abnormal neural connectivity. Aust N Z J Psychiatry 45:153–162. https://doi.org/10.3109/00048674.2010.534069
154. Nagae LM, Zarnow DM, Blaskey L, et al (2012) Elevated mean diffusivity in the left hemisphere superior longitudinal fasciculus in autism spectrum disorders increases with more profound language impairment. Am J Neuroradiol 33:1720–1725. https://doi.org/10.3174/ajnr.A3037
155. Little B, Gallagher P, Zimmerer V, et al (2019) Language in schizophrenia and aphasia: the relationship with non-verbal cognition and thought disorder. Cogn Neuropsychiatry 24:389–405. https://doi.org/10.1080/13546805.2019.1668758
156. Carletti F, Woolley JB, Bhattacharyya S, et al (2012) Alterations in White Matter Evident Before the Onset of Psychosis. Schizophr Bull 38:1170–1179. https://doi.org/10.1093/schbul/sbs053
157. Chawla N, Deep R, Khandelwal SK, Garg A (2019) Reduced integrity of superior longitudinal fasciculus and arcuate fasciculus as a marker for auditory hallucinations in schizophrenia: A DTI tractography study. Asian J Psychiatr 44:179–186. https://doi.org/10.1016/j.ajp.2019.07.043
158. Bubb EJ, Metzler-Baddeley C, Aggleton JP (2018) The cingulum bundle: Anatomy, function, and dysfunction. Neurosci. Biobehav. Rev. 92:104–127
159. Travers BG, Adluru N, Ennis C, et al (2012) Diffusion Tensor Imaging in Autism Spectrum Disorder: A Review. Autism Res 5:289–313. https://doi.org/10.1002/aur.1243
160. Urbain CM, Pang EW, Taylor MJ (2015) Atypical spatiotemporal signatures of working memory brain processes in autism. Transl Psychiatry 5:e617. https://doi.org/10.1038/tp.2015.107
161. Kring AM, Elis O (2013) Emotion Deficits in People with Schizophrenia. Annu Rev Clin Psychol 9:409–433. https://doi.org/10.1146/annurev-clinpsy-050212-185538
162. Shaw P, Stringaris A, Nigg J, Leibenluft E (2014) Emotion dysregulation in attention deficit hyperactivity disorder. Am. J. Psychiatry 171:276–293
163. Wang Q, Cheung C, Deng W, et al (2013) White-matter microstructure in previously drug-naive patients with schizophrenia after 6 weeks of treatment. Psychol Med 43:2301–2309. https://doi.org/10.1017/S0033291713000238
164. Ellison-Wright I, Bullmore E (2009) Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res 108:3–10. https://doi.org/10.1016/j.schres.2008.11.021
165. Chiang HL, Chen YJ, Shang CY, et al (2016) Different neural substrates for executive functions in youths with ADHD: A diffusion spectrum imaging tractography study. Psychol Med 46:1225–1238. https://doi.org/10.1017/S0033291715002767
166. Aoki Y, Cortese S, Castellanos FX (2018) Research Review: Diffusion tensor imaging studies of attention-deficit/hyperactivity disorder: meta-analyses and reflections on head motion. J. Child Psychol. Psychiatry Allied Discip. 59:193–202
167. Smitha KA, Akhil Raja K, Arun KM, et al (2017) Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. Neuroradiol. J. 30:305–317
168. Mak LE, Croy BA, Kay V, et al (2018) Resting-state functional connectivity in children born from gestations complicated by preeclampsia: A pilot study cohort.

Pregnancy Hypertens 12:23–28. https://doi.org/10.1016/j.preghy.2018.02.004
169. Janak PH, Tye KM (2015) From circuits to behaviour in the amygdala. Nature 517:284–292
170. Tsujimoto S, Genovesio A, Wise SP (2011) Frontal pole cortex: Encoding ends at the end of the endbrain. Trends Cogn. Sci. 15:169–176
171. Veer IM, Oei NYL, Spinhoven P, et al (2011) Beyond acute social stress: Increased functional connectivity between amygdala and cortical midline structures. Neuroimage 57:1534–1541. https://doi.org/10.1016/j.neuroimage.2011.05.074
172. Roy AK, Fudge JL, Kelly C, et al (2013) Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. J Am Acad Child Adolesc Psychiatry 52:290-299.e2. https://doi.org/10.1016/j.jaac.2012.12.010
173. Hulvershorn LA, Mennes M, Castellanos FX, et al (2014) Abnormal amygdala functional connectivity associated with emotional lability in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 53:. https://doi.org/10.1016/j.jaac.2013.11.012
174. Raichle ME, MacLeod AM, Snyder AZ, et al (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98:676–682. https://doi.org/10.1073/pnas.98.2.676
175. Li S, Hu N, Zhang W, et al (2019) Dysconnectivity of multiple brain networks in schizophrenia: A meta-analysis of resting-state functional connectivity. Front. Psychiatry 10:482
176. Castellanos FX, Margulies DS, Kelly C, et al (2008) Cingulate-Precuneus Interactions: A New Locus of Dysfunction in Adult Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry 63:332–337. https://doi.org/10.1016/j.biopsych.2007.06.025
177. Gabrielsen TP, Anderson JS, Stephenson KG, et al (2018) Functional MRI connectivity of children with autism and low verbal and cognitive performance. Mol Autism 9:. https://doi.org/10.1186/s13229-018-0248-y
178. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, et al (2009) Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci U S A 106:1279–1284. https://doi.org/10.1073/pnas.0809141106
