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Prenatal developmental origins of behavior and mental health:

the influence of maternal stress in pregnancy

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Highlights

- Maternal psychological distress, life event stress, and objective exposure affect offspring outcome.
- Functional and structural brain changes underlie the problems observed in the offspring.
- Alterations in stress system, immune system, and gut microbiome play a significant role.
- Epigenetic and telomere biology mechanisms are beginning to be explored.
- Interventions focused on offspring also need to be guided by knowledge of changes in biological systems.

Abstract

Accumulating research shows that prenatal exposure to maternal stress increases the risk for behavioral and mental health problems later in life. This review systematically analyzes the available human studies to identify harmful stressors, vulnerable periods during pregnancy, specificities in the outcome and biological correlates of the relation between maternal stress and offspring outcome. Effects of maternal stress on offspring neurodevelopment, cognitive development, negative affectivity, difficult temperament and psychiatric disorders are shown in numerous epidemiological and case-control studies. Offspring of both sexes are susceptible to prenatal stress but effects differ. There is not any specific vulnerable period of gestation; prenatal stress effects vary for different gestational ages possibly depending on the developmental stage of specific brain areas and circuits, stress system and immune system. Biological correlates in the prenatally stressed offspring are aberrations in neurodevelopment, neurocognitive function, cerebral processing, functional and structural brain connectivity involving amygdalae and

(pre)frontal cortex, changes in hypothalamo-pituitary-adrenal (HPA)-axis and autonomous nervous system.

Keywords: Fetal programming; maternal psychological distress; life events; disaster exposure; objective stress; anxiety; pregnancy-specific anxiety; depression; autism; attention deficit hyperactivity disorder (ADHD); schizophrenia; psychiatric disorders; telomere biology; epigenetics; gut microbiome; cortisol; HPA-axis; heart rate variability; autonomic nervous system

"The burden of mental disorders continues to grow with significant impacts on health and major social, human rights and economic consequences in all countries of the world."
World Health Organization (2016)

CONTENT

1. Introduction

1.1. The Developmental Origins of Health and Disease (DOHAD) hypothesis

Characteristics of the early environment, starting in utero or even before, can represent major risk factors for a lifetime of physical and mental health problems for the individual (Gluckman et al., 2008; Hanson and Gluckman, 2011; Seckl and Holmes, 2007; Van den Bergh, 2011). The 'fetal programming hypothesis' (Seckl and Holmes, 2007), the 'developmental programming hypothesis' (Barker, 2004; Langley-Evans, 2006; Langley-Evans, 2015), and the 'Developmental Origins of Health and Disease (DOHaD) hypothesis' (Barker, 2004; Barker, 1990) specifically state that, during critical or sensitive periods of development, a disturbance in environmental factors, such as exposure to nutrient restriction, exposure to glucocorticoids or synthetic glucocorticoids, has an organizational effect on biological systems with a long development and/or intrinsic plasticity to react and adapt to environmental influences. These systems include the central nervous system (CNS), autonomic nervous system (ANS), neuro-endocrine (hypothalamic-pituitary-adrenal (HPA) axis), cardiovascular, and immune systems (Bale, 2015; Bale et al., 2010; Griffiths and Hunter, 2014; Harris and Seckl, 2011; Meaney et al., 2007; Räikkönen et al., 2011; Seckl, 2004; Stroud et al., 2016; Stroud et al., 2014). Their plasticity is highest during early development when the organ systems are still immature (Bock et al., 2014; Faulk and Dolinoy, 2011). Following exposure to prenatal challenges, induced changes, such as an altered set-point in HPA-axis, changes in glucocorticoid receptor sensitivity,

changes in proteins and neurotransmitters involved in neuronal development and function in the CNS (Matthews, 2000, 2002; Schwab et al., 2001; Wyrwoll and Holmes, 2012), will enhance susceptibility to somatic diseases and mental health problems which, in interaction with genetic liabilities and postnatal challenges, will determine ultimate health status. Indeed, over the past 30 years, in addition to extensive experimental animal studies, human studies have gathered robust epidemiological and mechanistic data showing that the most powerful early environmental factors capable of influencing offspring development and health in later life are prenatal stressors, including maternal stress, malnutrition and maternal immune-related factors. Among the first observations were that a lower birth weight - taken as a proxy measure of prenatal exposure to environmental adversity - is a risk factor for the development of cardiovascular and metabolic diseases such as arterial hypertension, coronary heart disease, obesity, and type 2 diabetes (Barker, 1990; Barker, 1995; Barker and Osmond, 1986), as well as mental health problems such as depression (Gale and Martyn, 2004; Thompson et al., 2001) and schizophrenia (Hack et al., 2004; Rifkin et al., 1994). Although much less examined, accumulating evidence mostly gathered during the last decade, is showing how maternal psychological distress, as well as stress from exposure to life events and natural disasters during pregnancy, gives rise to behavior and mental health problems.

1.2. Objectives and study selection criteria

The general aim of our review article is to gain a better understanding of the relationships between maternal stress during pregnancy and behavioral and mental health problems in later life in humans. This review, which is restricted to human studies, has the following objectives:

(1) *To summarize the results of longitudinal prospective studies on the associations between prenatal stress and the development of* behavioral and mental health problems *in the offspring (section 2.1).*

Outcomes in the *behavioral domain* identified are the following: neurodevelopment (including state-regulation, sleep problems, neurobehavioral maturity and motor development), cognitive development, and temperament; together, these could be seen as a cluster of cognitive, behavioral and affective self-regulation factors. The '*mental health'* domain includes outcomes identified as: anxiety, depression (often combined into 'internalizing problems'), bipolar disorder, posttraumatic stress disorder (PTSD); aggressive behavior, conduct disorder (often combined into 'externalizing problems'); impaired social behavior; eating disorders; autism and autism spectrum disorders (ASD); attention deficit hyperactivity disorder (ADHD); borderline personality; suicides and suicide attempts; schizophrenia and psychosis.

Within each of the sections 2.1.1 to 2.1.4, we organize the results according to the kinds of maternal stress to which the offspring in the studies were exposed: (i) 'maternal psychological distress', which includes general or pregnancy-specific anxiety, and depressive symptoms; (ii) major life events experienced by the mother (such as illnesses or deaths in the close family, financial and relationship problems, house moves, car accident, etc.); and (iii) exposure to a disaster (maternal hardship due to a natural disaster) and the subjective distress and cognitive appraisal related to it. The vast research literature on 'proximal risk or adversity', e.g. focusing on or including effects of drug and alcohol abuse in pregnancy is not reviewed in our paper.

(2) *To identify the biological correlates of maternal stress in the offspring that were studied in humans; we describe the findings of the studies by biological system (section 2.2 to 2.4).* The

identified biological correlates are: (i) functional brain correlates (neurocognitive function; cerebral processing; functional brain connectivity) (section 2.2), (ii) HPA-axis function (cortisol reactivity and basal cortisol) (section 2.3), (iii) ANS-function (fetal autonomic function including heart rate (HR), heart rate variability (HRV); and postnatal autonomic function, e.g. indexed by vagal tone as measured by respiratory sinus arrhythmia (RSA) (section 2.4).

(3) *To identify the biological systems that undergo changes in their developmental trajectory which may underlie the behavioral and mental health problems observed, and to describe the available evidence that these biological systems reveal underlying mechanisms (section 3).* The identified biological systems are: (i) the stress system (3.1), (ii) immune system (3.2), (iii) gut microbiome (3.3), and (iv) telomere biology (3.4).

(4) To reach a general conclusion (section 4).

For this review, we chose to include studies in Section 2.1 that met the following criteria: (1) prospective and longitudinal; (2) published between 2010 and early 2017; (3) quasi-experimental, epidemiological or clinical (but not an intervention) design. A search was performed of electronic databases (MEDLINE, Web of Sciences, PsychINFO and Google Scholar) through 2016. The electronic search was based on the following concepts ; (1) terms related to maternal stress during pregnancy (e.g., stress, anxiety, pregnancy anxiety, depression, life events, bereavement, exposure, natural disaster; and (2) terms related to offspring behavior and mental health outcomes (e.g., neurodevelopment, state-regulation, motor development, cognitive development, neurocognition, temperament, negative affectivity, extraversion, orienting/regulation, effortful control, difficult temperament, mental health, mental disorders,

psychopathology, psychiatric problems). We did not take into account studies that had only birth outcome (e.g., weight, length or head circumference at birth, or premature birth).

