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Effects of Maternal Stress and Nutrient Restriction during Gestation on Offspring Neuroanatomy in Humans

Katja Franke^a, Bea van den Bergh^{b,c}, Susanne R. de Rooij^d, Nasim Kroegel^{a,e}, Peter W. Nathanielsz^{f,g}, Florian Rakers^a, Tessa J. Roseboom^{d,h}, Otto.W. Witte^a, Matthias Schwab^a

^aDepartment of Neurology, Jena University Hospital, Jena, Germany. ^bResearch Group on Health Psychology, Faculty of Psychology and Educational Sciences, KU Leuven, Leuven, Belgium.

^cDepartment for Welfare, Public Health and Family, Flemish Government, Brussels, Belgium

^dDepartment of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, University of Amsterdam, The Netherlands. ^eacatech – National Academy of Science and Engineering, Berlin, Germany. ^fTexas Pregnancy & Life Course Health Research Center, Southwest National Primate Research Center, Texas Biomedical Research Institute, San Antonio, TX 78227, US. ^gDept. of Animal Science, University of Wyoming, Laramie, WY 82071, US.

^hDepartment of Obstetrics and Gynaecology, Academic Medical Centre, University of Amsterdam, The Netherlands.

Abstract

Cognitive and mental health are major determinants of quality of life, allowing integration into society at all ages. Human epidemiological and animal studies indicate that in addition to genetic factors and lifestyle, prenatal environmental influences may program neuropsychiatric disorders in later life. While several human studies have examined the effects of prenatal stress and nutrient restriction on brain function and mental health in later life, potentially mediating effects of prenatal stress and nutrient restriction on offspring neuroanatomy in humans have been studied only in recent years. Based on neuroimaging and anatomical data, we comprehensively review the studies in this emerging field. We relate prenatal environmental influences to neuroanatomical abnormalities in the offspring, measured *in utero* and throughout life. We also assess the relationship between neuroanatomical abnormalities and cognitive and mental disorders. Timing- and gender-specific effects are considered, if reported. Our systematic review provides evidence for adverse effects of an unfavorable prenatal environment on structural brain development that may contribute to the risk for cognitive, behavioral and mental health problems throughout life.

1. Introduction

The trajectory of neurodevelopment is critical for offspring mental and cognitive health as well as quality of life (Rando and Simmons, 2015; Schuurmans and Kurrasch, 2013; Seckl and Holmes, 2007; Tarry-Adkins and Ozanne, 2014). Neurodevelopment begins at the embryonic stage and continues through adolescence and early adulthood (Ernst and Korelitz,

2009). Environmental influences are capable of modifying the development of physiological systems with high plasticity such as the cardiovascular system, the digestive system, the immune system and the central nervous system during critical phases of fetal development, allowing a rapid adaptation of the organism to changes in the postnatal environment to ensure the immediate survival of the fetus (Hanson and Gluckman, 2014). Plasticity and, hence, vulnerability of physiological systems for environmental influences is especially high during early maturation, i.e. during fetal life. More specifically, the prenatal environment, in particular, prenatal stress and nutrient restriction, trigger persistent modifications on the epigenome of the differentiating cell, leading to changes in organ structure and function (Barnes and Ozanne, 2011; Cao-Lei et al., this issue; Lillycrop and Burdge, 2011; Tarrade et al., 2015). This physiological adaptation to the (suboptimal) intrauterine and “the anticipated” postnatal environment may improve chances of reproduction at the expense of a predisposition to certain disorders, especially after the reproductive period (Barker, 1998).

The developing brain is specifically susceptible to prenatal stress and nutrient restriction due to its lengthy period of development and its intrinsic plasticity, the latter being a basic property of the brain allowing learning and adaptation in later life (Bale, 2015; Griffiths and Hunter, 2014; Paus, 2005). In particular, the central nervous system develops gradually, and involves a complex organization of neuro- and gliogenesis, cell differentiation, migration and synaptogenesis. These highly coordinated processes also exhibit a high energy demand during development, with the brain consuming over half of the available energy during growth (Gibbons, 1998). Consequently, even modest nutrient restriction during prenatal development in non-human primates that did not affect fetal birth weight compromises fetal cerebral development (Antonow-Schlorke et al., 2011).

Functional neurobiological correlates of prenatal stress and nutrient restriction in the offspring have been extensively examined and reviewed (Charil et al., 2010; Faa et al., 2014; Hoeijmakers et al., 2014; Talge et al., 2007; van den Bergh et al., this issue). These correlates include aberrations in neurocognitive function, cerebral processing, functional brain connectivity, involving amygdalae and (pre)frontal cortex, changes in hypothalamo-pituitary-adrenal (HPA)-axis and autonomous nervous system. Additionally, prenatal stress and nutrient restriction are widely linked to increased vulnerability for various cognitive, behavioral, and psychosocial problems, such as developmental delays during childhood, impairments in life-long learning, cognitive deficits, behavioral and psychiatric disorders, including increased risks of attention deficit/hyperactivity disorder (ADHD) and anxiety, language delay as well as later-life neurodegenerative disorders (de Rooij et al., 2010; Faa et al., 2014; Hoeijmakers et al., 2014; van den Bergh et al., this issue).

These disturbances are often related to an altered maturation of the HPA axis (for review see Charil et al., 2010), which itself is highly susceptible to early environmental influences such as prenatal stress or nutrient restriction (Antonelli et al., 2016; Desplats, 2015; Malter Cohen et al., 2013). During the past years, it has become increasingly evident that the link between prenatal stress and neuropsychiatric outcome is also mediated by alterations in structural brain development (Mueller and Bale, 2008; van den Bergh et al., this issue). A wealth of experimental studies has demonstrated that prenatal stress affects the morphology of the offspring's brain, at both macroscopic and microscopic levels (for review see Charil et al.,

2010). Experimental studies have also provided strong evidence that fetal nutrient restriction causes widespread disturbances of early organizational processes in cerebral development that result in permanent impairments in brain structure and function (Antonow-Schlorke et al., 2011; Grantham-McGregor and Baker-Henningham, 2005; Keenan et al., 2013; Morgane et al., 1993; Muller et al., 2014; Olness, 2003; Rodriguez et al., 2012; Wainwright and Colombo, 2006; Walker et al., 2007), subsequently determining altered postnatal cognitive and behavioral performances (Keenan et al., 2013; Muller et al., 2014; Rodriguez et al., 2012).

However, knowledge of the effects of prenatal environmental influences on brain development is mostly obtained in rodent studies and not directly transferable to the human situation. Rodents are polytocous and altricial species, which show substantially different trajectories of fetal and neonatal brain development compared to monotocous and precocial mammals, including humans (Fontana and Partridge, 2015; Ganu et al., 2012). While several human studies have examined the effects of prenatal stress and nutrient restriction on functional brain development and mental health in later life (for review see van den Bergh et al., this issue), the mediating effects of prenatal stress and nutrient restriction on structural brain development have only been increasingly studied in recent years in light of the rapid advances in MRI technology.

2. Objectives and study selection criteria

The innovative and rapidly emerging field of research justifies a first narrative review based on the database available. The scope of our systematic review is to reveal the current state of knowledge on the effects of prenatal stress and nutrient restriction on structural brain development in humans based on macroscopic anatomical birth data such as birth weight, head circumference at birth and neuroimaging data.

We related neuroanatomical abnormalities to the prenatal environmental influence, the age at which this influence appeared and the age at which the neuroanatomical abnormalities became measurable. We assessed the relationship between neuroanatomical abnormalities and cognitive and mental disorders under consideration of gender-specific effects. Our systematic review aims to contribute to a better understanding of the consequences of an unfavorable prenatal environment on life-long brain health and to highlight relevant future research avenues in order to facilitate early treatment or preventative interventions.

We undertook a PubMed and Google Scholar search using the search terms “prenatal / maternal / gestation”, “stress / anxiety / depression / malnutrition / nutrient restriction / undernutrition / birth weight”, together with “head circumference / brain structure / brain volume / MRI / DTI” in “humans” in any combination, including all studies published until August 2019. We found 45 eligible papers, including a total of about 88,000 offspring (range: 13 – 78,000). Examining the effects of maternal psychological stress during pregnancy on the offspring neuroanatomy, our review included 1 study in the fetus with 132 individuals, 12 studies in the newborn with a total of about 83,000 individuals, 5 studies in young children with a total of about 450 individuals, 6 studies in school-aged children with a total of about 900 individuals, and 2 studies in young adults with a total of about 400

individuals. Examining the effects of maternal malnutrition during pregnancy on the individuals neuroanatomy, our review included 2 studies in the fetus with a total of about 100 individuals, 3 studies in children with a total of about 450 individuals, 6 studies in teenagers with a total of about 950 individuals, 4 studies in young adults with a total of about 400 individuals, and 4 studies in older adults with a total of about 1,400 individuals.

3. Determination of offspring neuroanatomy

Past studies examining the effects of maternal stress, anxiety, or depression during pregnancy on structural brain development in humans used anatomical measures, such as head circumference at birth. More recent studies analyzed neuroimaging data, utilizing diverse magnetic resonance imaging (MRI) modalities, pulse sequences and experimental protocols, as well as a variety of analytical techniques for processing MRI data in order to examine and quantify the multidimensional aspects of changes in brain structure throughout the lifespan. The most common imaging modality is T1-weighted MRI, used to estimate anatomical marks reflecting the stage of brain development and ageing, including global and regional gray and white matter (WM) volumes, volumetric data for subcortical regions, voxel-wise based markers, cortical thickness and cortical surface area. T2-weighted MRI and diffusion tensor imaging (DTI) provide additional measures, including WM integrity, fiber density, axonal diameter, myelination in WM, or water diffusion in brain tissue. For an overview of the different MRI modalities and its deriving parameters (i.e. the various measures of the brain structure), please refer to Franke et al. (this issue).

4. Effects of prenatal stress on offspring neuroanatomy

Prenatal stress, i.e. fetal exposure to high concentrations of maternal cortisol or to other stress transmitters such as reduced uterine perfusion, maternal cytokines, serotonin and oxidative stress (for review see Rakers et al., this issue), mainly results from maternal psychological stress, pregnancy-specific anxiety and depression. Depressive disorders during pregnancy are present in about 10% of women, with about 5% meeting criteria for probable major depression (Melville et al., 2010). Other influences on fetal development, such as maternal smoking, substance abuse, preeclampsia and obesity, are beyond the scope of our review since they may have direct (i.e. stress hormone independent) effects on fetal development. A condensed overview of studies exploring the associations between maternal psychological stress, anxiety, or depression during pregnancy and neuroanatomical MRI measures can be found in Table 1.

4.1 Effects of maternal psychological stress

Our systematic review of the publication database revealed a total of 11 studies on the effects of maternal psychological stress during pregnancy, including a total of about 83,000 individuals: 9 studies examined the effects of maternal psychological stress based on pregnancy-unrelated stressful life events (e.g. natural disasters, illnesses in the close family or financial and relationship problems), on head circumference at birth as an indirect measure for structural brain development during gestation (Dancause et al., 2011; Lou et al., 1994; Obel et al., 2003; Tegethoff et al., 2010) as well as on measures based on structural MRI (Favaro et al., 2015; Jones et al., 2019), resting-state MRI (Scheinost et al., 2016), or

DTI-based measures (Jensen et al., 2018; Sarkar et al., 2014) during childhood and adulthood. Two studies were found that examined the relation between maternal saliva cortisol concentrations (i.e. an objective measure for the subjective experience of stress) at several time points during pregnancy and MRI-based brain volume measures during childhood (Buss et al., 2012) and neonatal amygdala connectivity (Graham et al., 2019).

Amongst these studies, the earlier studies used gross anatomical birth measures to examine the relationship between maternal psychological stress and structural brain development. A study in a small sample from a population-based data set from Denmark ($n=120$) reported that pregnancy-unrelated stressful life events (e.g., separation, death of a spouse or partner, job loss, theft,) during pregnancy, in combination with a lack of a social network, are negatively associated with offspring head circumference at birth, corresponding to a reduction of at least 5% of brain volume at birth (Lou et al., 1994). In a later study within the whole population-based data set ($n=4,211$), Obel et al. (2003) could not find associations between head circumference at birth and the extent of stressful life events during pregnancy. However, in another large-scale population-based study from Denmark ($n=78,017$), maternal life stress (i.e., perceived burdens in major areas of life) during pregnancy was positively associated with offspring head circumference at birth; yet, this association was rather small (Tegethoff et al., 2010).