179. Murdaugh DL, Shinkareva S V., Deshpande HR, et al (2012) Differential Deactivation during Mentalizing and Classification of Autism Based on Default Mode Network Connectivity. PLoS One 7:e50064. https://doi.org/10.1371/journal.pone.0050064
180. Spencer MD, Chura LR, Holt RJ, et al (2012) Failure to deactivate the default mode network indicates a possible endophenotype of autism. Mol Autism 3:15. https://doi.org/10.1186/2040-2392-3-15
181. Weiner KS, Zilles K (2016) The anatomical and functional specialization of the fusiform gyrus. Neuropsychologia 83:48–62. https://doi.org/10.1016/j.neuropsychologia.2015.06.033
182. Tang J, Falkmer M, Horlin C, et al (2015) Face recognition and visual search strategies in autism spectrum disorders: Amending and extending a recent review by Weigelt et al. PLoS One 10:. https://doi.org/10.1371/journal.pone.0134439
183. Bortolon C, Capdevielle D, Raffard S (2015) Face recognition in schizophrenia disorder: A comprehensive review of behavioral, neuroimaging and neurophysiological studies. Neurosci. Biobehav. Rev. 53:79–107
184. Onitsuka T, Shenton ME, Kasai K, et al (2003) Fusiform gyrus volume reduction and facial recognition in chronic schizophrenia. Arch Gen Psychiatry 60:349–355. https://doi.org/10.1001/archpsyc.60.4.349
185. Humphreys K, Hasson U, Avidan G, et al (2008) Cortical patterns of category-Selective activation for faces, places and objects in adults with autism. Autism Res

1:52–63. https://doi.org/10.1002/aur.1
186. Kleinhans NM, Richards T, Sterling L, et al (2008) Abnormal functional connectivity in autism spectrum disorders during face processing. Brain 131:1000–1012. https://doi.org/10.1093/brain/awm334
187. Frith CD (2007) The social brain? Philos Trans R Soc B Biol Sci 362:671–678. https://doi.org/10.1098/rstb.2006.2003
188. Eack SM, Wojtalik JA, Keshavan MS, Minshew NJ (2017) Social-cognitive brain function and connectivity during visual perspective-taking in autism and schizophrenia. Schizophr Res 183:102–109. https://doi.org/10.1016/j.schres.2017.03.009
189. Kim SY, Choi US, Park SY, et al (2015) Abnormal activation of the social brain network in children with autism spectrum disorder: An fMRI study. Psychiatry Investig 12:37–45. https://doi.org/10.4306/pi.2015.12.1.37
190. Burns JK (2006) Psychosis: A costly by-product of social brain evolution in Homo sapiens. Prog. Neuro-Psychopharmacology Biol. Psychiatry 30:797–814
191. Redman CWG, Sacks GP, Sargent IL (1999) Preeclampsia: An excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol 180:499–506. https://doi.org/10.1016/S0002-9378(99)70239-5
192. Mihu D, Razvan C, Malutan A, Mihaela C (2015) Evaluation of maternal systemic inflammatory response in preeclampsia. Taiwan J Obstet Gynecol 54:160–166. https://doi.org/10.1016/j.tjog.2014.03.006
193. Cornelius DC (2018) Preeclampsia: From Inflammation to Immunoregulation. Clin Med Insights Blood Disord 11:1179545X1775232. https://doi.org/10.1177/1179545X17752325
194. Cackovic M, Buhimschi CS, Zhao G, et al (2008) Fractional excretion of tumor necrosis factor-alpha in women with severe preeclampsia. Obstet Gynecol 112:93–100. https://doi.org/10.1097/AOG.0b013e31817c4304
195. Guven MA, Coskun A, Ertas IE, et al (2009) Association of maternal serum CRP, IL-6, TNF-alpha, homocysteine, folic acid and vitamin B12 levels with the severity of preeclampsia and fetal birth weight. Hypertens pregnancy 28:190–200. https://doi.org/10.1080/10641950802601179
196. Gu Y, Lewis DF, Deere K, et al (2008) Elevated Maternal IL-16 Levels, Enhanced IL-16 Expressions in Endothelium and Leukocytes, and Increased IL-16 Production by Placental Trophoblasts in Women with Preeclampsia. J Immunol 181:4418–4422. https://doi.org/10.4049/jimmunol.181.6.4418
197. Sharma A, Satyam A, Sharma JB (2007) Leptin, IL-10 and inflammatory markers (TNF-α, IL-6 and IL-8) in pre-eclamptic, normotensive pregnant and healthy non-pregnant women. Am J Reprod Immunol 58:21–30. https://doi.org/10.1111/j.1600-0897.2007.00486.x
198. Udenze I, Amadi C, Awolola N, Makwe CC (2015) The role of cytokines as inflammatory mediators in preeclampsia. Pan Afr Med J 20:219. https://doi.org/10.11604/pamj.2015.20.219.5317
199. Ribeiro VR, Romao-Veiga M, Romagnoli GG, et al (2017) Association between cytokine profile and transcription factors produced by T-cell subsets in early- and late-onset pre-eclampsia. Immunology 152:163–173. https://doi.org/10.1111/imm.12757
200. Williamson RD, McCarthy FP, Kenny LC, McCarthy CM (2019) Activation of a TLR9 mediated innate immune response in preeclampsia. Sci Rep 9:. https://doi.org/10.1038/s41598-019-42551-w
201. Rahimzadeh M, Norouzian M, Arabpour F, Naderi N (2016) Regulatory T-cells and preeclampsia: An overview of literature. Expert Rev. Clin. Immunol. 12:209–227

202. Toldi G, Rigó J, Stenczer B, et al (2011) Increased Prevalence of IL-17-Producing Peripheral Blood Lymphocytes in Pre-eclampsia. Am J Reprod Immunol 66:223–229. https://doi.org/10.1111/j.1600-0897.2011.00987.x
203. Seki H, Matuoka K, Inooku H, Takeda S (2007) TNF-alpha from monocyte of patients with pre-eclampsia-induced apoptosis in human trophoblast cell line. J Obstet Gynaecol Res 33:408–16. https://doi.org/10.1111/j.1447-0756.2007.00551.x