Because there are few prospective studies of biological correlates and biological systems that reveal clues as to the underlying mechanisms effecting offspring prenatally exposed to maternal stress, we also included retrospective studies and studies published before 2010 in section 2.2 and section 3. The terms related to biological correlates include: neurocognitive function, cerebral processing; functional brain connectivity; HPA-axis, cortisol reactivity, basal cortisol; ANS-function, heart rate, heart rate variability, alpha-amylase dyspnea. The terms related to biological systems include: stress system, immune system, gut microbiome and telomere biology. The search was complemented by hand-searches of the references from relevant reviews and from direct communications with research groups.

Figure 1 gives a schematic representation of the variables and study designs of the studies reviewed in section 2, i.e., as the relationship between three blocks (blocks (1)(2)(3)) of variables. Most of the studies reviewed examine the relation between (1) maternal stress and (3) offspring behavior or mental health (see section 2.1); some studies examine the link between (1) maternal stress and (2) offspring biological correlates (see section 2.2 to 2.4); and a few studies examine the links between (1) maternal stress, (2) biological correlates and (3) offspring behavior or mental health problems in one design (results of the latter studies are integrated in sections 2.1 to 2.4).

In section 3 it is explained how changes in biological systems - such as the stress system, immune system, gut microbiome and telomere biology - may explain the links described in section 2 and represented in Figure 1, and the available evidence is summarized.

2. Maternal stress during pregnancy, offspring behavior and mental health, and their biological correlates in the offspring: an overview of the research literature since 2010

Pregnancy is seen as a major event in any woman's life and the transition to parenthood involves major challenges in not only the psychological domain, but also in the biological, familial and social domains (Jones et al., 2014; Raphael-Leff, 1991). If during pregnancy major life events (such as the death of a relative, or exposure to a natural disaster) occur and/or the woman has difficulties in attaining a balance between personal, family-related and employment-related issues, pregnancy may become a stress-inducing period, especially in anxiety- or depression-prone, susceptible women (Graignic-Philippe et al., 2014). The estimation of the percentage of woman experiencing stress during pregnancy varies widely. For instance, in studies using clinical diagnostic tools, 8–12% of pregnant women meet criteria for a mental disorder during pregnancy, commonly an anxiety or mood disorder (Fisher et al., 2012; Howard et al., 2015; Melville et al., 2010). This percentage is likely to be an underestimation of women experiencing psychological distress. For instance, in a recent, large-scale community study using standardized self-report scales about 30% of pregnant women reported some type of stress in their daily lives, including job strain, anxiety symptoms or depressive symptoms (Loomans et al., 2013). In fact, most of the studies in this research field use standardized self-report scales to measure psychological distress. Apart from these studies, an additional series of studies have assessed the effects of major life events that mothers are exposed to during pregnancy on child behavior and mental health, while still other studies use objective exposure measures such as a natural disaster (e.g., an ice storm,Walder et al., 2014) or other population tragedies. The latter studies control for the objective severity of exposure to a stressor before determining the effect of the pregnant woman's perceived (subjective) stress (Brock et al., 2014; King et al., 2015; Laplante et al.,

2004) . These events have sudden onsets which allow the researcher to more accurately link the timing of the stressor to vulnerable periods in fetal development. Also, when exposure to the stressor is "independent" of the mother's influence (e.g., death of a relative, natural disaster) this approach allows the researcher to disentangle the effects of the objective degree of exposure (e.g., the degree of loss, change, threat) from maternal cognitive appraisal or subjective distress from the event.

Since it is important to give clear, unambiguous information about the type of stress measured in human prenatal stress studies (Graignic-Philippe et al., 2014; O'Donnell and Meaney, 2016), we include the name of the self-report or life event scales used and reported, or of the disaster exposed to, for studies reviewed in Tables 1-4 (cf. section 2.1) and Tables 5-7 (cf. section 2.2).

2.1. Neurodevelopment, cognitive development, temperament and mental health in offspring prenatally exposed to maternal stress

In infancy, the measurement of early regulatory behaviors is important, since they are the earliest signs of behavioral and neuropsychiatric problems (Räikkönen et al., 2015). Like other aspects of development in infant, child and adolescent, such as cognition, motor and social development, regulatory behaviors can be measured with standardized behavioral or observation scales, cognitive tests and parent-report questionnaires at any age, or with self-report questionnaires starting from the age of 8-9 years. Temperament forms the biological basis of personality. Temperament traits describe individual differences in emotional reactivity and self-regulation. Both poorer cognitive development (Koenen et al., 2009) and individual differences in temperament traits (Caspi et al., 1996; Gartstein et al., 2012) have been shown to predict risk of later psychopathology.

We mainly focus our review on the effects of prenatal stress on offspring behavior and mental health as studied using epidemiological, clinical and quasi-experimental studies published from 2010 onwards; we refer the reader to our previous publications (Räikkönen et al., 2011; Van den Bergh et al., 2005b) for a detailed overview of studies published before 2010. Study characteristics and results of prospective studies published since our previous review (Räikkönen et al., 2011) are described in Table 1 (aspects of neurodevelopment), Table 2 (cognitive development) Table 3 (temperament) and Table 4 (mental health). The text mainly focuses on general findings and, when feasible, on comparing them with those of studies published before 2010.

Methodological caveats of the earlier studies, such as shared method variance inflating the associations in studies using maternal reports of offspring outcomes, have been addressed more thoroughly in the more recent publications reviewed here. Importantly, almost all recent studies have more carefully examined whether maternal stress after pregnancy mediates or moderates the effects of maternal stress during pregnancy on offspring outcome. Other possible confounding factors, including maternal substance use during pregnancy, education level and maternal IQ, as well as infant birth weight and gestation length, and even blood level (Lin et al., 2017) have been adjusted for in analyses more consistently. When not described otherwise, the results given are always controlled for these latter covariates.

Additional methodological improvements include the fact that the sample sizes of many studies have become larger, and follow-ups longer, in recent publications; this observation will be illustrated with specific examples in section 2.1.4. While studies have often been conducted in relatively small samples due to the requirements of face-to-face infant neurodevelopmental and neuro-psychological testing, several large-scale studies have been conducted; these latter studies

make use of standardized parent-report questionnaires. The large-scale studies vary considerably in the number of mother infant-pairs they include, ranging between 500 and 1500 mother-infant pairs (Chong et al., 2016; Glasheen et al., 2013; Li et al., 2013; McMahon et al., 2013; Pickles et al., 2016; Pluess et al., 2011; Rijlaarsdam et al., 2016; Stroustrup et al., 2016; Whitehouse et al., 2010), between 1500 and 3500 pairs (Betts et al., 2015; Grace et al., 2016; Leis et al., 2014; Robinson et al., 2011; Ronald et al., 2011; Tearne et al., 2015; Van Batenburg-Eddes et al., 2013; Zhu et al., 2015), and between 3500 and 10.000 pairs (Betts et al., 2014; Braithwaite et al., 2013; Capron et al., 2015; Cents et al., 2013; Evans et al., 2012; Loomans et al., 2012; Pearson et al., 2013; Rai et al., 2012; Winsper et al., 2015). The registry studies (see Table 4) all included more than 10.000 subjects (Abel et al., 2014; Bekkhus et al., 2011; Class et al., 2014; Kingsbury et al., 2016; Li et al., 2010), with the biggest samples including up to 5 million cases (Su et al., 2015).

2.1.1. Neurodevelopment: state-regulation and motor development – *See Table 1*

Effects of maternal psychological distress and major life events. Negative effects of maternal depression in pregnancy were seen on state-regulation and sleep problems (Gerardin et al, 2011; Pacheco & Figueirido, 2012; Räikkönen et al., 2015), autonomic stability and neurobehavioral maturity (Figueiredo et al., 2017; Pacheco & Figueiredo, 2012) in the neonate. In the study of Gerardin et al. (2011), negative effects were especially seen in boys, also on motor skills. Motor development as measured with the Bayley scales was not significantly affected at 18 months of age (Koutra et al., 2013), while Lin et al. (2017), using the Gesell Developmental scale, found a negative effect on gross, and a marginally significant effect ($p = .051$) for fine motor skills, at 24-36 months.