A more recent study considered the effects of timing and severity of exposure to objective and subjective stress due to a natural disaster on fetal development during pregnancy using anatomical birth measures (Project “Ice Storm”; Dancause et al., 2011). In January 1998, a series of severe ice storms caused power outages that lasted between a few hours to more than six weeks in over 1.4 million households in the Québec area. Around 600,000 people temporarily moved out of their homes to escape the cold and thousands of people were injured or hospitalized. Additionally, the ice storm resulted in huge financial and job losses. Whereas objective stress (i.e., severity of exposure to the cold, the need to obtain sheltering, financial and job loss, etc.) during early pregnancy was positively associated with offspring head circumferences at birth, subjective maternal stress during early pregnancy but not during mid- and late pregnancy was negatively associated with head circumferences ($n=172$; Dancause et al., 2011). All associations were controlled for confounding variables such as age, obstetric complications, socioeconomic status and trait anxiety. Additionally, exposure to greater subjective maternal stress during pregnancy predicted smaller head-circumference-to-birth-length ratios in boys but not in girls (Dancause et al., 2011).

In contrast to studies on head circumference at birth, MRI and DTI studies allow a better insight into the effects of maternal psychological stress on structural neurodevelopment of the offspring. In preterm-born neonates ($n=26$), maternal stress exposure during the 1st and 2nd trimester, as documented by the physician, was negatively associated with left amygdala connectivity at original term date, with this effect remaining stable also after correcting for gestational age at birth and birth weight (Scheinost et al., 2016). In term-born neonates ($n=70$), maternal saliva cortisol concentrations, measured in early, mid and late pregnancy, were associated with aberrations of the development of amygdala connectivity in term-born neonates at 4 weeks of age in a gender-related manner (Graham et al., 2019). In the female neonate, these associations were positive, whereas in the male neonate, these associations

were negative. Additionally, the neonatal amygdala connectivity was paralleled by increased internalizing symptoms at 2 years of age in the female offspring (Graham et al., 2019).

In the 6–9-year-old offspring (n=22), Sarkar et al. (2014) reported associations of stressful life events during pregnancy with aberrations in the development of WM integrity. These changes in WM integrity were suggested to reflect hypermyelination and advanced brain maturation (Sarkar et al., 2014). The aberrations occurred in the right uncinate fasciculus that connects the limbic region to the prefrontal cortex. Developmental aberrations of the uncinate fasciculus are linked to antisocial behavior and autistic spectrum disorder (Wolff et al., 2012). Likewise, according to the study by Jensen et al. (2018) in male offspring aged 18–21 years (n=393), stressful life events during early gestation were negatively associated with WM integrity in the corpus callosum. However, no associations were found between maternal stress during pregnancy and DTI derived measures of functional connectivity (Jensen et al., 2018). In contrast, in the study by Favaro et al. (2015) in female offspring aged 15–40 years (n=35), retrospectively reported maternal stress during pregnancy was positively correlated to functional connectivity between the left medial-orbitofrontal cortex and the rostral part of the pregenual anterior cingulate cortex. These aberrations were in turn associated with actual depressive symptoms in the adult female offspring (Favaro et al., 2015).

The study by Buss et al. (2012) prospectively examined the association of maternal cortisol in early, mid- and late gestation as an objective marker for maternal stress with measures of amygdala and hippocampus volume and affective problems in the 7 year-old offspring (n=65). In girls, but not in boys, higher maternal cortisol levels in early but not late gestation were related to increased right amygdala volume, a brain region closely associated with stress reactivity and vulnerability for affective disorders (Bellani et al., 2011; Whalen and Phelps, 2009). Indeed, increased maternal cortisol levels in early gestation were also associated with affective problems in girls (Buss et al., 2012). In contrast, Jones et al. (2019) did not find an association between subjective maternal stress during pregnancy due to exposure to a natural disaster (i.e. Ice storm) based on amygdala volume in the 11.5 year-old offspring (n=68), when adjusting for postnatal confounders. However, in 11.5 year-old female offspring, disaster-related objective maternal stress during the 2nd half but not 1st half of pregnancy was positively associated with right and left amygdala volumes, which were associated to increased externalizing problems. These effects remained stable after adjusting for postnatal confounders (Jones et al., 2019). In contrast, retrospectively reported maternal stress during pregnancy was associated with decreased GM volume in the left medial temporal lobe of the cerebral cortex as well as in the left and right amygdalae in 15–40 year-old female offspring (n=35; Favaro et al., 2015). These aberrations were in turn associated with actual depressive symptoms in the adult female offspring (Favaro et al., 2015).

In summary, the results of these studies underscore that maternal psychological stress during pregnancy, especially during the first half of gestation, may contribute to neurodevelopmental structural abnormalities that mainly include changes in amygdala volume and connectivity and a decrease in GM volume. These effects are in accordance with experimental studies showing that maternal stress in rat and sheep induces more pronounced effects on fetal neuronal network and myelin formation during early to midgestation

(Hermes et al., 2019; Xu et al., 2013). In agreement with this, human behavioral studies showed that maternal psychological stress during early pregnancy has the most pronounced adverse effects on behavior and cognitive functioning (for review see van den Bergh et al., this issue). Yet, most insights of structural alterations in brain development, which might explain the behavioral and mental health problems in offspring prenatally exposed to maternal stress, are still based on animal research (e.g., Bock et al., 2015; Charil et al., 2010). However, animal data may not entirely reflect the complexity of functional and structural correlates underlying behavioral and mental health problems in humans.

4.2 Effects of maternal anxiety

A total of six studies explored the effects of prenatal maternal anxiety, including a total of about 400 individuals; four studies examined the effects of maternal trait anxiety during pregnancy on structural brain development. Of these, one study assessed antenatal head circumference as an indirect measure for fetal structural brain development (Field et al., 2003). The other three studies used MRI-based volume (Qiu et al., 2013), cortical thickness (Qiu et al., 2015b), or DTI measures in neonates (Rifkin-Graboi et al., 2015). Two other studies examined the effects of pregnancy-related anxiety on MRI-based volume measures during childhood (Acosta et al., 2019; Buss et al., 2010). All six studies are described in more detail below.

In contrast to observations in maternal psychological stress during pregnancy, maternal trait anxiety was not found to have an effect on the fetus' head circumference, at 18–24 weeks of gestation (n=132; Field et al., 2003).

One of the most important studies on maternal anxiety and depression during pregnancy comprises the prospective longitudinal study “Growing up in Singapore towards Healthy Outcomes” (GUSTO; Soh et al., 2014), including 1176 offspring, born between December 2009 and April 2011. Pregnant mothers were recruited at 13 weeks of gestation. Maternal depression and anxiety were measured at 26–28 weeks of gestation as well as at 3 months after delivery. A total of 175 newborns underwent structural MRI and DTI at 6–14 days after birth. Of these, a follow-up MRI scan was performed in 35 infants at six weeks of age and in another 42 infants at six months of age. Maternal trait anxiety, as assessed at 26 weeks of gestation, did not show any effect on cortical thickness and bilateral hippocampal volume at birth (Qiu et al., 2013; Qiu et al., 2015b). However, maternal trait anxiety during pregnancy was negatively correlated with the growth of both the left and right hippocampi over the first six months of life (Qiu et al., 2013). Notably, the slowed growth of the right hippocampus became statistically stronger when controlling for postnatal maternal anxiety at 3 months after delivery, whereas the effect for left hippocampal growth diminished (Qiu et al., 2013). Thus, the authors concluded that only right hippocampal growth during early infancy is constrained by maternal trait anxiety during the 2nd trimester. Although maternal trait anxiety during pregnancy was not related to regional brain volumes and cortical thickness in the neonate, a DTI study in the same cohort (Rifkin-Graboi et al., 2015) could show associations with variations of measures in the neonates' WM fiber tract in the dorsolateral prefrontal cortex and the right insula (i.e. regions important for cognitive-emotional responses to stress), the right middle occipital (i.e. regions important for sensory processing)

and the right angular gyrus, the uncinate fasciculus and the posterior cingulate parahippocampus (i.e. regions involved in social cognition and social-emotional functioning).

Especially maternal pregnancy-related anxiety seems to have lasting effects on offspring structural brain development. Pregnancy-related anxiety during the 1st and early 2nd trimester was linked to GM volume reduction in several cortical and cerebellar regions in the 6–9 year-old offspring (n=35; Buss et al., 2010). This effect was independent of postnatal maternal stress. In contrast, pregnancy-related anxiety during the 3rd trimester was associated with increased volume of the left amygdala in the 4 year-old offspring (n=27), with this effect being stronger in the female offspring (Acosta et al., 2019). This effect was independent of maternal pre- or postnatal depressive symptoms and postnatal anxiety. These developmental aberrations of the left amygdala volume were furthermore found to partly mediate the associations between maternal anxiety and child emotional and behavioral difficulties in the 4 year-old offspring (Acosta et al., 2019).

In summary, the very few studies available suggest that especially pregnancy-related anxiety has adverse effects on neurodevelopment in the offspring. Whereas pregnancy-related anxiety has been associated with delays in amygdala, cortical, and cerebellar development in the offspring, maternal anxiety has been associated with delays in hippocampal development in the offspring as well as with aberrations in fiber maturation in brain regions important for cognitive and behavioral functioning. However, we cannot specify vulnerable phases of prenatal development since the few studies did not examine the effects of maternal anxiety over the entire gestation nor did they examine the same outcome parameters in the fetus. Nevertheless, these changes might in part explain the well-documented associations between maternal anxiety and offspring cognitive and behavioral functioning during the whole lifespan (for review see van den Bergh et al., this issue).

4.3 Effects of maternal depression

Eight studies, including a total of about 1,300 individuals, examined the effects of maternal depression during pregnancy on cerebral MRI and DTI-based measures in neonates (Rifkin-Graboi et al., 2013), early infancy (Posner et al., 2016; Qiu et al., 2015a), early childhood (Lebel et al., 2016; Soe et al., 2018; Wen et al., 2017), and middle childhood (El Marroun et al., 2016; Sandman et al., 2015).

The recent Canadian study by Lebel et al. (2016) reported that depression in women during the 2nd, but not the 1st and 3rd trimesters of pregnancy was associated with cortical thinning in the right frontal and temporal cortex in 3–5 year-old offspring (n=52). These effects were stronger in girls. There was also a trend of maternal depression during the 2nd trimester being associated with decreased integrity of fiber tracts emanating from the frontal cortex, which diminished after controlling for postnatal maternal depression. Furthermore, postpartum maternal depression was additionally related to offspring cortical thinning in the right frontal cortex and decreased integrity of fiber tracts originating from that region, even after correction for maternal depression during pregnancy (Lebel et al., 2016). These results suggest that the effects of maternal depression during pregnancy on offspring cortical thickness may be further intensified by postnatal maternal depression. Similarly, in another

prospective study, maternal reports of depressive symptoms at 19, 25 and 31 weeks of pregnancy were associated with cortical thinning in 6–9 year-old offspring, showing the strongest association with maternal depression at 25 weeks of gestation ($n=81$; Sandman et al., 2015). The most pronounced effects were found in the prefrontal, medial postcentral, lateral ventral precentral and postcentral regions of the right hemisphere. Cortical thinning in prefrontal areas of the right hemisphere mediated the association between maternal depression and increased childhood externalizing behavioral problems. All associations were controlled for confounding variables, including maternal depression at the time of MRI and behavioral assessment during middle childhood (Sandman et al., 2015). Likewise, the Dutch population-based prospective study by El Marroun et al. (2016) also showed that maternal depressive symptoms assessed at 21 weeks of gestation were associated with a thinner superior frontal cortex as well as larger caudal middle frontal area in the left hemisphere in 6–9 year-old offspring ($n=654$), whereas neither postnatal maternal depressive symptoms, nor paternal depressive symptoms showed any effects on offspring brain morphology.

Utilizing the GUSTO sample (see 4.2) and controlling for confounding variables, no effects of maternal depression, as assessed at 26–28 weeks of pregnancy, on the neonates' amygdalae volumes were observed ($n=157$; Rifkin-Graboi et al., 2013). Although no effects of maternal depression at 26–28 weeks of pregnancy on the neonates' amygdalae volumes were found, a negative association with the neonates' WM fiber measures in the right amygdala was observed (Rifkin-Graboi et al., 2013). Since the amygdala is involved in stress reactivity and vulnerability for mood disorders and emotional processing (Abercrombie et al., 1998; Hamilton and Gotlib, 2008; Keller et al., 2008), the authors conclude that these results suggest a prenatal transmission of vulnerability for depression from mother to their offspring. Likewise, six week-old infants in the maternal depression group showed decreased structural connectivity between the right amygdala and right ventral prefrontal cortex as well as increased bottom-up excitatory and decreased top-down excitatory influences between the amygdala and prefrontal regions, in addition to decreased reciprocal inter-cortical connections between these prefrontal cortical regions ($n=65$; Posner et al., 2016). At six months of age, increased functional connectivity between the left, but not right, amygdala and the cortical regulatory network of emotion regulation as well as the sensory and perceptual systems was observed ($n=24$; Qiu et al., 2015a). The results were neither confounded by postnatal maternal depression, nor by any of the other confounding variables (i.e., household income, birth weight, gender). These patterns of functional connectivity in the 6 month-old offspring were consistent with connectivity patterns observed in adolescents and adults with major depressive disorders (Roy et al., 2009). However, prenatal maternal depressive symptoms during the 2nd trimester of gestation were associated with lower functional connectivity between the amygdalae and the cortico-striatal circuitry in the female, but not male 4.5 year-old offspring ($n=128$; Soe et al., 2018).