204. LaMarca B, Speed J, Fournier L, et al (2008) Hypertension in response to chronic reductions in uterine perfusion in pregnant rats effect of tumor necrosis factor-α blockade. Hypertension 52:1161–1167. https://doi.org/10.1161/HYPERTENSIONAHA.108.120881
205. Gadonski G, LaMarca BBD, Sullivan E, et al (2006) Hypertension produced by reductions in uterine perfusion in the pregnant rat: Role of interleukin 6. Hypertension 48:711–716. https://doi.org/10.1161/01.HYP.0000238442.33463.94
206. Cornelius DC, Amaral LM, Wallace K, et al (2016) Reduced uterine perfusion pressure T-helper 17 cells cause pathophysiology associated with preeclampsia during pregnancy. Am J Physiol Integr Comp Physiol 311:R1192–R1199. https://doi.org/10.1152/ajpregu.00117.2016
207. Cornelius DC, Amaral LM, Harmon A, et al (2015) An increased population of regulatory T cells improves the pathophysiology of placental ischemia in a rat model of preeclampsia. Am J Physiol Integr Comp Physiol 309:R884–R891. https://doi.org/10.1152/ajpregu.00154.2015
208. Cottrell JN, Amaral LM, Harmon A, et al (2019) Interleukin-4 supplementation improves the pathophysiology of hypertension in response to placental ischemia in RUPP rats. Am J Physiol Integr Comp Physiol 316:R165–R171. https://doi.org/10.1152/ajpregu.00167.2018
209. Harmon A, Cornelius D, Amaral L, et al (2015) IL-10 supplementation increases Tregs and decreases hypertension in the RUPP rat model of preeclampsia. Hypertens Pregnancy 34:291–306. https://doi.org/10.3109/10641955.2015.1032054
210. Ibrahim T, Przybyl L, Harmon AC, et al (2017) Proliferation of endogenous regulatory T cells improve the pathophysiology associated with placental ischaemia of pregnancy. Am J Reprod Immunol 78:e12724. https://doi.org/10.1111/aji.12724
211. Urakubo A, Jarskog LF, Lieberman JA, Gilmore JH (2001) Prenatal exposure to maternal infection alters cytokine expression in the placenta, amniotic fluid, and fetal brain. Schizophr Res 47:27–36. https://doi.org/10.1016/S0920-9964(00)00032-3
212. Fidel PL, Romero R, Wolf N, et al (1994) Systemic and local cytokine profiles in endotoxin-induced preterm parturition in mice. Am J Obstet Gynecol 170:1467–1475. https://doi.org/10.1016/S0002-9378(94)70180-6
213. Hao XQ, Zhang HG, Yuan ZB, et al (2010) Prenatal exposure to lipopolysaccharide alters the intrarenal renin-angiotensin system and renal damage in offspring rats. Hypertens Res 33:76–82. https://doi.org/10.1038/hr.2009.185
214. Wei Y, Du W, Xiong X, et al (2013) Prenatal exposure to lipopolysaccharide results in myocardial remodelling in adult murine offspring. J Inflamm (United Kingdom) 10:35. https://doi.org/10.1186/1476-9255-10-35
215. Wei YL, Li XH, Zhou JZ (2007) Prenatal exposure to lipopolysaccharide results in increases in blood pressure and body weight in rats. Acta Pharmacol Sin 28:651–656. https://doi.org/10.1111/j.1745-7254.2007.00593.x
216. Amash A, Holcberg G, Sapir O, Huleihel M (2012) Placental Secretion of Interleukin-1 and Interleukin-1 Receptor Antagonist in Preeclampsia: Effect of Magnesium Sulfate. J Interf Cytokine Res 32:432–441. https://doi.org/10.1089/jir.2012.0013
217. Lockwood CJ, Yen CF, Basar M, et al (2008) Preeclampsia-related inflammatory

cytokines regulate interleukin-6 expression in human decidual cells. Am J Pathol 172:1571–1579. https://doi.org/10.2353/ajpath.2008.070629
218. Sasaki Y, Darmochwal-Kolarz D, Suzuki D, et al (2007) Proportion of peripheral blood and decidual CD4+ CD25bright regulatory T cells in pre-eclampsia. Clin Exp Immunol 149:139–145. https://doi.org/10.1111/j.1365-2249.2007.03397.x
219. Aggarwal R, Jain AK, Mittal P, et al (2019) Association of pro- and anti-inflammatory cytokines in preeclampsia. J Clin Lab Anal 33:e22834. https://doi.org/10.1002/jcla.22834
220. Makris A, Xu B, Yu B, et al (2006) Placental deficiency of interleukin-10 (IL-10) in preeclampsia and its relationship to an IL10 promoter polymorphism. Placenta 27:445–451. https://doi.org/10.1016/j.placenta.2005.05.003
221. Hung TH, Charnock-Jones DS, Skepper JN, Burton GJ (2004) Secretion of Tumor Necrosis Factor-α from Human Placental Tissues Induced by Hypoxia-Reoxygenation Causes Endothelial Cell Activation in Vitro: A Potential Mediator of the Inflammatory Response in Preeclampsia. Am J Pathol 164:1049–1061. https://doi.org/10.1016/S0002-9440(10)63192-6
222. Jones AJ, Gokhale PJ, Allison TF, et al (2015) Evidence for bystander signalling between human trophoblast cells and human embryonic stem cells. Sci Rep 5:. https://doi.org/10.1038/srep11694
223. Wang X, Athayde N, Trudinger B (2003) A proinflammatory cytokine response is present in the fetal placental vasculature in placental insufficiency. Am J Obstet Gynecol 189:1445–1451. https://doi.org/10.1067/S0002-9378(03)00652-5
224. Dahlgren J, Samuelsson AM, Jansson T, Holmäng A (2006) Interleukin-6 in the maternal circulation reaches the rat fetus in mid-gestation. Pediatr Res 60:147–151. https://doi.org/10.1203/01.pdr.0000230026.74139.18
225. Zaretsky M V., Alexander JM, Byrd W, Bawdon RE (2004) Transfer of inflammatory cytokines across the placenta. Obstet Gynecol 103:546–550. https://doi.org/10.1097/01.AOG.0000114980.40445.83