Effects of maternal disaster exposure. Prenatal stress exposure predicted child motor development in the Australian QF2011 Queensland Flood Study. At 2 months of age, there was a

small but significant positive correlation between the degree of maternal exposure to the flood (rated from objective measures of threat, loss, scope and change) and infant gross motor skills. This positive effect was short-lived, however. At later ages, although maternal subjective stress measures (PTS symptoms, peritraumatic distress and dissociation from the flood) had no effect, greater maternal objective exposure predicted worse maternal-reported gross and fine motor functioning at ages 6 and 16 months, particularly if flood exposure occurred later in pregnancy, and if mothers appraised the flood as a negative experience (Simcock et al., 2016a). However, mothers' subjective stress (especially PTS symptoms) had a negative effect on the child's fine motor skills measured with the Bayley scales at age 16 months, particularly when exposure occurred later than 26 weeks gestation (Moss et al., 2017). Similarly, for infants whose mothers were exposed to the flood in later gestation, maternal cognitive appraisal of the flood as a negative, or very negative, experience for her and her family was also associated with worse gross motor skills (Moss et al., 2017). These stress-by-timing results replicate those from Project Ice Storm at age 5½ years; for instance, higher objective exposure to the ice storm in Quebec, Canada, predicted poorer bilateral coordination and visual motor integration particularly with exposure in late pregnancy (Cao et al., 2014). Similarly, in the Raine study, increased maternal stressful life events during pregnancy, particularly after the 18th gestation week, predicted poorer motor development scores in the offspring at ages 10, 14 and 17 years, independently of socio-demographic and prenatal covariates (Grace et al., 2016).

2.1.2 Cognitive development – *See Table 2*

Effects of maternal psychological distress and major life events. A recent aggregate-data meta-analysis summed up previous study findings among > 5000 children (Tarabulsy et al., 2014), including one study with 3139 (Henrichs et al., 2011) and one with 1714 subjects (Slykerman et

al., 2005). In studies using a prospective design, there was a very modest (*r*=-0.05), but statistically significant, negative correlation between prenatal stress and child cognitive outcomes, such as with word comprehension and nonverbal cognitive development in the study of Henrichs et al. (2011). The effect size was stronger for maternal life events (r = -0.31) than for subjective pregnancy-related stress or anxiety (r = -0.08) or non-pregnancy-related stress (r = -0.02) (Tarabulsy et al., 2014). All studies on the association between maternal psychological distress and infant cognition reviewed below (Table 2) were not yet included in the review of Tarabulsy et al. (2014).

Maternal depression and anxiety are shown to be related to neonate cognition as measured with a mother versus stranger's face/voice visual preference paradigm (Figuierido et al, 2010; the effects of maternal depression were not moderated nor mediated by mother's depression at childbirth (Pacheco & Figuieiredo, 2012).

In addition to prenatal stress, there is some evidence that the unborn child is sensitive to any "mismatch" between prenatal and postnatal maternal mood. Sandman et al. (2012) found that 3-, 6- and 12-month-old infants thrive best, at least on dimensions of critical psychomotor and mental development, when their prenatal and postnatal environments are congruent, that is, when maternal depression was either high or low on both occasions; their development appears to be compromised when maternal mood is not congruent on both occasions.

Two recent studies using observer-rated developmental tasks found a significant negative association between maternal psychological distress and cognitive development even after correction for covariates such as socio-economic class or maternal psychological distress in the postnatal period in infancy (Koutra et al., 2013) and toddlerhood (Schechter et al., 2016). However, in two studies that not only included statistical control of parental socioeconomic

status and household income but also included maternal IQ as a covariate, maternal psychological distress during pregnancy was only marginally predictive of language development at ages 2 to 3 years (p = .060; Lin et al., 2017) or had no significant association with child IQ at ages 3 to 6 years (Nulman et al., 2012a). In the ALSPAC study, maternal depression during pregnancy predicted lower IQ at age 8 years (Evans et al., 2012), while maternal anxiety during pregnancy predicted poorer working memory (but not attention control or selective attention skills) at age 8 as well as lower school grades in math (but not language) (Pearson et al., 2016). In the Raine study, maternal stressful life events during pregnancy were not associated with vocabulary development (Whitehouse et al., 2010), but they predicted other school achievements in a sex-specific way at age 10 years: in girls they found improved reading ability, and no effect on spelling, writing or mathematics; in boys they found improved reading, math abilities and writing scores (Li et al., 2013).

Effects of maternal disaster exposure. The QF2011 study found main effects of maternal objective exposure from the flood on problem-solving scores in 6-month-old infants (Simcock et al., 2016b) as well as a subjective stress x child sex interaction effect: at high levels of maternal subjective stress girls had significantly lower scores than boys, whereas no sex differences were evident at lower maternal stress levels. At 16 months of age, the objective degree of maternal exposure to the flood predicted lower cognitive scores on the Bayley scales, especially when the flood occurred at 30 weeks or later in pregnancy (Moss et al., 2017). Project Ice Storm found similar results across childhood (King et al., 2012). Both IQ scores and vocabulary scores from face-to-face evaluations at ages 2, 5, 8 and 11 years were significantly associated with the objective severity of maternal exposure to the disaster, with no additional effect from maternal distress. At age 11 years, sex moderated the effect: in boys, there was a linear decline in IQ with

increasing maternal objective exposure, while in girls there was no longer an effect of prenatal stress. For language, there was the same association with objective exposure at ages 5 and 8 years; however, at age 11, the results for boys remained while for girls at that age there was a positive association with maternal objective exposure.

2.1.3 Temperament – *See Table 3*

*Effects of maternal psychological distress and major life events***.** As can be seen in Table 3, most studies examining temperament use parent-report questionnaires to measure outcome behavior, while only some studies use behavioral observation scales (Braeken et al., 2013; Hill et al., 2013; Lin et al., 2014; Rothenberger et al., 2011b; Werner et al., 2013). Most studies continue their follow-up until the age of six months, while some studies continue he follow-up study until 10 months (Braeken et al., 2013; Peltola et al., 2017; van den Heuvel et al., 2015b), 24 months (Blair et al., 2011; Stroustrup et al., 2016) or 36 months (Bekkhus et al., 2011; Lin et al., 2017; Stroustrup et al., 2016).

As was seen in earlier studies (Räikkönen et al., 2011) and regardless of the kind of measurement of temperament or its timing, most evidence points to associations between prenatal stress and high scores on two partially overlapping temperament traits: namely, negative affectivity (sadness, distress to limitations, fear, discomfort, and anger) (Blair et al., 2011; Braithwaite et al., 2013; Green et al., 2016; Hill et al., 2013; Huynh, 2014; Lin et al., 2014; Nomura et al., 2014; Peltola et al., 2017; Pluess et al., 2011; Rouse and Goodman, 2014; van den Heuvel et al., 2015b; Zande and Sebre, 2014) and "difficult temperament" (negative affectivity, intense reactions, slowness in adapting to new situations and irregular routines; Chong et al., 2016; Della Vedova, 2014; Green et al., 2016; Lin et al., 2017; McMahon et al., 2013; Rode and Kiel, 2016; Stroustrup et al., 2016). In a very large-scale study (Bekkhus et al., 2011), child's

crying behavior and aggressive behavior were highest if the mother showed high anxiety and depression both during and after pregnancy, while maternal symptoms that lasted during pregnancy only were not associated with child aggressive or crying behavior at age 3 years. Some studies confirm a previous observation (DiPietro et al., 2006) of a positive association between maternal distress in pregnancy and better infant self-regulation (i.e., duration of orientation; Kantonen et al., 2015; Lin et al., 2014), less infant affective reactivity (Rothenberger et al., 2011b), and/or observed that maternal distress is associated with infant positive affectivity (Lin et al., 2014; Nomura et al., 2014; van den Heuvel et al., 2015b) and better social behavior (Lin et al., 2017). However, some studies found no associations between maternal distress during pregnancy and either self-regulation/adaptive functioning (Braeken et al., 2017; Zande and Sebre, 2014) or positive affectivity (Zande and Sebre, 2014) or other aspects of infant temperament (Baibazarova et al., 2013b; Bhat et al., 2015). Three studies reported in Table 3 also included maternal salivary cortisol in pregnancy as a measure of prenatal stress (Rothenberger et al., 2011b; Rouse and Goodman, 2014; Werner et al., 2013) but only the latter found an association: higher maternal cortisol predicted higher infant reactivity.

Some studies have investigated associations between a positive prenatal environment and infant temperament. Social support does not always have a positive effect (see Van den Bergh et al., 2005b), and has been shown to be unrelated to infant temperament in one study (Zande and Sebre, 2014). However support from the partner is shown to have a positive effect on infant temperament (Stapleton et al., 2012), but has seldom been measured. In comparison with studies conducted before 2010, new findings from two studies (both conducted the same sample) found a significant positive association between a positive maternal trait, (i.e., mindfulness) and

adaptive functioning (Braeken et al., 2017) in 4 month olds and higher self-regulation (van den Heuvel et al., 2015b) and in 10 month old infants.