In contrast to the results in the GUSTO sample, Wen et al. (2017) did not find any associations between maternal depression as assessed during 26–28 weeks of pregnancy and offspring structural connectivity, neither in the male, nor in the female 4.5 year-old offspring ($n=235$), when controlling for maternal postnatal depression. However, maternal depressive symptoms during pregnancy were associated with a larger right amygdala volume in 4.5

year-old female but not male offspring, even when controlling for postnatal maternal depressive symptoms (Wen et al., 2017).

Taken together, neuroimaging correlates of the prenatal transmission of phenotypes associated with maternal mood during pregnancy, especially during the 2nd trimester of gestation, are already apparent in newborns and remain detectable in infants and during childhood. However, vulnerable periods of fetal development related to maternal depression could not be determined since in most of the studies depression scores were collected only once at midgestation. The neuroimaging correlates include cortical thinning and decreased structural connectivity between the amygdala and prefrontal cortex, which resembled the patterns of advanced brain atrophy found in patients with major depressive disorder (Sandman et al., 2015).

4.4 Mechanisms mediating the effects of prenatal stress on offspring neuroanatomy

Unsurprisingly, examination of the mechanisms mediating the effects of prenatal stress on structural brain development has mostly been undertaken in experimental studies. Only two human studies have explored the mechanisms mediating the effects of maternal anxiety on structural brain development, utilizing MRI-based measures and DNA methylation pattern ($n=237$; Chen et al., 2015) or genotyping ($n=146$; Qiu et al., 2015b) in neonates.

The HPA axis with its primary end product cortisol (or corticosterone in rodents) constitutes the major part of the stress axis. The ability of cortisol to cross the human placenta makes it an important mediator of maternal stress to the fetus (Rakers et al., this issue). Once in the fetal circulation, cortisol promotes cell differentiation at the expense of cell division (Lemaire et al., 2000; Tauber et al., 2006). In addition, maternal stress-induced release of catecholamines into the maternal circulation reduces uterine blood flow (Rakers, this issue), which diminishes fetal growth and affects organ development (Diego et al., 2006; Lang et al., 2003). In addition, maternal cortisol can perturb the development of the fetal HPA axis by resetting the set point of the HPA axis' negative feedback mechanism by persistent epigenetic changes (DNA methylation) of the glucocorticoid receptor gene *NR3C1* promoter (Mueller and Bale, 2008). It is assumed that DNA methylation of the *NR3C1* promoter results in downregulation of the sensitivity of glucocorticoid receptors involved in the HPA axis' negative feedback mechanism and, subsequently, in a persistent hyperactivity of the fetal HPA axis (Rakers et al., 2013). The resulting increased cortisol plasma concentrations may prolong the maturational and cell division inhibiting effects of cortisol.

Other target genes of glucocorticoid signaling besides *NR3C1* that are crucially involved in fetal development and growth are *Brain Derived Neurotrophic Factor (BDNF)* (Numakawa et al., 2017) and also the *insulin-like growth factor 2 (IGF2)/H19* locus which encodes IGF2, the major growth hormone during fetal life (Baker et al., 1993). These genes may also play a significant role in mediating prenatal stress effects on structural brain development (Numakawa et al., 2017). Indeed, different forms of maternal stress during pregnancy are associated with DNA methylation of *BDNF* in the cerebral cortex in rodents (Blaze et al., 2017), in the umbilical cord blood and placental tissue (Kertes et al., 2017), as well as in the DNA of buccal cells in humans (Braithwaite et al., 2015). BDNF is a member of the neurotrophin family of growth factors. It is essential for neuronal survival, synaptic plasticity

and neuronal differentiation and is highly expressed in various parts of the CNS including the hippocampus and cerebral cortex (Numakawa et al., 2017). Consequently, homozygous BDNF knock-out mice suffer from growth retardation, impairments in coordination of movement and sensory deficits (Ernfors et al., 1994). In agreement with this, prenatal cold stress reduced BDNF expression in the rats' hippocampus with multiple effects on intracellular signaling and behavior (Lian et al., 2018). In humans, BDNF valine-66-methionine (Val66Met) polymorphism was found to be associated with structural plasticity in the cortex during learning and memory (Kleim et al., 2006; McHughen et al., 2010; Wang et al., 2014). Val66Met polymorphism has been suggested to moderate the impact of environmental conditions such as parental depression, early child care and parenting behavior in infancy and early childhood on offspring emotional and attention behavior (Gunnar et al., 2012; Hayden et al., 2010; Willoughby et al., 2013). These effects are probably mediated by changes in structural brain development, as supported in a study by Chen et al. (2015). In detail, neonatal, but not maternal, BDNF Val66Met polymorphism was strongly associated with maternal anxiety assessed at 26–28 weeks of gestation as well as with neonatal brain volume, especially amygdala and hippocampus volumes (Chen et al., 2015).

Of particular interest are also the reciprocally imprinted *IGF2/H19* genes. Imprinted genes are expressed according to parental origin. *IGF2* is expressed specifically from the paternal allele, whereas *H19* is specifically expressed from the maternal allele (Smith et al., 2007). Reduced levels of IGF-1 and dysregulation of the IGF-1 binding protein network have also been shown in the frontal cortex and hippocampus of prenatally stressed rats showing depression-like behavior (Basta-Kaim et al., 2014). Two recent smaller studies and one large cohort study have found evidence of associations between maternal stress during pregnancy and methylation of *IGF2* and *H19* in the offspring. Chen et al. (2014) reported increased methylation of *H19* in cord blood and placenta tissue of infants born to mothers with high self-reported stress and anxiety, whereas Vangeel et al. (2015) found decreased methylation of *IGF2* in association with maternal anxiety. A large cohort study showed that maternal anxiety and, to a lesser extent maternal psychological stress and depression, assessed at 28 weeks of gestation is associated with decreased *IGF2/H19* methylation in purified cord blood mononuclear cells in newborns, particularly in those with birth weights lower than 3.530 gram (Mansell et al., 2016). This association persisted when accounting for a range of lifestyle and birth-related covariates. Decreased methylation of *IGF2/H19* is assumed to lead to reduced *IGF2* expression (Mansell et al., 2016). However, there is no direct evidence that reduced brain growth associated with maternal stress during pregnancy is mediated by *IGF2*. Nevertheless, local *IGF2* in the brain produced by the choroid plexus regulates cortical neurogenesis during development (Liu et al., 2014). On the post-translational level, expression of other components of the IGF-system such as reduced levels of IGF-1 and dysregulation of the IGF-1 binding protein network have also been shown in the frontal cortex and hippocampus of prenatally stressed rats showing depression-like behavior (Basta-Kaim et al., 2014). During fetal growth, presence of IGF1 in the CNS is crucial for the developing neurons and oligodendrocytes and promotes neurite outgrowth and branching, synaptogenesis and myelin formation (D'Ercole and Ye, 2008; O'Kusky and Ye, 2012).

Further, Qiu et al. (2015b) observed that effects of maternal anxiety on neonatal frontal cortical thickness assessed at 26 weeks of gestation were modulated by functional variants of the *catechol-O-methyltransferase (COMT)* gene, which regulates catecholamine signaling in the prefrontal cortex and is implicated in anxiety, pain and stress responsivity. More specifically, the A-Val-G (AGG) haplotype modulated a positive association between maternal anxiety and offspring cortical thickness of the right ventrolateral prefrontal, right parietal cortex and the precuneus, whereas the G-Met-A (GAA) haplotype modulated a negative association between maternal anxiety and offspring cortical thickness in the dorsolateral prefrontal cortex and the bilateral precentral gyrus (Qiu et al., 2015b).

Taken together, these findings suggest that the association between prenatal anxiety and offspring neurodevelopment is modulated by the induction of complex functional genetic and epigenetic variations in the offspring, which seem to be brain tissue-and-region specific.

5. Effects of prenatal malnutrition on offspring neuroanatomy

The developing brain is highly dependent on the availability of nutrients and a lack of sufficient nutrients poses a serious threat to normal brain development as revealed in experimental studies (Ramel and Georgieff, 2014). In humans, there are only a few studies directly examining the effects of global maternal nutrient restriction or specific nutritional deficiencies during pregnancy on offspring structural brain development. Most studies used birth characteristics, such as infant length and weight at birth as indirect determinants of different causes of fetal nutrient restriction, such as maternal malnutrition, placental insufficiency, extreme maternal vomiting, multiple pregnancy etc. (Baker et al., 2009; Beard et al., 2009; Raznahan et al., 2012; Roseboom et al., 2011; Zhang et al., 2015). Studies that used offspring birth weight as an indirect measure of fetal nutrient restriction explored the associations of decreased birth weight within the normal range, small-for-gestational-age (SGA, defined as birth weight below the 10th percentile adjusted for gestational age) and low birth weight (LBW < 2000 grams) or very LBW (< 1500 g) with structural brain development. However, these studies are only observational and retrospective, thus limiting the ability to control pre- and postnatal confounders of structural brain development. A condensed overview of studies exploring the associations between prenatal nutrient restriction and neuroanatomical measures from neonates to older age can be found in Table 2.

5.1 Associations between maternal nutrient restriction during pregnancy and offspring neuroanatomy

Three studies, including a total of about 150 individuals, were found that examined the associations between global maternal nutrient restriction during pregnancy and MRI-based measures of aberrations in the neuroanatomical structure in the offspring during late adulthood (de Rooij et al., 2016; Franke et al., 2018; Hulshoff Pol et al., 2000). A further study, including 256 individuals, assessed the effects of micronutrient deficiency on brain development and cognitive performance in middle childhood (Ars et al., 2019).

Direct evidence for the effects of global nutrient restriction on offspring brain structure comes from the Dutch famine birth cohort study. The Dutch famine was a five-month period

at the end of World War II, during which the western part of the Netherlands was struck by a severe famine, with the daily ration providing only 400–800 kcal. Thus, the Dutch famine cohort provides a unique opportunity to study consequences of prenatal exposure to nutrient restriction since the famine comprised a relatively short period of severe nutrient restriction in a population well fed before and after the famine. Results from the Dutch famine birth cohort study have shown that an adverse prenatal environment, especially in the beginning of pregnancy, is associated with a range of adverse health effects including alterations of brain morphology that are even independent of birth weight and size at birth, which were within the normal range (Roseboom et al., 2006). A first observational study by Stein et al. (1975), which investigated the direct effects of famine on the development of the CNS, showed an increase in the prevalence of congenital anomalies of the CNS, including spina bifida and hydrocephalus, in offspring exposed to Dutch famine during the first trimester of pregnancy. The effects of exposure to nutrient restriction during early gestation on brain development also showed more subtle lasting effects. The first MRI study in 51 year-old schizophrenia patients from the Dutch famine cohort showed an increase in brain abnormalities with WM hyperintensities being predominant ($n=36$; Hulshoff Pol et al., 2000). A second MRI study that included a subsample of the Dutch famine cohort at the age of 68 years that compared individuals exposed to the famine in early gestation to unexposed offspring, demonstrated smaller intracranial and total brain volumes in males, but not in females ($n=118$; de Rooij et al., 2016). Additional analyses utilizing the innovative *BrainAGE* approach (Franke and Gaser, 2019; Franke et al., 2010), which was designed to indicate deviations in age-related spatiotemporal brain changes, have demonstrated that these males showed advanced brain aging by about 4 years compared to unexposed offspring ($n=118$; Franke et al., 2018). One explanation for the specific effects of global nutrient restriction on brain volume and ageing in men may be that the Dutch famine birth cohort subsample study was hampered by selective participation of more healthy females (survival of the fittest), since it has previously been shown that women exposed to the famine during early gestation demonstrated increased mortality (van Abeelen et al., 2012). In line with this, signs of accelerated cognitive aging have also been found in 56–59 year-old men and women exposed to famine during the early stage of gestation (de Rooij et al., 2010). However, it may also be possible that in men, the development of the CNS is more vulnerable to effects of global nutrient restriction, as demonstrated in a study of postnatal global nutrient restriction in Chilean children (Ivanovic et al., 2000).

Specific micronutrient deficiencies also appear to affect brain development. A study in children aged 6–8 years ($n=256$) showed that maternal folate deficiency in early pregnancy (i.e. plasma folate concentration <8 nmol/l) was gender-independently associated with a reduction in brain volume as well as poorer cognitive performance (Ars et al., 2019). Additionally, in a first randomized controlled trial, epigenetic analyses on DNA methylation of genes related to brain development in cord blood samples obtained during delivery showed gender-specific beneficial effects of continued supplementation with folate during the 2nd and 3rd trimesters of pregnancy for *IGF2* only in female offspring and *BDNF* only in male offspring ($n=86$; Caffrey et al., 2018).