226. Tosun M, Celik H, Avci B, et al (2010) Maternal and umbilical serum levels of interleukin-6, interleukin-8, and tumor necrosis factor-alpha in normal pregnancies and in pregnancies complicated by preeclampsia. J Matern Fetal Neonatal Med 23:880–6. https://doi.org/10.3109/14767051003774942
227. Guillemette L, Lacroix M, Allard C, et al (2015) Preeclampsia is associated with an increased pro-inflammatory profile in newborns. J Reprod Immunol 112:111–114. https://doi.org/10.1016/j.jri.2015.09.003
228. Giambrone AB, Logue OC, Shao Q, et al (2019) Perinatal Micro-Bleeds and Neuroinflammation in E19 Rat Fetuses Exposed to Utero-Placental Ischemia. Int J Mol Sci 20:4051. https://doi.org/10.3390/ijms20164051
229. Brown AS, Begg MD, Gravenstein S, et al (2004) Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 61:774–780. https://doi.org/10.1001/archpsyc.61.8.774
230. Jiang H yin, Xu L lian, Shao L, et al (2016) Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis. Brain Behav Immun 58:165–172. https://doi.org/10.1016/j.bbi.2016.06.005
231. Brown AS, Sourander A, Hinkka-Yli-Salomäki S, et al (2014) Elevated maternal C-reactive protein and autism in a national birth cohort. Mol Psychiatry 19:259–264. https://doi.org/10.1038/mp.2012.197
232. Ghassabian A, Albert PS, Hornig M, et al (2018) Gestational cytokine concentrations and neurocognitive development at 7 years. Transl Psychiatry 8:. https://doi.org/10.1038/s41398-018-0112-z

233. Rasmussen JM, Graham AM, Entringer S, et al (2019) Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. Neuroimage 185:825–835. https://doi.org/10.1016/j.neuroimage.2018.04.020
234. Spann MN, Monk C, Scheinost D, Peterson BS (2018) Maternal immune activation during the third trimester is associated with neonatal functional connectivity of the salience network and fetal to toddler behavior. J Neurosci 38:2877–2886. https://doi.org/10.1523/JNEUROSCI.2272-17.2018
235. Shi L, Fatemi SH, Sidwell RW, Patterson PH (2003) Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J Neurosci 23:297–302. https://doi.org/10.1523/jneurosci.23-01-00297.2003
236. Shi L, Tu N, Patterson PH (2005) Maternal influenza infection is likely to alter fetal brain development indirectly: The virus is not detected in the fetus. Int J Dev Neurosci 23:299–305. https://doi.org/10.1016/j.ijdevneu.2004.05.005
237. Zuckerman L, Rehavi M, Nachman R, Weiner I (2003) Immune activation during pregnancy in rats leads to a postpubertal emergence of disrupted latent inhibition, dopaminergic hyperfunction, and altered limbic morphology in the offspring: A novel neurodevelopmental model of schizophrenia. Neuropsychopharmacology 28:1778–1789. https://doi.org/10.1038/sj.npp.1300248
238. Zuckerman L, Weiner I (2005) Maternal immune activation leads to behavioral and pharmacological changes in the adult offspring. J Psychiatr Res 39:311–323. https://doi.org/10.1016/j.jpsychires.2004.08.008
239. Ozawa K, Hashimoto K, Kishimoto T, et al (2006) Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: A neurodevelopmental animal model of schizophrenia. Biol Psychiatry 59:546–554. https://doi.org/10.1016/j.biopsych.2005.07.031
240. Winter C, Djodari-Irani A, Sohr R, et al (2009) Prenatal immune activation leads to multiple changes in basal neurotransmitter levels in the adult brain: Implications for brain disorders of neurodevelopmental origin such as schizophrenia. Int J Neuropsychopharmacol 12:513–524. https://doi.org/10.1017/S1461145708009206
241. Straley ME, Van Oeffelen W, Theze S, et al (2017) Distinct alterations in motor & reward seeking behavior are dependent on the gestational age of exposure to LPS-induced maternal immune activation. Brain Behav Immun 63:21–34. https://doi.org/10.1016/j.bbi.2016.06.002
242. Mattei D, Ivanov A, Ferrai C, et al (2017) Maternal immune activation results in complex microglial transcriptome signature in the adult offspring that is reversed by minocycline treatment. Transl Psychiatry 7:e1120–e1120. https://doi.org/10.1038/tp.2017.80
243. Vogel Ciernia A, Careaga M, LaSalle JM, Ashwood P (2018) Microglia from offspring of dams with allergic asthma exhibit epigenomic alterations in genes dysregulated in autism. Glia 66:505–521. https://doi.org/10.1002/glia.23261
244. Schaafsma W, Basterra LB, Jacobs S, et al (2017) Maternal inflammation induces immune activation of fetal microglia and leads to disrupted microglia immune responses, behavior, and learning performance in adulthood. Neurobiol Dis 106:291–300. https://doi.org/10.1016/j.nbd.2017.07.017
245. Paolicelli RC, Bolasco G, Pagani F, et al (2011) Synaptic pruning by microglia is necessary for normal brain development. Science (80-) 333:1456–1458. https://doi.org/10.1126/science.1202529
246. Cunningham CL, Martínez-Cerdeño V, Noctor SC (2013) Microglia regulate the number of neural precursor cells in the developing cerebral cortex. J Neurosci

33:4216–4233. https://doi.org/10.1523/JNEUROSCI.3441-12.2013
247. Koyama R, Ikegaya Y (2015) Microglia in the pathogenesis of autism spectrum disorders. Neurosci. Res. 100:1–5