Effects of maternal disaster exposure. Project Ice Storm results show that having had more severe exposure to the ice storm (greater loss or change, for example), more illnesses (e.g., flu, fever), and/or more symptoms of PTSD in the 1st trimester predicted more difficult temperament and needing attention at age 6 months (Laplante et al., 2016). From QF2011, higher levels of objective flood exposure predicted more irritable temperament in boys (but not girls), more arrhythmic temperament (when exposure was early in pregnancy), and more active-reactive temperament (when subjective stress was very high) (Simcock et al., 2017). Furthermore, QF2011 infants had lower scores on a social-emotional scale the later in pregnancy they were exposed, and the more severe their mothers' objective exposure (Simcock et al., 2017).

2.1.4. Mental health – See Table 4

As written in the introduction of section 2.1, designs of the studies and their statistical methods have improved in recent studies. We illustrate some of these improvements here: (1) While most studies have used self-report symptom scales to assess psychological distress in the pregnant mothers, significant associations have also been found in the few studies where the mother has been diagnosed with a mental disorder (Gerardin et al., 2011; Pawlby et al., 2011; Plant et al., 2013; Plant et al., 2015); (2) Social support and maternal coping style are taken into account as variables that potentially can buffer the negative effects of life event stress (Zhu et al., 2015); (3) Family functioning, reported by mother and father, are measured as predictors or moderators (Velders et al., 2011); (4) Offspring eating disorders are being identified as offspring outcome measures (Su et al., 2015); (5) Some gene-by-environment studies find no moderating effect (e.g. of the serotonin transporter genotype; Braithwaite et al., 2013) while other studies do find

moderating effects of, for example, the Brain-Derived Neurotrophic Factor (BDNF) genotype (O'Donnell et al., 2014b), and the glucocorticoid receptor gene at rs41423247 (Velders et al., 2012); (6) Instead of merely statistically controlling for the influence of obvious covariates (as was already done in many studies published before 2010), some recent studies explicitly examine the effect on the offspring of maternal stress and: (i) the moderating effects of postnatal maternal distress and caring behavior, such as stroking the infant (Pickles et al., 2016; Sharp et al., 2015); (ii) additive effects of variables such as maternal childhood maltreatment (Plant et al., 2015) or offspring exposure to childhood maltreatment (Pawlby et al., 2011); (7) Mediating effects are increasingly examined. As examples of moderating, maternal depressive symptoms after pregnancy and maternal sensitivity towards the child (Edwards and Hans, 2016; Grant et al., 2010) , maternal positive discipline (Kok et al., 2013a) and maternal maltreatment (Plant et al., 2015), are mediators of effects of maternal depression during pregnancy on offspring outcome.

Although mounting evidence from both, small-scale and large-scale population studies corroborate the results from earlier studies on the associations between maternal stress in pregnancy and mental health problems in the offspring, the effects of psychological distress on attention, emotional, behavioral (e.g. externalizing problems) outcomes are not always confirmed in large-scale studies, as we will see.

Effects of maternal psychological distress. Maternal distress predicts behavioral problems in the first 10 years of life, such as externalizing, attention and aggressive behavior problems (Gerardin et al., 2011; Leis et al., 2014; Loomans et al., 2012; Pickles et al., 2016), anxious/depressed behavior and emotional problems, internalizing or anxiety problems (Davis and Sandman, 2012; Gerardin et al., 2011; Loomans et al., 2012), social behavior problems (Loomans et al., 2012), autistic traits (Rijlaarsdam et al., 2016), and total conduct

problems or psychiatric problems (Loomans et al., 2012; Nulman et al., 2012b). However, maternal depressive symptoms were not associated with attention problems (Van Batenburg-Eddes et al., 2013) nor with emotional or behavioral problems (Van Batenburg-Eddes et al., 2013; Velders et al., 2011) in 3-year-old offspring. Similarly, in the Wiral Child Health and Development Study, maternal general anxiety during pregnancy was no longer significantly associated with child psychiatric problems after adjustment for maternal concurrent mood (Pickles et al., 2016). In studies that include both maternal cortisol and psychological distress measures, some found that each measure was associated with anxiety problems in childhood independently (Davis and Sandman, 2012), while others found an independent effect only of maternal cortisol in pregnancy on child psychiatric problems (Isaksson et al., 2015). Cents et al. (2013) found that persistent high depressive symptoms during and after pregnancy predict high levels of internalizing and externalizing problems in 3-year-olds, while Glasheen et al. (2013) observed that boys of mothers with high pre- and postnatal anxiety had more conduct disorders at age 16, while girls of such mothers had lower risk of conduct disorders. Buss et al. (2012), measuring only cortisol in pregnancy, found associations between higher cortisol levels in earlier but not later gestation and higher risk of affective problems in girls.

Prospective studies with a long-term follow-up confirm that effects may last until at least early adulthood. Indeed, in the ALSPAC study, maternal distress in pregnancy predicted mother-rated attention and emotional problems in 4-year-old offspring (Van Batenburg-Eddes et al., 2013), child internalizing, externalizing and total behavior problems between the ages of 4 and 13 years (Braithwaite et al., 2013; O'Donnell et al., 2014a; O'Donnell et al., 2014b), risk of borderline personality disorder at age 11 years (Winsper et al., 2015), internalizing symptoms at age 15 years (O'Donnell et al., 2014b), and anxiety and depressive disorders at age 18 years

(Capron et al., 2015; Pearson et al., 2013). In the Mater University Study of Pregnancy (MUSP), maternal psychological distress during pregnancy predicted higher offspring self-rated internalizing - but not externalizing - problems at 14 years (Betts et al., 2014), and internalizing, externalizing and total psychiatric problems at age 21 years (Betts et al., 2015). Korhonen et al. (2014) found that high depression in pregnancy was associated with offspring externalizing – but not internalizing – problems at age 16. Fineberg et al. (2016) observed that more daily stress during pregnancy was associated with increased risk of schizophrenia in male offspring in adulthood.

Two large scale community studies suggest that more consistent effects of maternal stress during pregnancy are found when using mother-rated, rather than teacher-rated, child psychiatric problems, namely in the Amsterdam Born Children and their Development (ABCD) study (Loomans et al., 2011) and the ALSPAC study (Leis et al., 2014). The much smaller number of teacher- than mother-ratings of child problems may, at least partially, explain the discrepant findings (Leis et al., 2014).

Effects of major life events. In the Australian Raine study, more mother-rated attention-deficit hyperactivity disorder (ADHD) symptoms and - in boys only - also more autism symptoms in 2-year-old offspring (Ronald et al., 2011) as well as higher internalizing, externalizing, and total psychiatric problems in the offspring across ages 2 to 14 years (Robinson et al., 2011; Tearne et al., 2015) were found. In a Chinese study, increased parent-reported ADHD symptoms in 4-year-old children (Zhu et al., 2015) were observed. In the UK ALSPAC study higher offspring self-reported depressive symptoms were consistently found from ages 10 to 18 years (Kingsbury et al., 2016).

Effect of major life events: registry studies. While studies assessing the effects of the number of stressful life events during pregnancy lack specificity of event(s), registry studies have provided evidence on the effects of one specific stressor during pregnancy, namely, exposure to maternal bereavement. A cross-cohort study comprising Swedish participants with register-data (death, injury, accidents or life-threatening illnesses of close relatives), and those in ALSPAC with maternal self-reported data on stressful life events during pregnancy, did not find effects on offspring risk of autism in childhood or adolescence (Rai et al., 2012). In contrast, in the largest registry study available, from Sweden, maternal bereavement during pregnancy did predict increased offspring risk of autism spectrum disorders (Class et al., 2014). Bereavement occurring specifically during the 3rd trimester also predicted higher ADHD risk in the offspring. No significant effects were found on bipolar disorder, schizophrenia, suicides or suicide attempts (Class et al., 2014), or on affective or non-affective psychotic disorders (Abel et al., 2014). In a Swedish-Danish registry study, although bereavement exposure during pregnancy showed a non-significant association with the risk of eating disorders in the offspring before 3 years of age, when the death of a close relative of the mother occurred during the six months before conception there was a >1.5-fold significant increase in risk for eating disorders in the children (Su et al., 2015). In a Danish registry study, bereavement during pregnancy predicted increased ADHD risk in boys followed up from age 3 years onwards until young adulthood, while no significant associations were found among girls (Li et al., 2010).