In summary, the very few studies available on the effects of global maternal nutrient restriction and micronutrient deficiencies during pregnancy show that maternal nutrient

restriction and folate deficiency during early pregnancy seems to have a global effect on neurodevelopment reflected in decreased overall brain volume and disturbances in WM integrity. These effects occur even in the absence of low birth weight. Effects on the development of specific neural systems and brain regions have not yet been shown. The decrease in overall brain volume and WM integrity are still apparent during older age and associated with cognitive disturbances.

5.2 Associations between fetal growth measures at birth and offspring neuroanatomy

5.2.1 Effects of variations of birth weight within the normal range—Four studies, including a total of about 2,050 individuals, examined the associations between birth weight at term within the normal range (2400–4600 g) and MRI-based measures of aberrations in the neuroanatomical structure during childhood and adolescence (Qiu et al., 2012; Schlotz et al., 2014; Walhovd et al., 2012) and late adulthood (Muller et al., 2014).

In a study of 6 year-old boys born at term, the interaction of lower birth weight and lower gestational age predicted smaller caudate volumes as well as worse performance in a motor response task ($n=156$; Qiu et al., 2012). In line with that, lower birth weight was associated with a smaller cortex surface area, lower caudate volume and increased cortical thickness of the medial orbitofrontal cortex at age 16 years ($n=27$; Schlotz et al., 2014). At the functional level, the lower birth weight was associated with decreased inhibitory control, with caudate volume mediating this effect (Schlotz et al., 2014). A study by Walhovd et al. (2012) examining a large sample of term-born individuals aged between 6–21 years ($n=628$) also showed positive associations between birth weight and the cortical surface area as well as with total brain and caudate volumes. In line with these results, findings from a population-based study in older individuals with a mean age of 75 years revealed that a suboptimal intrauterine environment, as indicated by a lower ponderal index (relationship between mass and height at birth, thus measuring fetal growth), was associated with decreased total brain and WM volumes, probably indicating early brain aging ($n=1254$; Muller et al., 2014). Interestingly, a lower ponderal index was also associated with slower processing speed and reduced executive functioning, but only in those subjects with a low level of education (Muller et al., 2014). In summary, these studies provide further evidence that the developing brain is very sensitive to nutrient deficiencies. These effects are associated with behavioral and cognitive disturbances. However, it remains unclear, which of the underlying causes of reduced birth weight are responsible for aberrations in brain development and behavioral and cognitive disturbances.

5.2.2 Effects of being small-for-gestational-age (SGA) and low birth weight (LBW)—We found a total of nine studies, including a total of about 800 individuals, that examined the associations between birth length in relation to gestational age and MRI and DTI-based measures of brain development *in utero* (Sanz-Cortes et al., 2014; Sanz-Cortes et al., 2010), during childhood (De Bie et al., 2011), adolescence (Martinussen et al., 2005; Martinussen et al., 2009; Rogne et al., 2015; Vangberg et al., 2006) and early adulthood (Eikenes et al., 2012; Ostgard et al., 2014). Three additional studies examined the associations between LBW and structural neurodevelopment during adolescence (Aukland et al., 2011; Odberg et al., 2010; Vangberg et al., 2006).

Based on intrauterine MRI measurements at 37 weeks of gestation, SGA fetuses showed increased diffusion measures in the pyramidal tract ($n=13$; Sanz-Cortes et al., 2010) as well as larger volumes of brain stem and cerebellum ($n=98$; Sanz-Cortes et al., 2014), suggesting abnormal intrauterine brain development. The increased volumes were associated with altered motor behavior in the neonate (Sanz-Cortes et al., 2014). At 4–7 years of age, reduced cerebral and cerebellar GM and WM volumes, smaller volumes of subcortical structures as well as reduced cortical surface areas were shown in the SGA-born children ($n=55$; De Bie et al., 2011). Even in those SGA children, who showed a bodily catch-up growth at age 4–7 years, full catch-up growth was not observed for most neuroanatomical structures. The authors suggest that reduced cortical surface area without lower cortical thickness in SGA children may suggest a reduced folding pattern in SGA children. However, the authors did not examine the folding pattern (De Bie et al., 2011).

Five longitudinal studies in a sample of SGA-born individuals with MRI assessment at 15 (Martinussen et al., 2005; Martinussen et al., 2009; Rogne et al., 2015; Vangberg et al., 2006) and 20 years of age (Ostgard et al., 2014) revealed similar patterns of neuroanatomical changes. In detail, SGA-born adolescents showed reduced total brain volume and smaller regional brain volumes, especially smaller hippocampal volume, reduced cortical surface area, regional thinning of the parietal, temporal and occipital lobes and regional thickening in the frontal and occipital lobes ($n=107$; Martinussen et al., 2005; Martinussen et al., 2009). The hippocampus, cerebral GM and WM volumes, but not the cortical surface area, were correlated with several IQ scores (Martinussen et al., 2005; Martinussen et al., 2009). A subsequent study in the same cohort demonstrated that the decreased total and regional brain volumes were only present in those SGA-born 15 year-olds with clinically diagnosed fetal growth restriction, i.e. fetal growth at 25–37 weeks of gestation was below -2 SDs of the mean of the control group as evidenced by frequent ultrasound examinations ($n=188$; Rogne et al., 2015). In a follow-up study in this cohort at 20 years of age, SGA was still associated with decreased total and regional brain volumes and reduction in cortical surface area, particularly in the frontal, parietal and temporal lobes ($n=108$; Ostgard et al., 2014). Again, the most prominent reductions of total brain volume, WM, caudate nucleus and putamen volumes as well as reductions of cortical surface area were found in the SGA-born with fetal growth restriction (Ostgard et al., 2014).

Similar to the effects in SGA-born offspring, smaller total brain, cortical GM, cerebellar WM and thalamus volume, as well as reduced cortical surface area and cortical thickness were found in very LBW-born adolescents aged 15 years ($n=108$; Martinussen et al., 2005; Martinussen et al., 2009). Additionally, cortical, thalamus, hippocampus, cerebellar WM volumes and cortical surface area were identified as significant predictors of total and performance IQ scores (Martinussen et al., 2005; Martinussen et al., 2009). In another sample of LBW-born young adults aged 19 years, comparable results were seen, i.e. global loss of WM and thinning of the corpus callosum were shown ($n=213$; Aukland et al., 2011; Odberg et al., 2010). These changes were again accompanied by lower IQ (Odberg et al., 2010).

With regards to WM integrity, increased diffusion measures in the pyramidal tract have been detected in the SGA fetus at 37 weeks of gestation ($n=13$; Sanz-Cortes et al., 2010). In

contrast, Vangberg et al. (2006) showed reduced WM integrity in several brain regions in 15 year-old SGA-born individuals with very LBW, but not in SGA-born individuals without very LBW ($n=123$). The authors suggest that the reduced WM integrity measures might be caused by reduced myelination and probably reflected in reduced motor skills (Vangberg et al., 2006). Additionally, reduced WM integrity was shown in another cohort of SGA-born young adults aged 18–22 years ($n=103$; Eikenes et al., 2012).

Taken together, SGA and LBW have similar but, not surprisingly, more pronounced adverse effects on structural development than reduced birth weight within the normal range. These effects have been reproducibly shown from late gestation until early adulthood and include a decrease of total and regional brain volumes, reduced cortical surface area and cortical thinning as well as reduced WM integrity. These changes were also associated with impaired behavioral and cognitive functions.

5.3 Mechanisms mediating the effects of prenatal nutrient restriction on offspring neuroanatomy

During neuroglial growth, the developing brain requires half of the fetal energy consumed (Gibbons, 1998). Experimental studies provide strong evidence that even small changes in fetal nutrient supply causes widespread disturbances of organizational processes in cerebral development that result in permanent impairments in brain structure and function (Antonow-Schlorke et al., 2011; Grantham-McGregor and Baker-Henningham, 2005; Keenan et al., 2013; Morgane et al., 1993; Muller et al., 2014; Olness, 2003; Rodriguez et al., 2012; Wainwright and Colombo, 2006; Walker et al., 2007). According to the time-course of brain development, nutritional insults during early gestation predominantly affect cell proliferation and migration while reduced nutrition supply during late gestation primarily affect neuronal and glial differentiation, dendritic arborization, myelination and synaptogenesis (Dobbing and Sands, 1970; Georgieff, 2007). The specific effects of fetal nutrient restriction differ considerably between brain regions and neural systems since the various brain regions mature at different time points. The regulatory pathways of brain development that are affected by fetal nutrient restriction are complex and only partly understood (Hsu and Tain, 2019; Langley-Evans, 2009). It has been shown in non-human primates that even a moderate global nutrient restriction has complex suppressing effects on fetal growth hormone expression in the brain such as on the IGF signaling system, BDNF and glial neurotrophic factor S-100 β (Antonow-Schlorke et al., 2011; McDonald et al., 2007; Xie et al., 2013). These interferences are likely to be mediated *via* lifelong changes in epigenetic regulation of gene expression at the level of DNA methylation (Tobi et al., 2014, 2015). For example, low levels of DNA methylation of *IGF2* could still be shown in peripheral blood of the Dutch famine survivors, 60 years after the exposure (Heijmans et al., 2008). Moreover, maternal malnutrition can induce systemic inflammation in the fetus, including rises in TNF- α , IL1 β and IL-6 (Bolton and Bilbo, 2014), which may lead to lifelong changes in hippocampal function (Williamson et al., 2011).

6. Gender-specific effects on offspring neuroanatomy

6.1. Gender-specific effects of prenatal stress

In line with the postulation of sex-specific mechanisms of brain development and aging (Aiken and Ozanne, 2013; Azad et al., 2007; Grossi et al., 2005; Pinn, 2003), sex-related effects of prenatal stress on offspring behavior have been regularly reported in animal studies (Bale and Epperson, 2015; Charil et al., 2010) and could be reproduced in human samples (van den Bergh et al., this issue). Most human studies examining the relationship of prenatal stress and mental health in later life suggested that boys are more vulnerable to the effects of prenatal stress, whereas only a few studies found girls to be more vulnerable, especially for emotional problems (van den Bergh et al., this issue).

At the structural level, maternal depressive symptoms during the 2nd trimester of gestation were associated with more reduced cortical thickness in 3–5 year-old girls than in boys (Lebel et al., 2016). In contrast, MRI-based brain volume measures assessed at different ages during childhood showed that maternal psychological stress, anxiety, or depression during pregnancy increase the amygdala volume predominantly in female offspring (Acosta et al., 2019; Buss et al., 2012; Jones et al., 2019; Wen et al., 2017). However, Rifkin-Graboi et al. (2013) did not find any gender effects for the interaction between maternal depressive symptoms during the 3rd trimester of gestation and amygdala volumes, nor with measures of amygdala integrity in the newborn. Likewise, no gender effects for the association of prenatal stress and bilateral hippocampus volumes in newborns and at 6-months follow-up were found (Qiu et al., 2013).

Maternal psychological stress and depression during pregnancy seem to have complex gender-related effects on the development of brain connectivity, whereas gender-specific effects of maternal anxiety during pregnancy on brain connectivity has not yet been examined. Higher maternal cortisol plasma levels throughout the whole pregnancy were associated with increased connectivity of the right and left amygdala to cortical brain regions in newborn girls and with decreased connectivity in newborn boys (Graham et al., 2019). In contrast, right amygdala–dorsolateral prefrontal cortex and left amygdala–fusiform gyrus connectivity was decreased in girls and increased in boys. The changes in amygdala connectivity were associated to behavioral changes at age 2 years only in girls (Graham et al., 2019). In contrast, maternal depressive symptoms during the 2nd trimester of gestation were associated with lower functional connectivity between the amygdala and the cerebral cortex in 4.5 year-old girls but not boys (Soe et al., 2018).

Although the results of these few studies have to be interpreted with caution since sex-specific analyses further reduced the rather small study groups, the results suggest more pronounced effects of maternal stress, anxiety and depression during pregnancy on structural neurodevelopment in female offspring. Interestingly, this is in contrast to most behavioral human studies which found boys to be more vulnerable to maternal stress, anxiety and depression during pregnancy (van den Bergh et al., this issue). The reasons for this discrepancy remain unknown and might be due to the small number of studies examining the association between prenatal stress and structural brain development.