248. Straley ME, Togher KL, Nolan AM, et al (2014) LPS alters placental inflammatory and endocrine mediators and inhibits fetal neurite growth in affected offspring during late gestation. Placenta 35:533–538. https://doi.org/10.1016/j.placenta.2014.06.001
249. Gayle DA, Beloosesky R, Desai M, et al (2004) Maternal LPS induces cytokines in the amniotic fluid and corticotropin releasing hormone in the fetal rat brain. Am J Physiol - Regul Integr Comp Physiol 286:. https://doi.org/10.1152/ajpregu.00664.2003
250. Banks W (2005) Blood-Brain Barrier Transport of Cytokines: A Mechanism for Neuropathology. Curr Pharm Des 11:973–984. https://doi.org/10.2174/1381612053381684
251. Cai Z, Pan ZL, Pang Y, et al (2000) Cytokine induction in fetal rat brains and brain injury in neonatal rats after maternal lipopolysaccharide administration. Pediatr Res 47:64–72. https://doi.org/10.1203/00006450-200001000-00013
252. Meyer U, Nyffeler M, Engler A, et al (2006) The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology. J Neurosci 26:4752–4762. https://doi.org/10.1523/JNEUROSCI.0099-06.2006
253. Matta SM, Hill-Yardin EL, Crack PJ (2019) The influence of neuroinflammation in Autism Spectrum Disorder. Brain. Behav. Immun. 79:75–90
254. Müller N (2018) Inflammation in Schizophrenia: Pathogenetic Aspects and Therapeutic Considerations. Schizophr Bull 44:973–982. https://doi.org/10.1093/schbul/sby024
255. Nolan AM, Nolan YM, O'Keeffe GW (2011) IL-1β inhibits axonal growth of developing sympathetic neurons. Mol Cell Neurosci 48:142–150. https://doi.org/10.1016/j.mcn.2011.07.003
256. Crampton SJ, Collins LM, Toulouse A, et al (2012) Exposure of foetal neural progenitor cells to IL-1β impairs their proliferation and alters their differentiation - A role for maternal inflammation? J Neurochem 120:964–973. https://doi.org/10.1111/j.1471-4159.2011.07634.x
257. Kaushik DK, Thounaojam MC, Kumawat KL, et al (2013) Interleukin-1β orchestrates underlying inflammatory responses in microglia via Krüppel-like factor 4. J Neurochem 127:233–244. https://doi.org/10.1111/jnc.12382
258. Anthony DC, Bolton SJ, Fearn S, Perry VH (1997) Age-related effects of interleukin-1 beta on polymorphonuclear neutrophil-dependent increases in blood-brain barrier permeability in rats. Brain 120 (Pt 3:435–444. https://doi.org/10.1093/brain/120.3.435
259. Smith SEP, Li J, Garbett K, et al (2007) Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 27:10695–10702. https://doi.org/10.1523/JNEUROSCI.2178-07.2007
260. Wu WL, Hsiao EY, Yan Z, et al (2017) The placental interleukin-6 signaling controls fetal brain development and behavior. Brain Behav Immun 62:11–23. https://doi.org/10.1016/j.bbi.2016.11.007
261. Gumusoglu SB, Fine RS, Murray SJ, et al (2017) The role of IL-6 in neurodevelopment after prenatal stress. Brain Behav Immun 65:274–283. https://doi.org/c
262. West PK, Viengkhou B, Campbell IL, Hofer MJ (2019) Microglia responses to interleukin-6 and type I interferons in neuroinflammatory disease. Glia 67:1821–1841
263. Jarskog LF, Xiao H, Wilkie MB, et al (1997) Cytokine regulation of embryonic rat dopamine and serotonin neuronal survival in vitro. Int J Dev Neurosci 15:711–716. https://doi.org/10.1016/S0736-5748(97)00029-4

264. Wei H, Chadman KK, McCloskey DP, et al (2012) Brain IL-6 elevation causes neuronal circuitry imbalances and mediates autism-like behaviors. Biochim Biophys Acta - Mol Basis Dis 1822:831–842. https://doi.org/10.1016/j.bbadis.2012.01.011
265. Al-Gubory KH, Fowler PA, Garrel C (2010) The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. Int. J. Biochem. Cell Biol. 42:1634–1650
266. Myatt L, Cui X (2004) Oxidative stress in the placenta. Histochem. Cell Biol. 122:369–382
267. Aouache R, Biquard L, Vaiman D, Miralles F (2018) Oxidative Stress in Preeclampsia and Placental Diseases. Int J Mol Sci 19:1496. https://doi.org/10.3390/ijms19051496
268. Ahmad IM, Zimmerman MC, Moore TA (2019) Oxidative stress in early pregnancy and the risk of preeclampsia. Pregnancy Hypertens 18:99–102. https://doi.org/10.1016/j.preghy.2019.09.014
269. Dordević NZ, Babić GM, Marković SD, et al (2008) Oxidative stress and changes in antioxidative defense system in erythrocytes of preeclampsia in women. Reprod Toxicol 25:213–218. https://doi.org/10.1016/j.reprotox.2007.11.001
270. Erdem M, Harma M, Harma IM, et al (2012) Comparative study of oxidative stress in maternal blood with that of cord blood and maternal milk. Arch Gynecol Obstet 285:371–375. https://doi.org/10.1007/s00404-011-1993-8
271. Dsouza V, Rani A, Patil V, et al (2016) Increased oxidative stress from early pregnancy in women who develop preeclampsia. Clin Exp Hypertens 38:225–232. https://doi.org/10.3109/10641963.2015.1081226
272. Ferguson KK, Meeker JD, McElrath TF, et al (2017) Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. In: American Journal of Obstetrics and Gynecology. Mosby Inc., pp 527.e1-527.e9
273. Genc H, Uzun H, Benian A, et al (2011) Evaluation of oxidative stress markers in first trimester for assessment of preeclampsia risk. Arch Gynecol Obstet 284:1367–1373. https://doi.org/10.1007/s00404-011-1865-2