Effects of maternal disaster exposure. Using a natural disaster as the stressor in a prospective design, Project Ice Storm has shown moderate effects of maternal objective exposure, but especially of maternal subjective distress from the storm, even controlling for the objective degree of exposure, on maternal ratings of internalizing and externalizing problems in

the children at ages 4, 5, 6, 8, 9 and 11 years (King et al., 2012). Project Ice Storm has also demonstrated that the severity of maternal objective exposure to the disaster and subjective stress explain similar amounts of variance in the severity of autistic-like traits in the children at age 6 years; as well, the effect of objective exposure was greatest when the ice storm happened during the first trimester (Walder et al., 2014). More severe eating disorder symptoms in the Project Ice Storm children at age 13 were associated with third trimester exposure to the disaster, in combination with more severe objective exposure to the storm (St-Hilaire et al., 2015). These results suggest the possibility that much of the effect of an independent stressor, as seen in the population registry studies, may be in large measure due to the objective degree of exposure experienced as a function of the death of a relative and not solely due to maternal distress in bereavement.

2.1.5. Conclusion and implications

We have reviewed here recent research – published, in press, or already online and available between 2010 and 2016 - on the effects of maternal psychological distress, life event stress and disaster exposure stress during pregnancy on offspring behavior (including neonatal state-regulation, sleeping, neurobehavioral maturation and infant and child motor development, cognitive development and temperament) and mental health problems from numerous epidemiological and some behavioral, clinical and quasi-experimental studies. With regard to neurodevelopmental outcomes, the effects of maternal stress exposure on motor development are clear. Since 2010, only very few studies have examined the effects of maternal psychological distress on state-regulation in the neonate, neurobehavioral maturation or on motor development; the new evidence here adds to the evidence of studies published before 2010 (section 2.1.1). The available evidence favors an interpretation that maternal stress negatively predicts child

cognitive development, but requires further replication (section 2.1.2); studies using brain imaging measures (see below; section 2.2) should be seen as complementary evidence. Evidence from both, small scale and large-scale studies have provided evidence that maternal psychological distress and exposure to life event and natural disasters predicts negative affectivity and difficult temperament characteristics in the offspring. More studies on effects on offspring extraversion-and effortful-control-related temperament characteristics are needed (section 2.1.3). Although most studies show that psychological distress, life events stress and objective stress exposure during pregnancy are associated with increased risk of psychiatric problems and diagnosed mental health disorders in the offspring, some studies however do not confirm these results. The significant effects are evident whether offspring psychopathology is evaluated via maternal or self-reports, diagnostic interviews or register-derived diagnoses. However, associations with teacher-reported child psychiatric problems are less consistent which could imply that rater's bias plays a role.

Future studies should determine the extent to which partner support of the pregnant mother, and positive family functioning might protect the woman and her unborn child against stress during pregnancy, since these variables have been addressed in only a small number of studies (Capron et al., 2015; Kok et al., 2013b; O'Donnell et al., 2014a; Pearson et al., 2013; Van Batenburg-Eddes et al., 2013; Velders et al., 2012; Velders et al., 2011). Some studies have found gender effects, but results have been inconsistent, with some studies suggesting that boys are more vulnerable to the effects of maternal stress during pregnancy (Fineberg et al., 2016; Gerardin et al., 2011; Glasheen et al., 2013; Li et al., 2010; Loomans et al., 2011; Zhu et al., 2015), while others have found girls to be more vulnerable, particularly for emotional problems (Buss et al., 2012). It is important to keep in mind that the patterns of effects of different kinds of

prenatal stress, timed at different times in gestation, for different outcomes, may differ, as is the case in animals and in programming of physical health problems (Hanamsagar and Bilbo, 2016). Throughout this review, we have noted several studies that have found critical periods in gestation that are vulnerable to the effects of prenatal stress; in fact, the entire length of gestation represents a series of critical periods that are each vulnerable for one or more offspring outcomes, since different functions and structures of the brain are developing in each period. Future studies are warranted that will further clarify what the differential effects of the different critical periods are, as most existing studies have measures of pregnancy stress available only once or twice during arbitrary time-points during pregnancy; the disaster exposure studies, and the registry studies, however, are able to provide greater fine tuning to the questions of timing in pregnancy. Future studies should also further clarify if any of the associations are differentially related to either the degree or duration of stress experienced, or the type of stress experienced (i.e., subjective stress, general or pregnancy-related anxiety, depressive symptoms, life events, stress exposure), whether maternal stress after pregnancy mediates and/or moderates the prenatal effects, and if other factors (including genetic vulnerability, offspring sex, and parenting and paternal factors) play a role in these associations. Furthermore, more consistency should be reached in the measures of maternal distress during pregnancy, as well as in offspring outcome measures. For the latter, the NIH toolbox, a comprehensive set of neurobehavioral measures to assess cognition, emotion, motor and sensation (e.g., Zelazo et al., 2013), could be used.

2.2. Functional brain correlates in offspring prenatally exposed to maternal stress

Knowledge of functional and structural alterations of the brain that may explain the behavioral and mental health problems in offspring that were prenatally exposed to maternal distress comes mainly from animal research (e.g., Adrover et al., 2015; Bock et al., 2014; Bock et al., 2015;

Charil et al., 2010; Pallarés et al., 2013a; Pallarés et al., 2013b). For instance, with regard to brain development, preclinical studies revealed convincing evidence for the fact that prenatal stress (or early postnatal stress in rodents, a time-period which parallels the prenatal period in humans): (i) affects neuronal and synaptic development – changes most often studied in the limbic system (hippocampus, amygdala) and prefrontal cortex- and alters the excitatory-inhibitory balance of cortical neurons; (ii) induces epigenetic changes which (re)program brain structural and functional organization and behavioral development; (iii) programs large-scale neuronal networks, or brain network connectivity, e.g. in the cortico-limbic circuitry; (iv) have effects that are dependent on the time window, duration and intensity of the stressor; (v) are associated with offspring sex-specific cognitive and behavioral changes (Bock et al., 2014; Singh-Taylor et al., 2015).

However, animal studies cannot reflect the complex behavioral and mental health problems experienced by humans entirely and, consequently, the underlying functional and structural correlates. Thus, studies using batteries of neurocognitive tasks (section 2.2.1) as well as studies examining cerebral processing (section 2.2.2) and functional brain connectivity (2.2.3) were conducted in several prospective studies and in two retrospective studies (Schwabe et al., 2012; Soe et al., 2016); they reveal the functional brain correlates of behavioral and mental health problems in human offspring who were prenatally exposed to maternal distress. Studies design and results of these studies are summarized in Table 5 (neurocognitive function), Table 6 (cerebral processing) and Table 7 (functional connectivity).

2.2.1. Neurocognitive function (computerized tasks) – see Table 5

Some studies have investigated the impact of prenatal exposure to maternal stress on brain function with the use of computerized neurocognitive tasks measuring inhibition, sustained

attention, and other executive functions. Using a battery of neurocognitive tasks enables researchers to specify which functions are altered and which ones remained intact. In the first study using such a battery to examine offspring effects of maternal psychological distress during pregnancy, it was found that 15-year-old adolescents prenatally exposed to high levels of maternal anxiety reacted more impulsively in a task measuring divided attention, but did not differ from the control group in a 'Stop' task assessing response inhibition (Van den Bergh et al., 2005a) ; these adolescents - but only the males - also showed more decline in performance on a continuous performance task, indicating sustained attention difficulties (Van den Bergh et al., 2006). From these results it was concluded that the cognitive problems of adolescents whose mothers were highly anxious at 12-22 weeks of pregnancy seem to be related to problems with endogenous cognitive control, that is, when behavior must be internally regulated without the help of external cues. This interpretation was supported in assessments two years later; when the same sample was examined at the age of 17 years with five well-established cognitive tasks, they performed selectively lower in the task requiring endogenous cognitive control, but not in the task requiring exogenous cognitive control (Mennes et al., 2006). At both ages, effects were found for maternal anxiety between weeks 12 and 22 of pregnancy, but not for weeks 23–31 or 32–40 weeks of pregnancy.

More recently, Plamondon et al. (2015) showed that maternal stressful life events in the third trimester of pregnancy predicted poorer spatial working memory in 4-year-olds, but only for boys who experienced poorer postnatal care; the boys who had received high levels of maternal care in toddlerhood seemed to be protected from the negative effects of maternal stress during pregnancy on spatial working memory. However, these effects on spatial working memory only held for maternal life events, and not for maternal anxiety during pregnancy.