6.2 Gender-specific effects of prenatal malnutrition

With regard to prenatal malnutrition, only four studies have examined the gender-specific effects on offspring neuroanatomy (Aukland et al., 2011; de Rooij et al., 2016; Franke et al., 2018; Qiu et al., 2012). Developmental programming models suggest that long-term (health) outcomes of adverse intrauterine conditions are more prominent in male rather than in female offspring (Aiken and Ozanne, 2013), however the effects of maternal nutrient restriction in the aged subjects of the Dutch Hunger Winter cohort on total brain volume and individual brain aging were only shown in men (de Rooij et al., 2016; Franke et al., 2018). The few available studies could not yet conclusively determine a gender-related effect between prenatal malnutrition and structural brain development. Qiu et al. (2012) showed an interactive effect of birth weight and gestational age on caudate volume in 6 year-old boys, whereas Aukland et al. (2011) did not observe a significant interaction effect between LBW and offspring gender on corpus callosum volume in the 19 year-olds, although a larger overall callosal area was reported for males. Regarding the effects of specific nutritional deficiencies, folic acid supplementation during the 2nd and 3rd trimesters of pregnancy showed gender-related effects for DNA methylation in cord blood, with a significant effect for changes in the methylation pattern of *IGF2* only in the female newborn and a significant effect for changes in the methylation pattern of *BDNF* only in male newborns (Caffrey et al., 2018). Animal studies on the effects of prenatal malnutrition on offspring neuroanatomy, which also take gender-specific effects into account, are rare. For example, in an MRI study in baboons prenatally exposed to a moderate maternal malnutrition that did not affect birth weight, the relationship between the decrease in gray matter or the increase in white matter and aging was gender-specific (Franke et al., 2017). However and similar to most human studies (Aukland et al., 2011), a 40% restriction of caloric intake in pregnant rats was associated with a gender-independent reduction of the corpus callosum volume in offspring (Olivares et al., 2012).

7. Summary and conclusions

Prenatal stress and nutrient restriction are widely linked to increased vulnerability for various cognitive, behavioral and psychosocial problems during later life (van den Bergh et al., this issue). Although the effects of prenatal stress and nutrient restriction on offspring structural brain development as an important potential mediator of this link have been less studied in humans, several significant and reproducible associations have been found between prenatal stress or nutrient restriction and changes in the offspring brain structure from newborns until old age.

Older studies have mostly used gross anatomical measures at birth, such as head circumference as an easy accessible surrogate marker of brain development during gestation. These studies revealed fairly heterogeneous results. Smaller head circumferences were found in the offspring following maternal stressful life events during the first 30 weeks of gestation (Lou et al., 1994) as well as following increased subjective maternal stress due to a natural disaster during the 1st trimester of gestation, especially in boys (Dancause et al., 2011). In contrast, higher objective stress due to a natural disaster during the 1st trimester of gestation was associated with larger head circumferences at birth (Dancause et al., 2011). Similarly,

positive associations between maternal life stress during the first 30 weeks of gestation and head circumference at birth were found in a large population-based study (Tegethoff et al., 2010). However, the effects of maternal stress were rather small in all of the studies, explaining only 1 – 3% of the variation in head circumferences. In addition, two other studies could not find any associations between stressful life events during the first 30 weeks of gestation and head circumference in the newborn (Obel et al., 2003) or between maternal trait anxiety and head circumference of fetuses during the 2nd trimester of gestation (Field et al., 2003). Given the small effects of maternal stress in relation to the normal variations of head circumferences at birth, head circumference is – though easily accessible – too poor a parameter to determine the effects of prenatal stress on structural brain development. Its unsuitability is underscored by the fact that only two MRI studies which examined maternal stress or pregnancy-related anxiety in the 2nd trimester of gestation were in line with the studies reporting smaller head circumference at birth by showing either GM volume reductions throughout the brain in children (Buss et al., 2010) and in adults (Favaro et al., 2015). Specifically, maternal depressive symptoms were associated with lower cortical thickness in the offspring, especially in frontal areas, which was still evident during childhood (El Marroun et al., 2016; Lebel et al., 2016; Sandman et al., 2015). However, another study found no effects of antenatal maternal trait anxiety during the 2nd trimester of gestation on global cortical thickness in the newborn offspring (Qiu et al., 2015b). Interestingly, offspring with decreased GM volume or cortical thickness showed behavioral correlates such as affective problems in the studies that examined behavioral outcome (Buss et al., 2010) and externalizing behavior (Lebel et al., 2016).

The amygdala seems to be particularly sensitive to maternal stress, pregnancy-related anxiety and depression during pregnancy. Maternal stress during early pregnancy (Buss et al., 2012) as well as maternal depression during mid-gestation (Wen et al., 2017) were associated with an increased volume of the right amygdala during childhood in female offspring. In contrast, maternal pregnancy-related anxiety during the second half of pregnancy was associated with increased left amygdala volume in offspring of both genders during childhood (Acosta et al., 2019). Moreover, objective, but not subjective, stress during the second half of pregnancy was associated with increased amygdala volume at both sides in the female offspring during childhood (Jones et al., 2019). In another study examining only female offspring, stressful life events during the first 30 weeks of gestation were associated with decreased GM (but not total) volumes in the left and right amygdala (Favaro et al., 2015). The biological basis for the predominant effect on the right amygdala remains unclear. However, maternal emotional well-being is hypothesized to selectively affect neural structures that are implicated in the processing of negatively valenced emotional information and in the accompanying of stress responses (Abercrombie et al., 1998; Hamilton and Gotlib, 2008; Keller et al., 2008; Wen et al., 2017). Specifically, the activation of the right amygdala is associated with a negative attentional bias and is considered as an endophenotype for both anxiety and depression (Beck, 2008). Thus, particularly the right amygdala could be regarded as a neural origin for the transgenerational transmission of risk for mood disorders from mother to child (Wen et al., 2017). In line with this, the increased right amygdala volume was found to mediate the association between enhanced maternal cortisol levels during early gestation and affective problems in 6–9 year-old girls (Buss et

al., 2012) as well as between maternal stress during the 2nd trimester of gestation and externalizing problems in 11.5 year-old girls (Jones et al., 2019). Similarly, increased left amygdala volumes mediated in part the association between maternal anxiety and emotional and behavioral difficulties in 4 year-old girls (Acosta et al., 2019).

The volume of other brain structures was less affected by prenatal stress. Apart from the above mentioned widespread GM volume reductions, no effects of maternal stress, or anxiety during gestation were found on offspring hippocampal volumes at birth (Qiu et al., 2013), during childhood (Buss et al., 2012) or adulthood (Favaro et al., 2015). However, maternal trait anxiety during the 2nd trimester of gestation was associated with slower growth of both the left and right hippocampus over the first 6 months of life (Qiu et al., 2013).

Extending the examination of mere volume changes by inclusion of the analysis of WM microstructural organization, all but two studies (Jensen et al., 2018; Wen et al., 2017) showed an association between prenatal stress and establishment of the structural and functional network integrity. Maternal stress, trait anxiety and depression during the first half of pregnancy were mostly associated with decreased functional connectivity between the amygdala and subcortical regions (Graham et al., 2019; Rifkin-Graboi et al., 2013; Rifkin-Graboi et al., 2015; Scheinost et al., 2016; Soe et al., 2018) and increased functional connectivity between the amygdala and the cerebral cortex, in particular the prefrontal cortex (Favaro et al., 2015; Graham et al., 2019; Posner et al., 2016; Qiu et al., 2015a; Sarkar et al., 2014). The latter effects were distinct in female offspring (Graham et al., 2019; Soe et al., 2018). The underlying alterations in WM microstructural organization included regions and networks that are especially involved in the cognitive-emotional responses to stress, social-emotional functioning, sensory processing and major depressive disorder (Graham et al., 2019; Qiu et al., 2015a; Rifkin-Graboi et al., 2015; Sarkar et al., 2014), which is in line with the results reported for amygdala volume.

Taken together, maternal stress, pregnancy-related anxiety, and depression during pregnancy seem to primarily affect structural neurodevelopment of the amygdala and its connectivity. This effect remained evident far into adulthood and was predominantly shown in female offspring. Thereby, the amygdala and its connectivity seem to be vulnerable to prenatal stress over almost the entire pregnancy. Since the effects could be shown by all studies that examined the amygdala, results can be taken as being quite robust, although the total number of studies is relatively low. The studies suggested that a partial contribution of prenatal stress-induced neurodevelopmental structural abnormalities to the evolvement of cognitive and behavioral disorders is likely, but it has not yet been conclusively demonstrated. There was no clear relationship between the timing of maternal stress, anxiety and depression and the neurodevelopmental outcome in the offspring. Maternal anxiety and depressive symptoms were mostly scored at midgestation. However, it remains unclear to what extent these symptoms occurred during the remaining pregnancy. Hence, only studies examining external stressful events like natural disasters allow determining vulnerable periods during pregnancy. Only 7 out of the 26 studies examined the effects of such events, however, the results of these studies are not clear-cut. Some studies reported effects on offspring structural brain development only when prenatal stress occurred during early pregnancy (Buss et al.,

2012; Dancause et al., 2011), whereas other studies also reported effects on offspring structural brain development when maternal pregnancy-related anxiety or depression occurred during 2nd and early 3rd trimester of gestation (Acosta et al., 2019; Buss et al., 2010; Jones et al., 2019; Lebel et al., 2016; Sandman et al., 2015). Thus, there does not seem to be a specific vulnerable period for prenatal stress during gestation. Nevertheless, it is likely that the effects of prenatal stress on structural neurodevelopment vary, depending on the gestational age in a similar manner to the effects of neuro-cognitive functioning, cerebral processing and behavioral outcomes (van den Bergh et al., this issue) given the complex sequence of development of specific brain areas and functional systems.

Studies on the effects of prenatal malnutrition unfailingly reported consistent alterations in offspring brain morphology such as decreases in total, cortical, subcortical and cerebellar GM and WM volumes and smaller cortical surface area together with cortical thinning. These changes reflecting alteration of the trajectory of brain development are already detectable during late gestation and remain present until old age (Ars et al., 2019; Aukland et al., 2011; De Bie et al., 2011; de Rooij et al., 2016; Franke et al., 2018; Hulshoff Pol et al., 2000; Martinussen et al., 2005; Martinussen et al., 2009; Muller et al., 2014; Odberg et al., 2010; Ostgard et al., 2014; Qiu et al., 2012; Rogne et al., 2015; Schlotz et al., 2014; Walhovd et al., 2012). The most pronounced effects of prenatal malnutrition have been found in subjects who suffered from fetal growth restriction (Ostgard et al., 2014). However, effects of prenatal malnutrition on brain structure were shown to already occur within in the normal range of birth weight, thus highlighting the sensitivity of the developing brain to nutrient deficiencies. In addition, evidence from the Dutch famine birth cohort study shows that even severe maternal nutrient restriction during the 1st trimester of pregnancy is not necessarily associated with low weight or small body size at birth, but is still associated with neurostructural alterations at old age (de Rooij et al., 2016; Franke et al., 2018). In agreement with the studies in the Dutch famine birth cohort, studies in non-human primates have shown that a moderate global nutrient restriction of 30% during the first half of gestation already induces major disturbances of neuronal and glial proliferation, migration and neuronal network formation in the absence of an effect on fetal weight (Antonow-Schlorke 2011). Thus, maternal nutrient restriction during early pregnancy alters the trajectory of offspring structural brain development even though the energy-consuming brain growth spurt which mainly results from glial multiplication and myelination occurs during the 3rd trimester (Dobbing and Sands, 1979). However, no firm conclusion can be drawn, as the other human studies reviewed herein were not designed to identify gestational periods vulnerable for nutrient deficiencies.

The alterations of structural brain development and aging caused by nutrient restriction appear to correlate with neurobehavioral and cognitive outcomes in the offspring (Sanz-Cortes et al., 2014) during childhood (Qiu et al., 2012), adolescence (Martinussen et al., 2005; Martinussen et al., 2009; Rogne et al., 2015; Schlotz et al., 2014), adulthood (Eikenes et al., 2012; Odberg et al., 2010) and senescence (Muller et al., 2014). Similarly, alterations of brain structure due to prenatal stress or nutrient restriction were associated with behavioral disturbances in non-human primates (Keenan et al., 2013). These associations suggest that these structural brain changes mediate, at least in part, a link between prenatal stress or nutrient restriction and offspring cognitive, behavioral and emotional problems.

Although the number and sample size of human studies examining the association between nutrient restriction and alterations in structural neurodevelopmental aberrations in the offspring is limited, these studies are in agreement with experimental studies in several species from rodents to non-human primates. The experimental studies have convincingly demonstrated that even moderate nutrient restriction causes widespread disturbances of early organizational processes in the offspring's cerebral development at both macroscopic and microscopic levels, resulting in permanent impairment of brain structure (Antonow-Schlorke et al., 2011; Charil et al., 2010; Grantham-McGregor and Baker-Henningham, 2005; Keenan et al., 2013; Morgane et al., 1993; Muller et al., 2014; Olness, 2003; Rodriguez et al., 2012; Wainwright and Colombo, 2006; Walker et al., 2007). The agreement of data from human and experimental studies supports the validity of the limited human studies, however, the exact clinical implications of the experimental findings remain to be elucidated.