274. Hilali N, Kocyigit A, Demir M, et al (2013) DNA damage and oxidative stress in patients with mild preeclampsia and offspring. Eur J Obstet Gynecol Reprod Biol 170:377–380. https://doi.org/10.1016/j.ejogrb.2013.07.031
275. Sharma JB, Sharma A, Bahadur A, et al (2006) Oxidative stress markers and antioxidant levels in normal pregnancy and pre-eclampsia. Int J Gynecol Obstet 94:23–27. https://doi.org/10.1016/j.ijgo.2006.03.025
276. Mehendale S, Kilari A, Dangat K, et al (2008) Fatty acids, antioxidants, and oxidative stress in pre-eclampsia. Int J Gynecol Obstet 100:234–238. https://doi.org/10.1016/j.ijgo.2007.08.011
277. Roy S, Dhobale M, Dangat K, et al (2015) Differential oxidative stress levels in mothers with preeclampsia delivering male and female babies. J Matern Neonatal Med 28:1973–1980. https://doi.org/10.3109/14767058.2014.974537
278. Sikkema JM, Van Rijn BB, Franx A, et al (2001) Placental superoxide is increased in pre-eclampsia. Placenta 22:304–308. https://doi.org/10.1053/plac.2001.0629
279. Wang Y, Walsh SW (2001) Increased superoxide generation is associated with decreased superoxide dismutase activity and mRNA expression in placental trophoblast cells in pre-eclampsia. Placenta 22:206–212. https://doi.org/10.1053/plac.2000.0608
280. Walsh SW (2000) Placental isoprostane is significantly increased in preeclampsia. FASEB J 14:1289–1296. https://doi.org/10.1096/fj.14.10.1289
281. Tadesse S, Kidane D, Guller S, et al (2014) In vivo and in vitro evidence for placental

DNA damage in preeclampsia. PLoS One 9:e86791. https://doi.org/10.1371/journal.pone.0086791
282. Can M, Guven B, Bektas S, Arikan I (2014) Oxidative stress and apoptosis in preeclampsia. Tissue Cell 46:477–481. https://doi.org/10.1016/j.tice.2014.08.004
283. Madazli R, Benian A, Aydin S, et al (2002) The plasma and placental levels of malondialdehyde, glutathione and superoxide dismutase in pre-eclampsia. J Obstet Gynaecol (Lahore) 22:477–480. https://doi.org/10.1080/0144361021000003573
284. Roland-Zejly L, Moisan V, St-Pierre I, Bilodeau JF (2011) Altered placental glutathione peroxidase mRNA expression in preeclampsia according to the presence or absence of labor. Placenta 32:161–167. https://doi.org/10.1016/j.placenta.2010.11.005
285. Vanderlelie J, Venardos K, Clifton VL, et al (2005) Increased biological oxidation and reduced anti-oxidant enzyme activity in pre-eclamptic placentae. Placenta 26:53–58. https://doi.org/10.1016/j.placenta.2004.04.002
286. Sedeek M, Gilbert JS, Lamarca BB, et al (2008) Role of reactive oxygen species in hypertension produced by reduced uterine perfusion in pregnant rats. Am J Hypertens 21:1152–1156. https://doi.org/10.1038/ajh.2008.239
287. Pitkänen S, Robinson BH (1996) Mitochondrial complex I deficiency leads to increased production of superoxide radicals and induction of superoxide dismutase. J Clin Invest 98:345–351. https://doi.org/10.1172/JCI118798
288. Zhou X, Han TL, Chen H, et al (2017) Impaired mitochondrial fusion, autophagy, biogenesis and dysregulated lipid metabolism is associated with preeclampsia. Exp Cell Res 359:. https://doi.org/10.1016/j.yexcr.2017.07.029
289. Shi Z, Long W, Zhao C, et al (2013) Comparative Proteomics Analysis Suggests that Placental Mitochondria are Involved in the Development of Pre-Eclampsia. PLoS One 8:e64351. https://doi.org/10.1371/journal.pone.0064351
290. Zsengellér ZK, Rajakumar A, Hunter JT, et al (2016) Trophoblast mitochondrial function is impaired in preeclampsia and correlates negatively with the expression of soluble fms-like tyrosine kinase 1. Pregnancy Hypertens 6:313–319. https://doi.org/10.1016/j.preghy.2016.06.004
291. Shibata E, Nanri H, Ejima K, et al (2003) Enhancement of mitochondrial oxidative stress and up-regulation of antioxidant protein peroxiredoxin III/SP-22 in the mitochondria of human pre-eclamptic placentae. Placenta 24:698–705. https://doi.org/10.1016/S0143-4004(03)00083-3
292. Wang Y, Walsh SW (1998) Placental mitochondria as a source of oxidative stress in pre-eclampsia. Placenta 19:581–586. https://doi.org/10.1016/S0143-4004(98)90018-2
293. Zorov DB, Juhaszova M, Sollott SJ (2006) Mitochondrial ROS-induced ROS release: An update and review. Biochim. Biophys. Acta - Bioenerg. 1757:509–517
294. Roberts JM, Myatt L, Spong CY, et al (2010) Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med 362:1282–1291. https://doi.org/10.1056/NEJMoa0908056
295. Vaka VR, McMaster KM, Cunningham MW, et al (2018) Role of Mitochondrial Dysfunction and Reactive Oxygen Species in Mediating Hypertension in the Reduced Uterine Perfusion Pressure Rat Model of Preeclampsia. Hypertens (Dallas, Tex 1979) 72:703–711. https://doi.org/10.1161/HYPERTENSIONAHA.118.11290
296. Williamson RD, McCarthy FP, Manna S, et al (2020) L-(+)-Ergothioneine Significantly Improves the Clinical Characteristics of Preeclampsia in the Reduced Uterine Perfusion Pressure Rat Model. Hypertens (Dallas, Tex 1979) 75:561–568. https://doi.org/10.1161/HYPERTENSIONAHA.119.13929
297. Dikalova AE, Bikineyeva AT, Budzyn K, et al (2010) Therapeutic targeting of mitochondrial superoxide in hypertension. Circ Res 107:106–116.