Loomans et al. (2012) examined the effect of maternal anxiety during early pregnancy on neurocognitive functioning in 5-year-olds in a large community cohort (N = 922) and found that prenatal maternal anxiety was associated with higher intra-individual variability in children's reaction time (RT) in a simple reaction time task; in a subtest of 100 women with anxiety scores in the 90th percentile, the association was only significant for boys. In addition, maternal anxiety in the subsample was associated with higher mean RT (i.e., slower reactions) and more intra-individual variability in RT in a choice-RT task. In the Buss et al. (2011) study, high levels of pregnancy-specific anxiety during the course of pregnancy were associated with lower inhibitory control and lower visuospatial working memory performance in boys and girls, aged 6 to 9 years; higher state anxiety and depression were associated with lower visuospatial working memory but did not explain additional variance after accounting for pregnancy-specific anxiety. Lastly, a retrospective study by Schwabe (Schwabe et al., 2012) demonstrated that young adults (with a mean age of 24 years) whose mothers were exposed to maternal major negative life events during pregnancy, such as the death of the mother's partner, used more rigid response learning strategies in a virtual maze learning task.

Taken together, the studies conducted show that anxiety, pregnancy-specific anxiety and/or life events during pregnancy, are associated with worse performance in simple and choice reaction time tasks and in visuospatial memory in 4-to-9-year-olds, and with deficits in endogenous cognitive control and cognitive flexibility – but not in exogenous cognitive control - in adolescents and young adults.

2.2.2. Cerebral processing – See Table 6

Although neurocognitive tasks can be used to make inferences about underlying alterations in brain functioning, they do not measure actual brain function directly. A useful tool to study

neurocognitive functioning directly in infants and young children is the event-related potentials (ERP) method (de Haan, 2006). One study using ERPs examined the differential effect of maternal anxiety between weeks 12 and 22 on endogenous versus exogenous cognitive control in 17-year-old boys; maternal anxiety had a negative effect on endogenous cognitive control, while exogenous cognitive control was not affected. These results corroborate earlier results obtained with computerized neurocognitive tasks in the same cohort at the age of 14-15 (Van den Bergh et al., 2005a; Van den Bergh et al., 2006) and 17 years (Mennes et al., 2006). Since ERPs lack spatial specificity, specific cognitive processes can't be related to specific brain regions. Therefore, to complement their ERP results (Mennes et al., 2009) with spatial information about which areas in prefrontal cortex show differences in functionality related to prenatal exposure to maternal anxiety, Mennes et al. (2016) gathered fMRI data during processing of endogenous and exogenous cognitive control tasks in the follow-up phase of their study at age 20. High levels of maternal anxiety at weeks 12-22 of pregnancy were again associated with less efficient endogenous decision making. Importantly, this behavioral pattern was complemented by patterns of brain activation, i.e., brain regions that are typically implicated in endogenous cognitive control (e.g., inferior frontal junction), were not modulated in the adolescents whose mothers exhibited high levels of anxiety during weeks 12-22 of their pregnancy. Again, no association was shown between maternal anxiety during pregnancy and brain activation during a GO/No Go task requiring exogenous cognitive control, replicating the results in the sample at age 17 years (Mennes et al., 2009).

Several studies focused on the effects of maternal anxiety during pregnancy on auditory attention in the offspring (Harvison et al., 2009; Hunter et al., 2012; Otte et al., 2015; van den Heuvel et al., 2015a) which is a key aspect of early neurocognitive functioning and is an

essential building block for developmental milestones, such as speech and language acquisition (Benasich et al., 2006; Kushnerenko et al., 2013; Molfese, 2000); the available auditory attention ERP studies used different kinds of auditory stimuli. First, Harvison et al. (2009) used voice recordings of the neonate's mother and of a stranger. They found that newborns prenatally exposed to high maternal anxiety displayed lower negative slow wave amplitudes in response to their mother's voice compared to a female stranger's voice, while newborns prenatally exposed to low levels of maternal anxiety displayed the opposite pattern. This seems to indicate alterations in auditory attention, with more attention allocated to a stranger's voice compared to the mother's voice in infants born to mothers with high anxiety. More recently, van den Heuvel et al. (2015a) demonstrated that 9-month-old infants exposed to higher levels of maternal anxiety early in pregnancy allocated more attentional resources (i.e., higher N250) to frequently-occurring standard sounds in an oddball paradigm, possibly indicating lack of habituation to these sounds; interestingly, the opposite pattern was found for prenatal exposure to maternal mindfulness, suggesting potential benefits for mindfulness interventions during pregnancy. Otte et al. (2015) studied the same 9-month-old infants in an audio-visual paradigm in which the infants were presented with emotional facial expressions (happy/fearful) followed by emotional vocalizations (happy/fearful). The authors showed that infants prenatally exposed to higher levels of maternal anxiety displayed larger P350 amplitudes in response to fearful vocalizations, regardless of the type of visual prime, which may indicate increased attention, or enhanced vigilance, to fearful vocalizations.

One other recent EEG project (Soe et al., 2016), studying the effect of maternal depressive symptoms during and after pregnancy on infant frontal EEG activity at 6 and 18 months, concluded that neither prenatal nor postnatal maternal depressive symptoms

independently predicted frontal EEG at these ages. This results do not corroborate the finding of several earlier studies (reviewed in Soe et al., 2016) that maternal depression in pregnancy or in the early postnatal life period is associated with infant relative right frontal EEG asymmetry. However higher levels of depressive symptoms postnatally, as compared to the prenatal levels, were associated with greater right frontal activity and relative right frontal asymmetry at 6 months (Soe et al, 2016).

2.2.3. Functional brain connectivity - See Table 7

EEG power analysis. Brain regions are highly interconnected and a specific region's functioning is dependent on its connectivity to other regions. Therefore, altered functional brain connectivity may underlie changes in neurocognitive functioning in children prenatally exposed to maternal stress. Soe et al. (2016) focused on maternal depressive symptoms during pregnancy and investigated infant frontal functional connectivity with the use of EEG power in 258 toddlers at ages 6, 18 and 24 months. The functional connectivity measure in their study refers to the functionally integrated relationship among spatially separated brain regions, which is characterized by phase synchronization of EEG signals of two brain regions in the infant EEG alpha frequency band (6–9 Hz). The authors reported no association between prenatal exposure to maternal depression (nor postnatal exposure) and frontal functional connectivity. However, the authors did found that an increase in depressive symptoms from the prenatal to postnatal period predicted greater right frontal activity and relative right frontal asymmetry in 6-month-olds, but not in 18-month-olds. In addition, increasing maternal depressive symptoms predicted lower right frontal connectivity in 18-month-olds but not in 6-month-olds.

Functional magnetic resonance imaging (fMRI) studies. To date, two prospective and one retrospective study have focused on investigating functional brain connectivity in offspring

prenatally exposed to maternal stress. In a prospective study, Qiu et al. (2015a) focused on the association between maternal depressive symptoms during pregnancy and the 6-month-old offspring's functional connectivity of the amygdala as measured with fMRI. The results showed greater functional connectivity of the amygdala with several other brain regions: the left temporal cortex, insula, bilateral anterior cingulate, medial orbitofrontal and ventromedial prefrontal cortices. In the second prospective study, Scheinost et al. (2016a) supported their hypotheses: (1) that functional connectivity from the amygdala to other subcortical regions - performed with whole brain seed connectivity from the left and right amygdala - is decreased in very preterm neonates (born < 32 weeks gestation) compared to controls (both groups tested at the age of 40-44 gestational weeks); and (2) that prenatal maternal anxiety or depression in preterm neonates (born < 28 weeks, without major brain injury) also decreases amygdala-subcortical (including the thalamus) connectivity. They concluded that prenatal exposure to maternal distress during pregnancy seems to amplify the decrease in amygdala connectivity seen in very preterm born neonates.

In the retrospective study of Favaro et al. (2015), examining effects of maternal life events stress during pregnancy in young woman between the age of 15 and 44, maternal life event stress was associated with decreased gray-matter volume in left medial temporal lobe (MTL) and both amygdalae, but not total volume of amygdala nor with grey-matter or total hippocampal volume. Voxels in which significant correlations were found were used as seeds to explore resting-state functional connectivity. Prenatal exposure to maternal life event stress was positively correlated with co-activation (or functional connectivity) of the left medial temporal lobe with the pregenual anterior cingulate cortex. Importantly, connectivity between the left MTL and part of the left medial orbito-frontal cortex was associated with depressive symptoms

in the participants and, hence, seems to mediate the link between maternal life event stress in pregnancy and depressive symptoms in 15 to 40-year-old females. All results remained the same when only data from subjects over the age of 18 were analyzed.