8. Limitations and future directions

Our systematic review includes and gives a comprehensive overview of all studies published so far on the effects of prenatal stress and nutrient restriction on offspring brain structure in humans. However, the database is limited and heterogeneous, resulting in a number of limitations that hamper the drawing of a complete picture on this issue. The study results have to be interpreted with caution as most of the studies summarized in our systematic review included rather small study groups, defined study effects through different measurements and often exhibited retrospective and correlational study designs. Nevertheless, the majority of studies reported lasting adverse effects of prenatal stress and nutritional insults. However, the results are difficult to compare since the nature, extent and timing of the prenatal stress and nutritional insults, the MRI measures and the specific neurostructures that were examined vary between studies. Although more and larger human studies are urgently needed as a base for the development of focused and effective measures of primary prevention, possibilities of study conduction are limited. Study MRI's are not allowed in infants and young children for ethical reasons in many countries. To overcome this regulation, MRI studies need to start at school age. To obtain well-founded results and limit the effects of confounders as much as possible, more prospective studies are required. However, prospective studies are very challenging, especially with respect to effects in adults and at older age due to the long life-span in humans.

Since plasticity is one of the major intrinsic properties of the brain, brain development is also prone to postnatal environmental influences. These include factors such as maternal care (e.g., an anxious or depressed mother may continue to be anxious or depressed post delivery), the socioeconomic status, presence of communicable and non-communicable diseases and others (Champagne and Meaney, 2001; Nguyen et al., 2015; Sharp et al., 2012; Zhang et al., 2013). Similarly, the trajectory of structural brain aging is dependent on individual life-style factors like smoking or a history of cerebrovascular diseases (de Rooij et al., 2016; Franke et al., 2018). Some studies did statistically control for the effects of potential pre- and postnatal confounding factors and still showed persistent effects of prenatal stress induced by maternal stress (Buss et al., 2010), depression (Lebel et al., 2016; Sandman et al., 2015) and anxiety (Buss et al., 2012; Qiu et al., 2013) on offspring brain structure during infancy and childhood including their behavioral correlates (Buss et al.,

2010; Lebel et al., 2016). Similarly, persistent effects of maternal nutrient restriction during pregnancy could be shown on offspring brain structure from childhood (Ars et al., 2019) until older age (de Rooij et al., 2016; Franke et al., 2018; Hulshoff Pol et al., 2000) after control for postnatal confounders.

Studying the effects of maternal stress is complicated by the fact that stress perception is subjective. Therefore, objectification of stress by repeated measurement of maternal cortisol levels such as in the studies by Buss et al. (2012) and Graham et al. (2019) or model studies on the effects of fetal exposure to maternal stress hormones are desirable. Here, fetuses therapeutically exposed to synthetic glucocorticoids to accelerate fetal lung maturation in threatened preterm delivery (Panel, 2001) may offer a good model when the mother does not undergo preterm delivery. However, it is important to note that the effects of glucocorticoids on the fetus may differ from the effects of maternal stress. Maternal stress is transferred from mother to fetus not only by the endogenous glucocorticoid cortisol but also by other mechanisms such as the catecholamine-mediated impairment of uterine blood supply (Rakers et al., this issue). Synthetic glucocorticoids easily cross the placenta whereas the placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) inactivates cortisol to a great extent (Rakers et al., this issue). Cortisol binds to both glucocorticoid receptors and mineralocorticoid receptors but synthetic glucocorticoids bind predominantly to glucocorticoid receptors (Kliwer et al., 1998). Glucocorticoid receptors are ubiquitously expressed in the brain while MR are mainly located in the limbic system (Ahima et al., 1991). Activation of glucocorticoid receptors produces neurotoxic and apoptosis-inducing effects (Hassan et al., 1996; Packan and Sapolsky, 1990) and activation of mineralocorticoid receptors induces neuroprotective effects (Hassan et al., 1996). Moreover, the biological potency of synthetic glucocorticoids is higher than that of cortisol (Yang et al., 1990).

Also, studying the effects of maternal stress and anxiety during pregnancy on offspring neurodevelopment is complicated by the fact that personality traits in mothers as well as in fathers are related to personality traits in the offspring, with heritability rates between 40–60% (Eaves et al., 1999; Jang et al., 1996; Plomin et al., 1994; Power and Pluess, 2015) as well as to brain morphological changes in amygdala and various cortical areas (Potvin et al., 2015). Additionally, maternal trait anxiety was found to be associated with both psychological and biological stress measures during pregnancy (Pluess et al., 2010). Thus, the observed neuroanatomical changes in the offspring may be mostly inherited from both parents and not (mainly) caused by the state in the mother. However, most studies on maternal stress or pregnancy-related anxiety included in our review neither reported data on maternal and paternal trait anxiety, nor on morphological changes in the parents. Therefore, future studies investigating effects of maternal stress during pregnancy and pregnancy-related anxiety on child development should include measures of maternal as well as paternal trait anxiety and preferably also on maternal as well as paternal neuroanatomy.

On the other hand, effects of nutritional deficiencies *in utero* on offspring neuroanatomy are less likely to be inherited, but most likely only the result of trait-independent or external influences. Studies on fetal nutrient restriction were mostly based on birth weight and did not consider the origin of decreased birth weight. Different causes of decreased birth weight such as maternal nutrient restriction, placental insufficiency, extreme maternal vomiting or

multiple fetuses (Baker et al., 2009; Beard et al., 2009; Raznahan et al., 2012; Roseboom et al., 2011; Zhang et al., 2015) may have different effects on brain development. Depending on the cause of the fetal malnutrition, maternal stress may additionally be present (Lillicrop and Burdge, 2011; Ramel and Georgieff, 2014; Tarry-Adkins and Ozanne, 2014), which may modulate the effects of nutrient restriction. In turn, prenatal stress may also decrease birth weight (Diego et al., 2006; Lang et al., 2003) and affect neurostructural development independently of the maternal nutritional status since stress hormones like cortisol and catecholamines inhibit cell proliferation and promote cell differentiation (Bassett and Hanson, 1998; Lemaire et al., 2000; Sorensen et al., 2011; Tauber et al., 2006). In addition, maternal stress induced release of catecholamines into the maternal circulation reduces uterine blood flow (for a review see Rakers et al., this issue).

Consequently, for a more comprehensive view on the subject, prospective studies are needed controlling for pre- and postnatal confounder such as the origin of fetal nutrient restriction as well as postnatal nutrition and stress. Studies need to include larger samples and be designed in a gender-specific manner. Studies in non-human primates may support human data in helping to overcome the problems of human studies: the long life-span, individual variations in maternal stress sensitivity, varying causes of fetal nutrient restriction, postnatal confounders and the regulations for MRI scans in children. In agreement with human studies, a first experimental study of moderate maternal nutrient reduction during gestation on individual brain aging in the baboon revealed premature brain aging in the female offspring between late adolescence and young adulthood, with this effect occurring in the absence of fetal growth restriction or marked maternal weight reduction at birth (Franke et al., 2017). On the mechanistic level, it is desirable to include neuropsychiatric measures on a hypothesis-driven base in order to obtain more mechanistic insights in the relationship between structural neurodevelopmental aberrations and behavioral and cognitive outcomes. Future work should further explore how genetic, epigenetic and environmental interactions mediate the lifelong effects of prenatal stress and nutrient restriction on structural brain development and aging in order to better understand the effects of the prenatal environment on mental health and brain aging.

To facilitate preventive interventions starting during pregnancy, early identification of subjects at risk is inevitable. Most changes in brain structure described in the reviewed studies are visible in routine MRI scans. Routine MRI scan derived scores may function as markers of prenatal stress or nutrient restriction and for the risk for cognitive and behavioral problems. Results derived from MRI-based data give rise to several new markers for determining individual brain structure, which can capture shared as well as marker-specific information on changes in brain architecture (Cherubini et al., 2016; Groves et al., 2012). Innovative MRI-based markers of structural brain development and aging such as the *BrainAGE* score are already available and need to be further developed as a predictive marker for cognitive and behavioral problems (Cole and Franke, 2017; Franke and Gaser, 2019). The *BrainAGE* score allows estimating the biological brain age compared to the numerical age in children and during aging. By detecting structural neurodevelopmental aberrations, it may have the potential to predict cognitive, behavioral or mental health problems following prenatal stress and nutrient restriction (Franke et al., 2018). For early

risk stratification, progress in fetal MRI development is desirable to facilitate preventive and interventional measures starting during pregnancy.

In conclusion, the current data from human studies supports the evidence from experimental studies that prenatal stress and nutrient restriction are associated with gender-specific disturbances in structural brain development. Effects are not limited to the extreme range of maternal stress, anxiety and depression, or reductions in birth weight, but already occur with relatively short periods of stress and modest decreases in birth weight. The majority of studies included in our systematic review suggest that aberrations in structural brain development result in lifelong alterations of brain morphology in the offspring and thus contribute to the risk for cognitive, behavioral and emotional problems following prenatal stress and nutrient restriction.

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Highlights

- Maternal stress, anxiety and depression change offspring structural brain development
- Maternal nutrient restriction and micronutrient deficiencies affect offspring brain structure
- Prenatal stress affects mainly the amygdala, malnutrition affects total brain volume
- Structural changes associate with cognitive, behavioral and mental health problems
- Routine MRI-based markers may have the potential to predict cognitive and behavioral problems

Table 1.

Prenatal stress and offspring neuroanatomical brain correlates

Study	Prenatal exposure / measure of maternal stress	Timing of exposure / measure	Offspring age [range]	Sample size	Offspring measure(s)	Main study findings
Effects of maternal psychological stress & stressful life events during pregnancy						
Lou et al., 1994	Stressful life events	30 weeks of gestation	0 days (at birth)	120	Head circumference	<ul style="list-style-type: none"> Stressful life events, in combination with the lack of a social network was a significant determinant of a 5% smaller head circumference at birth ($p<0.01$).
Obel et al., 2003	Stressful life events	30 weeks of gestation	0 days (at birth)	4,211	Head circumference	<ul style="list-style-type: none"> No association between stress experienced due to life events during pregnancy and head circumference in the neonatal offspring. No sex differences for the association between maternal stress and head circumference.
Tegethoff et al., 2010	Life stress	30 weeks of gestation	0 days (at birth)	78,017	Head circumference	<ul style="list-style-type: none"> Maternal life stress during pregnancy was positively associated with offspring head circumference at birth ($R^2=0.03$, $p<0.001$).
Dancause et al., 2011	Objective & subjective stress due to a natural disaster (Ice storm)	Exposure during 1 st , 2 nd , 3 rd trimester or before pregnancy	0 days (at birth)	172 [4 groups]	Head circumference	<ul style="list-style-type: none"> Subjective maternal stress in early pregnancy was negatively associated with offspring head circumference ($R^2=0.02$, $p<0.05$). Objective maternal stress in early pregnancy was positively associated with offspring head circumference ($R^2=0.01$, $p<0.05$). Higher subjective maternal stress levels predicted smaller head circumference relative to birth length in male, but not in female, offspring ($R^2=0.02$, $p<0.05$).
Scheinost et al., 2016	Life stress	Documentation during pregnancy	36 – 40 weeks post-menstrual age	26 (born 25 – 28 weeks of gestation)	rs-fMRI	<ul style="list-style-type: none"> In preterm-born neonates, prenatal stress exposure was negatively associated with left amygdala connectivity to the brainstem, fusiform, hypothalamus, and thalamus ($p<0.05$; controlling for gestational age at birth and birth weight).
Graham et al., 2019	Maternal cortisol levels	Early, mid, late pregnancy	3.6 ± 1.7 weeks	70	rs-fMRI	<ul style="list-style-type: none"> In female offspring, maternal cortisol during gestation was positively associated with right and left amygdala connectivity to cortical brain regions, but negatively with the right amygdala–dorsolateral prefrontal cortex and left amygdala–fusiform gyrus connectivity. In male offspring, maternal cortisol during gestation was negatively associated with right and left amygdala connectivity to cortical brain regions, but positively with the right amygdala–dorsolateral prefrontal cortex and left amygdala–fusiform gyrus connectivity. In girls only, maternal cortisol was positively associated with internalizing symptoms, with this association being mediated by stronger neonatal amygdala connectivity.
Sarkar et al., 2014	Stressful life events	17 months after birth	7 ± 1 years [6 – 9]	22	DTI (D_{perp} ; FA); uncinate fasciculus	<ul style="list-style-type: none"> Maternal prenatal stressful life events were positively correlated with offspring right uncinate fasciculus FA ($r=0.48$; $p=0.02$). Maternal prenatal stressful life events were negatively correlated with offspring right uncinate fasciculus D_{perp} ($r=-0.45$; $p=0.04$). Trend for stronger effect of prenatal stress in females for right uncinate fasciculus FA ($p>0.10$) and D_{perp} ($p>0.10$). Maternal postnatal depression or postnatal stressful life events had no effects on DTI measures in the uncinate fasciculus.