https://doi.org/10.1161/CIRCRESAHA.109.214601
298. Mistry HD, Wilson V, Ramsay MM, et al (2008) Reduced selenium concentrations and glutathione peroxidase activity in preeclamptic pregnancies. Hypertension 52:881–888. https://doi.org/10.1161/HYPERTENSIONAHA.108.116103
299. Xu M, Guo D, Gu H, et al (2016) Selenium and Preeclampsia: a Systematic Review and Meta-analysis. Biol. Trace Elem. Res. 171:283–292
300. Khera A, Dong LF, Holland O, et al (2015) Selenium supplementation induces mitochondrial biogenesis in trophoblasts. Placenta 36:863–869. https://doi.org/10.1016/j.placenta.2015.06.010
301. Khera A, Vanderlelie JJ, Perkins A V. (2013) Selenium supplementation protects trophoblast cells from mitochondrial oxidative stress. Placenta 34:594–598. https://doi.org/10.1016/j.placenta.2013.04.010
302. Illsinger S, Janzen N, Sander S, et al (2010) Preeclampsia and HELLP syndrome: Impaired mitochondrial function in umbilical endothelial cells. Reprod Sci 17:219–226. https://doi.org/10.1177/1933719109351597
303. Phillips TJ, Scott H, Menassa DA, et al (2017) Treating the placenta to prevent adverse effects of gestational hypoxia on fetal brain development. Sci Rep 7:. https://doi.org/10.1038/s41598-017-06300-1
304. Scott H, Phillips TJ, Stuart GC, et al (2018) Preeclamptic placentae release factors that damage neurons: implications for foetal programming of disease. Neuronal Signal 2:NS20180139. https://doi.org/10.1042/ns20180139
305. Yoneyama M, Kawada K, Gotoh Y, et al (2010) Endogenous reactive oxygen species are essential for proliferation of neural stem/progenitor cells. Neurochem Int 56:740–746. https://doi.org/10.1016/j.neuint.2009.11.018
306. Chandrasekaran V, Lea C, Sosa JC, et al (2015) Reactive oxygen species are involved in BMP-induced dendritic growth in cultured rat sympathetic neurons. Mol Cell Neurosci 67:116–125. https://doi.org/10.1016/j.mcn.2015.06.007
307. Le Belle JE, Orozco NM, Paucar AA, et al (2011) Proliferative neural stem cells have high endogenous ROS levels that regulate self-renewal and neurogenesis in a PI3K/Akt-dependant manner. Cell Stem Cell 8:59–71. https://doi.org/10.1016/j.stem.2010.11.028
308. Wilson C, Muñoz-Palma E, González-Billault C (2018) From birth to death: A role for reactive oxygen species in neuronal development. Semin. Cell Dev. Biol. 80:43–49
309. Simon HU, Haj-Yehia A, Levi-Schaffer F (2000) Role of reactive oxygen species (ROS) in apoptosis induction. Apoptosis 5:415–418. https://doi.org/10.1023/A:1009616228304
310. Miller-Pinsler L, Pinto DJ, Wells PG (2015) Oxidative DNA damage in the in utero initiation of postnatal neurodevelopmental deficits by normal fetal and ethanol-enhanced oxidative stress in oxoguanine glycosylase 1 knockout mice. Free Radic Biol Med 78:23–29. https://doi.org/10.1016/j.freeradbiomed.2014.09.026
311. Fernandez A, Meechan DW, Karpinski BA, et al (2019) Mitochondrial Dysfunction Leads to Cortical Under-Connectivity and Cognitive Impairment. Neuron 102:1127-1142.e3. https://doi.org/10.1016/j.neuron.2019.04.013
312. Lanté F, Meunier J, Guiramand J, et al (2007) Neurodevelopmental damage after prenatal infection: Role of oxidative stress in the fetal brain. Free Radic Biol Med 42:1231–1245. https://doi.org/10.1016/j.freeradbiomed.2007.01.027
313. Ghanizadeh A, Berk M, Farrashbandi H, et al (2013) Targeting the mitochondrial electron transport chain in autism, a systematic review and synthesis of a novel therapeutic approach. Mitochondrion 13:515–519. https://doi.org/10.1016/j.mito.2012.10.001

314. Joseph N, Zhang-James Y, Perl A, Faraone S V. (2015) Oxidative stress and ADHD: A meta-analysis. J Atten Disord 19:915–924. https://doi.org/10.1177/1087054713510354
315. Pearson-Smith JN, Patel M (2017) Metabolic dysfunction and oxidative stress in epilepsy. Int. J. Mol. Sci. 18:2365
316. Rajasekaran A, Venkatasubramanian G, Berk M, Debnath M (2015) Mitochondrial dysfunction in schizophrenia: Pathways, mechanisms and implications. Neurosci. Biobehav. Rev. 48:10–21
317. Rossignol DA, Frye RE (2014) Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. Front. Physiol. 5:150
318. Gu F, Chauhan V, Kaur K, et al (2013) Alterations in mitochondrial DNA copy number and the activities of electron transport chain complexes and pyruvate dehydrogenase in the frontal cortex from subjects with autism. Transl Psychiatry 3:e299. https://doi.org/10.1038/tp.2013.68
319. Gu F, Chauhan V, Chauhan A (2014) Oxidative stress and mitochondrial dysfunction in ASDs. In: Frontiers in Autism Research: New Horizons for Diagnosis and Treatment. World Scientific Publishing Co., pp 407–427
320. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R (2014) Pre-eclampsia part 1: Current understanding of its pathophysiology. Nat. Rev. Nephrol. 10:466–480
321. Vitoratos N, Economou E, Iavazzo C, et al (2010) Maternal serum levels of TNF-Alpha and IL-6 long after delivery in preeclamptic and normotensive pregnant women. Mediators Inflamm 2010:. https://doi.org/10.1155/2010/908649
322. Bernardi F, Guolo F, Bortolin T, et al (2008) Oxidative stress and inflammatory markers in normal pregnancy and preeclampsia. J Obstet Gynaecol Res 34:948–951. https://doi.org/10.1111/j.1447-0756.2008.00803.x
323. Kabe Y, Ando K, Hirao S, et al (2005) Redox regulation of NF-κB activation: Distinct redox regulation between the cytoplasm and the nucleus. Antioxidants Redox Signal. 7:395–403
324. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB (2010) Oxidative stress, inflammation, and cancer: How are they linked? Free Radic. Biol. Med. 49:1603–1616
325. Cindrova-Davies T, Spasic-Boskovic O, Jauniaux E, et al (2007) Nuclear factor-κB, p38, and stress-activated protein kinase mitogen-activated protein kinase signaling pathways regulate proinflammatory cytokines and apoptosis in human placental explants in response to oxidative stress: Effects of antioxidant vitamins. Am J Pathol 170:1511–1520. https://doi.org/10.2353/ajpath.2007.061035
326. Hassan I, Kumar AM, Park H-R, et al (2016) Reactive Oxygen Stimulation of Interleukin-6 Release in the Human Trophoblast Cell Line HTR-8/SVneo by the Trichlorethylene Metabolite S-(1,2-Dichloro)-L-Cysteine. Biol Reprod 95:66–66. https://doi.org/10.1095/biolreprod.116.139261
327. Kamiński MM, Sauer SW, Klemke C-D, et al (2010) Mitochondrial Reactive Oxygen Species Control T Cell Activation by Regulating IL-2 and IL-4 Expression: Mechanism of Ciprofloxacin-Mediated Immunosuppression. J Immunol 184:4827–4841. https://doi.org/10.4049/jimmunol.0901662
328. Karan KR, Trumpff C, McGill MA, et al (2020) Mitochondrial Respiratory Capacity Modulates LPS-induced Inflammatory Signatures in Human Blood. Brain, Behav Immun - Heal 5:100080. https://doi.org/10.1016/j.bbih.2020.100080
329. McCarthy CM, Kenny LC (2016) Immunostimulatory role of mitochondrial DAMPs: alarming for pre-eclampsia? Am. J. Reprod. Immunol. 76:341–347
330. Zhang Q, Raoof M, Chen Y, et al (2010) Circulating mitochondrial DAMPs cause

inflammatory responses to injury. Nature 464:104–107. https://doi.org/10.1038/nature08780
331. Panda B, Panda A, Ueda I, et al (2012) Dendritic cells in the circulation of women with preeclampsia demonstrate a pro-inflammatory bias secondary to dysregulation of TLR receptors. J Reprod Immunol 94:210–215. https://doi.org/10.1016/j.jri.2012.01.008
332. Pineda A, Verdin-Terán SL, Camacho A, Moreno-Fierros L (2011) Expression of Toll-like Receptor TLR-2, TLR-3, TLR-4 and TLR-9 Is Increased in Placentas from Patients with Preeclampsia. Arch Med Res 42:382–391. https://doi.org/10.1016/j.arcmed.2011.08.003
333. Marschalek J, Wohlrab P, Ott J, et al (2018) Maternal serum mitochondrial DNA (mtDNA) levels are elevated in preeclampsia – A matched case-control study. Pregnancy Hypertens 14:195–199. https://doi.org/10.1016/j.preghy.2018.10.003
334. McCarthy CM, Kenny LC (2016) Therapeutically targeting mitochondrial redox signalling alleviates endothelial dysfunction in preeclampsia. Sci Rep 6:32683. https://doi.org/10.1038/srep32683
335. Dhillion P, Wallace K, Herse F, et al (2012) IL-17-mediated oxidative stress is an important stimulator of AT1-AA and hypertension during pregnancy. Am J Physiol - Regul Integr Comp Physiol 303:. https://doi.org/10.1152/ajpregu.00051.2012
336. Cunningham MW, Jayaram A, Deer E, et al (2020) Tumor necrosis factor alpha (TNF-α) blockade improves natural killer cell (NK) activation, hypertension, and mitochondrial oxidative stress in a preclinical rat model of preeclampsia. Hypertens Pregnancy 1–6. https://doi.org/10.1080/10641955.2020.1793999
337. Vaka VR, McMaster KM, Cornelius DC, et al (2019) Natural killer cells contribute to mitochondrial dysfunction in response to placental ischemia in reduced uterine perfusion pressure rats. Am J Physiol Regul Integr Comp Physiol 316:R441–R447. https://doi.org/10.1152/ajpregu.00279.2018
338. Tsukimori K, Fukushima K, Tsushima A, Nakano H (2005) Generation of reactive oxygen species by neutrophils and endothelial cell injury in normal and preeclamptic pregnancies. Hypertension 46:696–700. https://doi.org/10.1161/01.HYP.0000184197.11226.71