To date, in addition to the study by Favaro et al. (2015), 11 other prospective studies have examined the relationship between maternal psychological distress during pregnancy and structural brain measures in offspring during the neonatal period, in infancy and childhood, using structural MRI, diffusion-weighted imaging (DWI), diffusion-tensor imaging (DTI), or T1-weighted imaging (Buss et al., 2010; Buss et al., 2012; Chen et al., 2015; Davis et al., 2017; Lebel et al.; Qiu et al., 2015a; Qiu et al., 2015b; Rifkin-Graboi et al., 2013; Rifkin-Graboi et al., 2015; Sandman et al., 2015; Sarkar et al., 2014). These studies are reviewed in Franke et al., in this issue (Franke et al., this issue). Importantly, all of these studies found associations between maternal psychological distress during pregnancy and (micro)structural brain changes from the neonatal period to age 9 years which was the oldest age examined to date in prospective structural brain imaging studies. These studies add to the evidence obtained from individuals who were prenatally exposed to the Dutch famine showing structural brain changes at age 51 (Hulshoff Pol et al., 2000) and at age 68 years (de Rooij et al., 2016).

2.2.4. Conclusion and Implications

In summary, converging evidence from both neurocognitive tasks and more direct measures of brain functioning, such as EEG, ERP and fMRI, demonstrates that prenatal exposure to maternal anxiety or depression is associated with many aspects of offspring brain function, including impulsivity (Van den Bergh et al., 2005a), attention (Van den Bergh et al., 2006), endogenous cognitive control (Mennes et al., 2009; Mennes et al., 2006; Mennes et al., 2016; Van den Bergh et al., 2005a; Van den Bergh et al., 2006), auditory attention (Harvison et al.,

2009; Hunter et al., 2012; Otte et al., 2015; van den Heuvel et al., 2015a), and functional connectivity (Favaro et al., 2015; Qiu et al., 2015a; Soe et al., 2016). Some studies have demonstrated that there might be a gender effect, with boys' cognitive functioning being more affected by prenatal exposure to maternal stress than that of girls (Loomans et al., 2012; Van den Bergh et al., 2006), and others showing an effect particularly on girls' functional brain connectivity (Soe et al., 2016), as well as an effect of timing, with first trimester (Otte et al., 2015), or the first half of pregnancy (Mennes et al., 2009; Otte et al., 2015; Qiu et al., 2015a; Van den Bergh et al., 2005a; van den Heuvel et al., 2015a) being the most vulnerable period.

In future research, in order to make progress in this specific DOHaD research field, investigation of how alterations in functional brain correlates mediate the effect of maternal psychological distress during pregnancy on behavior and mental health are vital. To this end, more studies should include not only prenatal stress predictors and offspring outcome measures but also functional brain correlates, as done in the studies of Favaro et al. (2015; including functional and structural brain measures), Mennes et al. (2009; including simultaneous cerebral processing measures), and Soe et al. (2016; including functional connectivity). Although making inferences about changes in functional connectivity mediating the link between maternal stress in pregnancy and offspring externalizing/internalizing problems in infancy (Soe et al., 2016) or depressive symptoms in adolescence and adulthood (Favaro et al., 2015) may be premature, since mediation was not directly statistically tested, and because much of the mechanisms involved remain to be understood, at the least it can be concluded that the frontal and limbic functional connectivity patterns observed in these studies give rise to an increased neurodevelopmental risk status for externalizing and internalizing disorders in the offspring. It is also plausible that deficient endogenous cognitive control mediates the link between high

maternal anxiety and ADHD symptoms observed in a Belgian sample (Mennes et al, 2009, 2016; Van den Bergh et al, 2006), however, the mediation effect has not yet been tested directly.

In future research, more prospective studies should test the ways in which genetic differences and epigenetic regulatory mechanisms may play a role in mediating or moderating the relationship between maternal stress in pregnancy and functional and structural brain connectivity (Chen et al., 2015; Qiu et al., 2015b). Finally, future research may also focus on studying functional and structural connectivity in the fetal brain and examine whether, and in what ways, altered brain connectivity as measured in utero mediates the link between prenatal exposure to maternal stress and offspring behavior and mental health (Koyama et al., 2016; Scheinost et al., 2016b; van den Heuvel and Thomason, 2016).

2.3. HPA axis function correlates in offspring prenatally exposed to maternal stress

A number of prospective longitudinal studies have measured basal, diurnal or stress-related HPA-axis activity in offspring exposed to prenatal stress; most studies were conducted in small samples, but with a notable exception in the ALSPAC study (O'Donnell et al., 2013). While most of the studies found significant associations between prenatal stress and offspring HPA-axis function, the nature of the associations varied, which is related to the diversity of the timing and type of maternal stress measures used, of offspring age when examined, and of the type of offspring HPA axis function measure (Zijlmans et al., 2015b).

2.3.1. Cortisol reactivity

Maternal cortisol in pregnancy has been shown to predict offspring cortisol reactivity to stressors, although the direction of the results is not consistent across studies. Some studies show that greater maternal cortisol in pregnancy predicts greater cortisol response to a painful procedure in neonates (heel-stick, Davis et al., 2011), in 5-week-olds in response to bathing

(Tollenaar et al., 2011), and in 5-year-olds being vaccinated (Gutteling et al., 2004). Similar results were found for associations between prenatal maternal anxiety and increased cortisol response to the stressful "still-face" procedure in 7-month-olds (Grant et al., 2009). On the other hand, prenatal maternal cortisol has also been associated with *lower* cortisol response in 8-week-olds in response to vaccination (Tollenaar et al., 2011), 12-month-olds in response to maternal separation (Tollenaar et al., 2011), and in 17-month-olds in response to maternal separation (O'Connor et al., 2013).

There is one study on the effects of prenatal maternal stress from a natural disaster on offspring cortisol stress reactivity before and after a maternal separation in 94 2½ year-olds (Yong Ping et al., 2015). They found that the more severe the mothers' objective exposure and subjective stress (PTSD symptoms) from a major flood during pregnancy, the greater the child's cortisol increase in response to the stress. They also found that the later in pregnancy the flood occurred, the greater the cortisol response. Finally, maternal subjective stress had no effect on boys, but in girls greater subjective stress predicted greater cortisol reactivity. Thus, the effects of maternal stress in pregnancy on HPA axis reactivity in toddlers seems to depend on the aspect of the maternal stress experience (objective exposure versus subjective stress), and the sex of the child.

2.3.2. Basal cortisol

The effects of prenatal anxiety on basal, diurnal cortisol levels appear to vary according to the age of the child. In the ALSPAC study of prenatal maternal anxiety, although at age 10 more prenatal anxiety predicted higher cortisol at awakening and a higher cortisol awakening response (CAR) (O'Connor et al., 2005), in these same children at age 15 prenatal maternal anxiety predicted a lower CAR and a flatter diurnal curve (O'Connor et al., 2013). Similarly, Van den

Bergh (Van den Bergh et al., 2008) found that high levels of maternal anxiety at 12-22 weeks gestation also predicted a flatter diurnal cortisol profile at age 14-15, with lower morning and higher evening cortisol in both boys and girls; importantly, this study showed that this flatter diurnal cortisol profile mediated the link between high maternal anxiety and depressive symptoms in girls, but not in boys. Thus, although the association between prenatal maternal anxiety and offspring basal cortisol was similar in boys and girls, its mediating role in linking maternal anxiety during pregnancy with offspring depression may differ with age and sex of the child.

Other studies examined the associations between prenatal stress from a disaster and basal cortisol in the offspring with mixed results. Nine-month-old infants of mothers exposed to the trauma of the terrorist attacks in New York City on September 11, 2001 (n = 38), and who developed symptoms of PTSD, had lower diurnal cortisol levels (Yehuda et al., 2005) as did their mothers; these results suggest the possibility that low diurnal cortisol may be an inherited trait that infers vulnerability to PTSD in the face of trauma. Using a single, basal measure of cortisol at noontime, Huizink et al. (2008) found that cortisol was higher in adolescents whose mothers were exposed to the Chernobyl disaster, especially with second trimester exposure, than in adolescents of a reference group. These studies are difficult to compare given the different ages of the exposed offspring at the time of assessment, which, as we have seen with reactive cortisol, may influence the associations between prenatal stress and cortisol in the offspring.