Study	Prenatal exposure / measure of maternal stress	Timing of exposure / measure	Offspring age [range]	Sample size	Offspring measure(s)	Main study findings
Buss et al., 2012	Maternal cortisol levels	15, 19, 25, 31, 37 weeks of gestation	7.5 ± 0.9 years [6 – 9]	65	MRI (amygdala, hippocampus volumes)	<ul style="list-style-type: none"> In female offspring, maternal cortisol in earlier (at 15 weeks only) gestation was positively associated with right amygdala volume ($p=0.02$; a 1 SD increase in cortisol was associated with a 6.4% increase in right amygdala volume), independent of the effects of potential confounding pre- and postnatal factors (incl. maternal depressive symptoms at the time of the offspring assessment). In male offspring, no association was found between maternal cortisol and left amygdala, right or left hippocampus volume. In male offspring, no association was found between maternal cortisol and left or right amygdala volume, left or right hippocampus volume. Only in female offspring, maternal cortisol in early gestation was positively associated with affective problems, with this association being mediated by the right amygdala volume.
Jones et al., 2019	Objective & subjective stress due to a natural disaster (ice storm)	Exposure during 1 st , 2 nd , 3 rd trimester or before pregnancy	11.5 years	68 [4 groups]	MRI (amygdala volume)	<ul style="list-style-type: none"> In male offspring, subjective maternal distress due to exposure to natural disaster during 2nd half of pregnancy was positively associated with right normalized amygdala volume, with this effect diminishing when adjusting for postnatal factors. In female offspring, subjective maternal distress due to exposure to natural disaster during 2nd half of pregnancy was positively associated with right as well as left normalized amygdala volume, even after adjusting for postnatal factors. Only in female offspring, increased externalizing problems were mediated by larger right and left normalized amygdala volume.
Jensen et al., 2018	Stressful life events	18 weeks of gestation	19.6 ± 1.8 years [18 – 21]	393 (only male)	DTI (FA, MD), MTR, MWF	<ul style="list-style-type: none"> Prenatal stress was associated with lower MTR and MWF in the genu and splenium of the corpus callosum, and with lower MTR in global (lobar) WM. No associations between prenatal stress during early gestation and FA or MD.
Favaro et al., 2015	Stressful life events	Retrospective interview & medical documentation	25.6 ± 6.5 years [15 – 40]	35 (only female)	MRI (whole brain, amygdala, hippocampus volumes), rs-fMRI	<ul style="list-style-type: none"> Prenatal stress was negatively associated with GM volume in the left medial temporal lobe, left and right amygdala (controlling for age, postnatal stress, maternal smoking, obstetric complications), but neither with hippocampus GM volume, nor with total amygdala or hippocampus volumes. Prenatal stress exposure was positively associated with functional connectivity between the left medial-orbitofrontal cortex and the rostral part of the pre-genual anterior cingulate cortex (controlling for age, handedness, postnatal stress, obstetric complications, maternal smoking). Amygdalae GM volumes as well as GM volume in left medial temporal lobe was negatively correlated to depressive symptoms and trait, but not state anxiety in the offspring. Functional connectivity of the left medial-orbitofrontal cortex with part of the left medial orbito-frontal cortex was positively correlated with depressive symptoms in the offspring.
Effects of maternal anxiety during pregnancy						
Field et al., 2003	Trait anxiety (STAI)	23 weeks of gestation [18 – 24]	23 weeks of gestation [18 – 24]	132	Fetal head circumference	<ul style="list-style-type: none"> No differences between low vs. high maternal trait anxiety in head circumference of fetuses during 2nd trimester of pregnancy.
Qui et al., 2013	Trait anxiety (STAI)	26 – 28 weeks of gestation, 3 months after delivery	5 – 17 days (follow-up: 6 months)	175 (follow-up: 35)	MRI (hippocampal volume)	<ul style="list-style-type: none"> No effect of maternal trait anxiety during pregnancy on bilateral hippocampal volume at birth. Maternal anxiety did not vary as a function of offspring gender and no gender

Study	Prenatal exposure / measure of maternal stress	Timing of exposure / measure	Offspring age [range]	Sample size	Offspring measure(s)	Main study findings
						<p>differences were found in bilateral hippocampal volumes at birth, nor at 6 months follow-up.</p> <ul style="list-style-type: none"> • Slower growth of both the left and right hippocampus over the first 6 months of life in offspring of mothers with increased anxiety during pregnancy. • Effect for right hippocampal growth got stronger, whereas effect for left hippocampal growth diminished, when controlling for postnatal maternal anxiety.
Qui et al., 2015b	Trait anxiety (STAI)	26 – 28 weeks of gestation	5 – 17 days	146	MRI (cortical thickness)	<ul style="list-style-type: none"> • No main effects of antenatal maternal anxiety on offspring cortical thickness after adjusting for confounding variables.
Rifkin-Graboi et al., 2015	Trait anxiety (STAI)	26 – 28 weeks of gestation	5 – 17 days	54	DTI (FA)	<ul style="list-style-type: none"> • Maternal trait anxiety during 2nd trimester of gestation predicted variations in offspring in FA of regions important to cognitive-emotional responses to stress (i.e., the right insula and dorsolateral prefrontal cortex), sensory processing (e.g., right middle occipital), and socio-emotional function (e.g., the right angular gyrus, uncinate fasciculus, posterior cingulate, and parahippocampus).
Acosta et al., 2019	Anxiety (PRAQ)	24 & 34 weeks of gestation	4 years	27	MRI (amygdala volume)	<ul style="list-style-type: none"> • Pregnancy-related anxiety in 3rd trimester was positively associated with offspring normalized volume of the left amygdala ($p<0.05$; controlled for maternal pre- and postnatal depressive symptoms and postnatal anxiety). • Pregnancy-related anxiety in 2nd trimester was related to larger relative volume of the left amygdala in female compared to male offspring. • Left amygdala volume was negatively associated with behavioral difficulties.
Buss et al., 2010	Anxiety (pregnancy-related)	19, 25, 31 weeks	7.5 ± 0.9 years [6 – 9]	35	MRI (volumetrics)	<ul style="list-style-type: none"> • Maternal anxiety in week 19 of gestation was negatively associated with offspring GM volume in prefrontal cortex, premotor cortex, medial temporal lobe, lateral temporal cortex, postcentral gyrus, cerebellum, middle occipital gyrus, fusiform gyrus (controlling for postnatal maternal stress). • No associations were found between maternal anxiety in weeks 25 or 31 of gestation and regional GM volume.
Effects of maternal depression during pregnancy						
Rifkin-Graboi et al., 2013	Depression (EDPS)	26 – 28 weeks of gestation	6 – 14 days	157	MRI (amygdala volume); DTI (FA, AD)	<ul style="list-style-type: none"> • Prenatal EDPS scores were negatively associated with offspring FA ($p=0.009$) and AD ($p=0.0028$) in right amygdala, only trends for left amygdala (FA: $p=0.041$; AD: $p=0.084$). • No association between maternal EDPS scores and offspring amygdala volumes (right: $p=0.99$, left: $p=0.49$). • No gender effect for interaction between maternal EDPS and amygdala volume, FA, or AD.
Posner et al., 2016	Depression	34 – 37 weeks of gestation	5.8 ± 1.7 weeks	64	rs-fMRI, DTI	<ul style="list-style-type: none"> • Prenatal depression was negatively associated with offspring structural connectivity between the right amygdala and right ventral prefrontal cortex. • In the prenatal depression group, greater inverse (i.e. negative) functional connectivity in the offspring were found between the right amygdala and a large cluster spanning the mid-cingulate cortex and dorsal prefrontal cortex across the left and right hemispheres ($p<0.001$) as well as between the left amygdala and a large cluster within the dorsal prefrontal cortex spanning the left and right hemispheres ($p<0.02$). • There were no regions in which infants in the prenatal depression group showed reduced inverse functional connectivity. • No group differences were detected in positive functional connectivity. • Greater offspring fetal heart rate reactivity in response to a mild stressor

Study	Prenatal exposure / measure of maternal stress	Timing of exposure / measure	Offspring age [range]	Sample size	Offspring measure(s)	Main study findings
						positively correlated with prenatal maternal depression as well as with inverse functional connectivity between the left amygdala and the dorsal prefrontal cortex ($p=0.001$) and excitatory influence from the amygdala to the ventral prefrontal cortex ($p=0.0004$). • The left amygdala–dorsal prefrontal cortex functional connectivity mediated the effect of maternal depression on fetal heart rate reactivity in response to a mild stressor (indirect effect, $p=0.007$).
Qui et al., 2015a	Depression (EDPS)	26 – 28 weeks of gestation, 3 months after delivery	6 months	24	rs-fMRI	• Prenatal EDPS scores were positively associated with offspring functional connectivity of the left amygdala with bilateral medial prefrontal cortex, ACC, medial orbitofrontal cortex, ventromedial prefrontal cortex, left insula, left superior, middle and temporal cortex, left entorhinal cortex (controlled for postnatal EDPS scores, offspring sex, birth weight, household income). • Only maternal 2 nd trimester EPDS scores negatively correlated with offspring cortical thickness in right inferior frontal and middle temporal regions during early childhood (controlled for postpartum EPDS). • Correlation between 2 nd trimester maternal EDPS and cortical thickness in the right middle temporal area was weaker in male ($r=-0.55$; $p<0.01$) than in female ($r=-0.80$; $p<0.001$) offspring. • Only before correction for postpartum EPDS, maternal 2 nd trimester EPDS scores negatively correlated with offspring MD and RD in WM emanating from the inferior frontal area.
Lebel et al., 2016	Depression (EDPS)	1 st , 2 nd , 3 rd trimester, 3 months after delivery	3.6 ± 0.5 years [2.6 – 5.1]	52	MRI (cortical thickness); DTI (AD, MD, RD)	• Only in female offspring, greater prenatal maternal depressive symptoms were associated with larger right amygdala volume, also after adjusting for postnatal maternal depressive symptoms. • Prenatal maternal depressive symptoms were not associated with right or left amygdala FA values in the female offspring. • In the male sample, there were no significant effects of prenatal maternal depressive symptoms on the amygdala volume and microstructure.
Wen et al., 2017	Depression (EDPS, BDI)	26 – 28 weeks of gestation, 3 months (EDPS); 1, 2, 3, 4, 5 years after delivery (BDI)	4.5 years	235	MRI (amygdala volume); DTI (FA)	• Only in female offspring, prenatal maternal depressive symptoms were negatively associated with the functional connectivity between the amygdala and the cortico-striatal circuitry, especially the orbito-frontal cortex, insula, subgenual anterior cingulate, temporal pole, striatum. • Only in female offspring, greater pre- than post-natal depressive symptoms were associated with lower functional connectivity of the left amygdala with the bilateral subgenual anterior cingulate and left caudate as well as with lower functional connectivity of the right amygdala with the left orbito-frontal cortex, insula, temporal pole.
Soe et al., 2017	Depression (EDPS, BDI)	26 – 28 weeks of gestation, 3 months (EDPS); 1, 2, 3, 4, 5 years after delivery (BDI)	4.5 years	128	rs-fMRI	• Prenatal depression was negatively associated with offspring cortical thickness in the right frontal lobes ($p<0.01$; corrected for gestational age at birth, age of the child, sex, handedness, birth outcomes, current maternal depression). • Maternal depression especially at 25 gestational weeks was associated with offspring cortical thinning in 19% of the whole cortex and 24% of the frontal lobes ($p<0.01$; controlling for gestational age at birth, age of the child, sex, handedness, birth outcomes, current maternal depression). • Cortical thinning in right prefrontal areas mediated the effect of maternal depression on offspring externalizing behavior.
Sandman et al., 2015	Depression (CESD, BDI)	19, 25, 31 weeks of gestation (CESD); time of offspring MRI scan (BDI)	7.2 ± 0.8 years [6 – 9]	81	MRI (cortical thickness)	

Study	Prenatal exposure / measure of maternal stress	Timing of exposure / measure	Offspring age [range]	Sample size	Offspring measure(s)	Main study findings
El Marroun et al., 2016	Maternal & paternal depression (BSI)	21 weeks of gestation, 3 years after delivery	7.9 ± 1.0 years [6 – 9]	654	MRI (volumetrics, cortical thickness, surface area, gyrification)	<ul style="list-style-type: none"> • Prenatal depression was negatively associated with offspring cortical thickness in the left superiorfrontal cortex. • Prenatal depression was positively associated with offspring left caudal middle frontal area.
Mechanisms mediating the effects of prenatal stress on structural brain development						
Chen et al., 2015	Trait anxiety (STAI)	26 – 28 weeks of gestation	5 – 17 days	237	MRI (volumetrics); DNA methylation assay	<ul style="list-style-type: none"> • Offspring BDNF genotype (Val66Met) strongly influenced the association of antenatal anxiety on the neonatal epigenome as well as between the epigenome and neonatal brain structure. • Antenatal maternal anxiety had a greater impact on offspring DNA methylation with Met/Met compared to both Met/Val and Val/Val genotypes. • More cytosine–phosphate–guanine sites covaried with right amygdala volume in Met/Met carriers. • More cytosine–phosphate–guanine sites covaried with left hippocampus volume in Val/Val carriers.
Qui et al., 2015b	Trait anxiety (STAI)	26 – 28 weeks of gestation	5 – 17 days	146	MRI (cortical thickness); SNP genotyping	<ul style="list-style-type: none"> • Association between antenatal maternal anxiety and neonatal cortical thickness was modulated by COMT genotypes in different brain regions. • Associations between antenatal maternal anxiety and neonatal cortical thickness were modulated by the rs737865-<i>val158met</i>-rs165599 haplotypes, with A-Val-G (AGG) modulating positive associations in right ventrolateral prefrontal and right superior parietal cortex and precuneus, and G-Met-A (GAA) modulating negative associations in bilateral precentral gyrus and dorsolateral prefrontal cortex.

AD: axial diffusivity; BDI: Beck Depression Inventory; BDNF: brain-derived neurotrophic factor; BSI: Brief Symptom Inventory; CBCL: Child Behavior Checklist; CESD: Center for Epidemiological Studies Depression Scale; COMT: catechol-O-methyltransferase; Dperp: perpendicular diffusivity; DTI: diffusion tensor imaging; EDPS: Edinburgh Postnatal Depression Scale; FA: fractional anisotropy; MD: mean diffusivity; Met: methionine; MRI: magnetic resonance imaging; MTR: magnetization transfer ratio; MWF: myelin water fraction; POMS: Profile of Mood States Anger Scale; PRAQ: pregnancy-related anxiety questionnaire; SD: standard deviation; SNP: single-nucleotide polymorphism; STAI: Spielberger Trait Anxiety Inventory; RD: radial diffusivity; rs-fMRI: resting-state functional MRI;

Table 2.

Maternal malnutrition and offspring neuroanatomical brain correlates

Reference	Indicator of fetal (mal-)nutrition	Age at MRI	Sample size	Measure of interest	Main study results
Associations between direct evidence of maternal malnutrition during gestation and neurostructural development					
Ars et al., 2016	Prenatal maternal folate, total homocysteine, vitamin B12 levels	6 – 8 years	256	Structural MRI: whole brain volumetry	<ul style="list-style-type: none"> Maternal folate insufficiency in early pregnancy was positively associated with offspring TBV (controlling for offspring sex, age at MRI scan, breast-feeding status at 6 months, maternal age at study enrollment, smoking during pregnancy, pre-pregnancy BMI, maternal education level). Neither prenatal plasma B12 nor homocysteine levels predicted any brain volume outcomes.
Hulshoff Pol et al., 2000	Schizophrenia patients & HC with / without exposure to famine in 1 st trimester of gestation	51 years	36 [4 groups]	Structural MRI: whole brain volumetry	<ul style="list-style-type: none"> Decreased ICV in only patients with schizophrenia with exposure to Dutch famine in 1st trimester of gestation. Increased brain abnormalities, predominantly WM hyperintensities, in all participants prenatally exposed to Dutch famine during 1st trimester of gestation.
de Rooij et al., 2016	Exposure to famine in 1 st trimester of gestation vs. no exposure	68 years	118 [2 groups]	Structural MRI: whole brain volumetry	<ul style="list-style-type: none"> Smaller ICV and TBV only in male offspring at age 68 years, who had been exposed to the famine in early gestation (controlling for age at MRI scan, head circumference at birth and at age 68).
Franke et al., 2018	Exposure to famine in 1 st trimester of gestation vs. no exposure	68 years	118 [2 groups]	Structural MRI: BrainAGE	<ul style="list-style-type: none"> Advanced brain aging by about 4 years only in male offspring at age 68 years, who had been exposed to the famine in early gestation.
Associations between nutrition-related birth measures and neurostructural development: Birth weight within the normal range					
Qiu et al., 2012	Birth weight [2500 – 4630 g], Gestational age [37 – 41 weeks]	6 years	157 (boys)	Structural MRI: caudate	<ul style="list-style-type: none"> Birth weight was positively associated with TBV. Interactive effects of birth weight and gestational age predicted caudate volume (corrected for TBV), with lower birth weight and shorter gestation being associated with smaller caudate volumes.
Walhovd et al., 2012	Birth weight [mean: 3450 g]	6 – 21 years	628	Structural MRI: whole brain, regional volumes, surface area	<ul style="list-style-type: none"> Birth weight was positively associated with regional cortical surface area in multiple regions as well as TBV and caudate volumes (controlling for age at MRI scan, sex, household income, and genetic ancestry factors).
Schlott et al., 2014	Birth weight (at term) [2400 – 4500 g]	16 years	27	Structural MRI: regional volumes, cortical thickness, surface area	<ul style="list-style-type: none"> Birth weight was positively associated with surface area of lateral and medial orbitofrontal cortex, right inferior frontal gyrus, as well as caudate volume (controlling for maternal smoking, alcohol consumption, parity, social class). Birth weight was negatively associated with cortical thickness in medial orbitofrontal cortex (controlling for maternal smoking, alcohol consumption, parity, social class). Birth weight positively affected behavioral inhibitory control indirectly via caudate volume.
Muller et al., 2014	PI	75 years	1254	Structural MRI: whole brain volumetry	<ul style="list-style-type: none"> PI was positively associated with TBV, CSF, and WM volumes (corrected for ICV; controlling for late-life lifestyle and cardiovascular risk factors).
Associations between nutrition-related birth measures and neurostructural development: Length in relation to gestational age					

Reference	Indicator of fetal (mal-)nutrition	Age at MRI	Sample size	Measure of interest	Main study results
Sanz-Cortes et al., 2010	Fetal growth: SGA vs. AGA	Pregnancy (37 weeks of gestation)	13 [2 groups]	<i>In utero</i> DWI: regional ADC	<ul style="list-style-type: none"> • In SGA fetuses, ADC levels in the pyramidal tract were increased by about 12%. • A trend towards higher ADC values in SGA fetuses was observed in the frontal lobe (5.7%), occipital lobe (3.3%), and corpus callosum (5.5%). • No effects for ADC values in the basal ganglia.
Sanz-Cortes et al., 2014	Fetal growth: SGA vs. AGA	Pregnancy (37 weeks of gestation)	98 [2 groups]	<i>In utero</i> MRI: brain stem & cerebellum	<ul style="list-style-type: none"> • Larger brain stem and cerebellum volumes in SGA (controlling for maternal smoking, neonatal sex, and gestational age at MRI). • In SGA, increased brain stem and cerebellum volumes were correlated with neurobehavioral outcomes.
De Bie et al., 2011	Fetal growth: SGA vs. AGA	4 – 7 years	55 [2 groups]	Structural MRI: whole brain, regional volumes, cortical thickness, surface area	<ul style="list-style-type: none"> • Reduced cerebral and cerebellar GM and WM volumes, smaller volumes of subcortical structures in SGA-born children (controlling for age at MRI scan). • Reduced cortical surface area as well as regional differences in prefrontal cortical thickness in SGA-born children (controlling for age at MRI scan). • Bodily catch-up growth in SGA children did not implicate full brain catch-up growth.
Vangberg et al., 2006	Fetal growth: SGA, HC	15 years	123 [2 groups]	DTI: regional FA	<ul style="list-style-type: none"> • No effects for FA.
Martinussen et al., 2005	Fetal growth: SGA, HC	15 years	107 [2 groups]	Structural MRI: whole brain, cortical thickness, surface area	<ul style="list-style-type: none"> • Lower total cortical surface area in SGA. • Lower TBV in SGA. • No effects for cortical GM volume. • Regional thinning of the parietal, temporal and occipital lobes, as well as regional thickening in the frontal and occipital lobes in SGA. • No associations between surface area and cortical volume with IQ in SGA.
Martinussen et al., 2009	Fetal growth: SGA, HC	15 years	107 [2 groups]	Structural MRI: whole brain & regional volumes	<ul style="list-style-type: none"> • Smaller TBV, and proportionally smaller regional brain volumes in SGA (controlling for age at MRI scan and sex). • In SGA, positive associations between hippocampus volume with TBV and verbal IQ; cerebral WM with verbal IQ; cerebral cortex volume with VMI motor scores. • In HC, positive associations between cerebral cortical volume with all IQ measures; hippocampus volume with total IQ and total VMI scores; thalamus volume with VMI visual perception scores.
Rogne et al., 2015	Fetal growth: SGA (incl. fetal growth restriction, 13), HC	15 years	188 [2 groups]	Structural MRI: regional volumes	<ul style="list-style-type: none"> • Smaller thalamic and cerebellar WM volumes only in SGA with fetal growth restriction, as evidenced by frequent ultrasounds in 25 – 37 weeks of gestation (adjusting for ICV; controlling for age at MRI scan and sex).
Ostgard et al., 2014	Fetal growth: SGA (incl. fetal growth restriction, 5), HC	20 years	108 [2 groups]	Structural MRI: whole brain, regional volumes, cortical thickness, surface area	<ul style="list-style-type: none"> • Smaller putamen volume in SGA (controlling for age at MRI scan and sex). • Regional reductions in cortical surface area, particularly in the frontal, parietal, and temporal lobes, in SGA (controlling for age at MRI scan and sex). • Pronounced reduction of cortical surface area, TBV, cerebral WM, caudate nucleus, and putamen volumes in SGA group with fetal growth restriction (controlling for age at MRI scan and sex). • No associations between brain measures and IQ.
Eikenes et al., 2012	Fetal growth: SGA, HC	18 – 22 years	103 [2 groups]	DTI: regional FA	<ul style="list-style-type: none"> • Reduced FA in ventral association tracts and internal/external capsules in SGA. • FA did not relate to intrauterine head growth in the 3rd trimester in SGA. • FA was positively correlated to brain growth in the 3rd trimester and maternal smoking in SGA.

Reference	Indicator of fetal (mal-)nutrition	Age at MRI	Sample size	Measure of interest	Main study results
Associations between nutrition-related birth measures and neurostructural development: Low birth weight					
Vangberg et al., 2006	Fetal growth: very LBW [1500 g], HC	15 years	123 [2 groups]	DTI: regional FA	<ul style="list-style-type: none"> • Very LBW was associated with reduced FA in several WM regions, including corpus callosum, internal capsule, and superior fasciculus.
Martinussen et al., 2005	Fetal growth: very LBW [1500 g], HC	15 years	108 [2 groups]	Structural MRI: whole brain & volumetry, cortical thickness	<ul style="list-style-type: none"> • Very LBW was associated with lower total cortical surface area. • Very LBW was associated with lower TBV and cortical GM volume. • Very LBW was associated with lower regional cortical thickness in the parietal, temporal and occipital lobes, as well as with greater regional cortical thickness in the frontal and occipital lobes. • Areas of change were greatest in those with shortest gestational age at birth and very LBW. • In very LBW, surface area and cortical volume were positively associated with IQ.
Martinussen et al., 2009	Fetal growth: very LBW [1500 g], HC	15 years	108 [2 groups]	Structural MRI: whole brain & regional volumes	<ul style="list-style-type: none"> • Very LBW was associated with lower volumes for thalamus and cerebellar WM (controlling for age at MRI scan and sex). • In very LBW, positive associations were found between: cerebellar WM and hippocampus volumes with total and performance IQ; cerebellar WM volume with total VMI and VMI visual perception scores; thalamus volume with total VMI scores. • In HC, positive associations were found between: cerebral cortical volume with all IQ measures; hippocampus volume with total IQ and VMI scores; thalamus volume with VMI visual perception scores.
Odberg et al., 2010	Fetal growth: LBW [2000 g], HC	19 years	213 [2 groups]	Structural MRI: regional volumes, cortical thickness	<ul style="list-style-type: none"> • LBW was associated with volume loss in WM and prominent lateral ventricles (controlling for sex, prenatal, perinatal, and early postnatal data). • LBW was associated with thinning of the corpus callosum (controlling for sex, prenatal, perinatal, and early postnatal data).
Aukland et al., 2011	Fetal growth: LBW [2000 g], HC	19 years	213 [2 groups]	Structural MRI: corpus callosum	<ul style="list-style-type: none"> • LBW was associated with smaller size of corpus callosum (uncorrected). • After adjusting for forebrain volume, only the reduction of the posterior third subregion of the corpus callosum remained significant. • A significant main effect of sex indicated a larger overall callosal area in males, but no interaction effect was observed.

ADC: apparent diffusion coefficient; AGA: appropriate growth for gestational age; CSF: cerebro-spinal fluid; DTI: diffusion tensor imaging; DWI: diffusion- weighted imaging; FA: fractional anisotropy; GM: gray matter; HC: healthy controls; ICF: intra-cranial volume; IQ: intelligence quotient; LBW: low birth weight (2000 g); MRI: magnetic resonance imaging; PI: ponderal index : SGA: small for gestational age; TBV: total brain volume; VMI: visual-motor integration; WM: white matter