2.3.3. Conclusion and Implications

The associations between various measures of prenatal maternal stress and offspring reactive and diurnal cortisol are complex and inconsistent. As well, there is little research in this field that allows one to conclude that higher or lower cortisol is the better outcome. Although these

prospective studies seem to imply that offspring HPA axis function might constitute a mechanism for an increased vulnerability to behavior and mental health problems, as found in the mediational study by Van den Bergh et al. (2008), more studies are needed that directly examine how offspring HPA axis function mediates the link between measures of maternal stress, and offspring behavior and mental health, and at different developmental ages according to gender.

2.4. ANS function correlates in offspring prenatally exposed to maternal stress

Besides the HPA axis, the autonomic nervous system (ANS) is the second key physiological mechanism by which organisms react to stress. The activities of the ANS are considered automatic or self-regulating; the ANS controls responses without intervention of the conscious mind (Carlson, 2007). The main function of the ANS is to keep the body in a balanced internal state (Andreassi, 2007; Silbernagl and Despopoulos, 2009), by regulating activities such as respiration, digestion, body temperature, and metabolism. The ANS is traditionally divided into two main branches: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). Heart Rate (HR) is regulated through both branches in complex way (Lahiri et al., 2008). Heart rate variability (HRV) reflects oscillations in the interval between consecutive heart beats (or cardiac cycle length variability); specifically, HRV is the variability in the intervals between R waves (i.e., the RR interval). Detection of HRV is a non-invasive, accurate means of studying the beat-by-beat autonomic control of the cardiovascular system. The current research on ANS correlates of prenatal stress focuses on both fetal and postnatal autonomic functioning.

2.4.1. Fetal autonomic functioning

Fetal heart rate (FHR) measurement while mother at rest. Maternal depression during pregnancy has been linked to higher baseline FHR (Allister et al., 2001; Dieter et al., 2008;

Emory and Dieter, 2006), as well as to reduced baseline FHR, (DiPietro et al., 1996) which suggests that prenatal exposure to maternal stress may reduce fetal parasympathetic activity (Doyle et al., 2015). In contrast, no significant association was found between maternal negative mood and baseline FHR (Doyle et al., 2015). However, there is evidence for a significant interaction between maternal negative mood and fetal sex, with increased levels of maternal negative mood being associated with decreased baseline FHR in male fetuses only (Doyle et al., 2015). Furthermore, other studies have failed to find a significant relationship between maternal anxiety and baseline FHR (DiPietro et al., 2010; Groome et al., 1995; Monk et al., 2000; Monk et al., 2003; Sjöström et al., 2002). However, two older studies showed evidence for a positive association between maternal anxiety and the duration of a FHR pattern that is typically seen in periods during which the fetus is highly active (Fetal Sate 4F), namely FHR pattern D; fetal HRV within FHR pattern D was also associated with maternal anxiety (Sjöström et al., 2002). These results are comparable to a study that showed a positive association between maternal anxiety level and fetal HRV in specific FHR patterns that are typical for periods during which the fetus is active (Fetal State 2F) or highly active (Fetal State 4F)(Van den Bergh, 1990). Additionally, higher levels of maternal pregnancy-specific stress have been associated with increased baseline fetal HRV (DiPietro et al., 2002; DiPietro et al., 2010).

Response to a maternal stressor. The autonomic effect of maternal psychological functioning on the fetus was also studied by examining fetal responses to maternal lab-induced stress. In a small randomized controlled trial study no effect was found of inducing emotions by showing a film clip of a normal delivery. While the clip did induce emotions, the latter had no effect of fetal behavioral states, fetal activity and associated FHR patterns. However base level maternal state anxiety was related with fetal activity and associated FHR patterns B and D (Van den Bergh et

al, 1989). In other studies fetuses of depressed, anxious or anxio-depressive comorbid mothers tend to have significantly higher increases in FHR (Monk et al., 2011; Monk et al., 2000; Monk et al., 2003; Monk et al., 2004) and fetal HRV (DiPietro et al., 2003) when the mother was introduced to a stress-inducing Stroop color–word task.

Response to a fetal stressor. Vibroacoustic stimulations of the fetus have been used as direct fetal stressor. Fetuses of depressed mothers showed slowed FHR reactions to a vibroacoustic stimulus and a longer period to return to FHR baseline levels (Allister et al., 2001). In the study of Dieter et al. (2008) fetuses of depressed mothers showed lower basal heart rate and during the vibratory stimulation phase they showed an increase in heart rate while fetuses of non-depressed mothers displayed a FRH decrease.

2.4.2. Postnatal autonomic functioning

Newborns of mothers with high levels of anxiety measured in the second pregnancy trimester tend to have reduced PNS activity as indexed by vagal tone, measured as respiratory sinus arrhythmia (RSA) (Field et al., 2003). Similarly, lower RSA has been found in neonates of mothers with depressive symptoms in the third semester (Jones et al., 1998). Ponirakis et al. (1998) conducted a factor analysis combining anxiety- and depression-related variables in trait and state negative emotionality factors. In their study pregnant adolescents were assessed during early pregnancy and in the third trimester. Women with higher negative trait emotionality in early pregnancy (before 16 weeks of gestation) had significantly lower RSA. No significant relations were found between the state negative emotionality in early pregnancy, or the trait and state negative emotionality factors in the third trimester and infant RSA (Ponirakis et al., 1998).

The relation between prenatally depressed or anxious mothers and reduced HRV in infants was not replicated in a study investigating the effects of mothers' prenatal psychiatric

status in four months old infants (Kaplan et al., 2008) and 14 months old infants (Dieter et al., 2008). Remarkably, a maternal history of psychiatric disorder has been associated with higher HR and lower high-frequency HRV in the 14 months old infant (Dierckx et al., 2009). Similarly, there is evidence that HRV (i.e. high-frequency HRV and root mean square of successive differences (RMSSD), may be lower in infants of women with a past anxiety disorder, compared to healthy controls (Braeken et al., 2013). Furthermore, in the same study, there was a positive correlation between both HRV measures for mothers with a past anxiety disorder and those of their infants at age 2-4 months (Braeken et al., 2013). Peltola et al. (2017) found that baseline RSA moderated the association between maternal anxiety during pregnancy and infant negative affectivity at the age of 8 to 10 months. More specifically, they showed that among infants with higher RSA, a positive association between anxiety and infant negative affectivity was observed, while among infants with low RSA no such association was found. In the study of Gao et al. (2016) in which prenatal exposure to proximal adversity (see remark below) was measured retrospectively, found a similar moderation effect showing that prenatal adversity exposure was associated with psychopathic traits in 8 to 10 years olds but only in the group of children with high RSA. On the other hand, in a large study with 2624 mother-child pairs – the Generation-R study - no significant associations were found between prenatal maternal stress scales (state anxiety, depressive symptoms, pregnancy-related anxiety, parenting daily hassles and job strain), measured at gestational week 16, and cardiac autonomic measures at rest (i.e., pre-ejection period, HR, RSA and cardiac autonomic balance) in the offspring at age 5-6 years (van Dijk et al., 2012).

At least two studies measured infant ANS reactivity to one or more lab tasks. One study, assessing depression post-delivery showed that neonates of depressed mothers had lower

baseline RSA and lower heart period across tasks (involving cry stimuli), and slower cardiacvascular recovery following the cry sound than neonates of non-depressed mothers (Jones, 2012). One study, assessing maternal anxiety prospectively and assessing infants ANS reactivity to task such as a novel toy exploration and the Still-face procedure, found that anxiety significantly predicted lower RSA in infants aged 29 weeks, but only in boys (Tibu et al., 2014).

Lastly, the group of Van den Bergh found that prenatal exposure to maternal stress has also been associated with increased perception of dyspnea 28 years later in adulthood (von Leupoldt et al., 2017). Dyspnea is the aversive cardinal symptom found in several respiratory, cardiovascular and neuromuscular diseases. The underlying mechanism for the observed association remains unclear.

2.4.3. Conclusion and implications

Taken together, these studies show that there is growing evidence suggesting an association between offspring ANS function and prenatal exposure to maternal stress, depression, and anxiety. Clearly, mothers and their children share genes, and links between maternal ANS function and offspring HRV might be explained by a shared underlying pro-anxiety phenotype. Another possibility, involving ANS activity, is that utero-placental blood flow is reduced due to increased catecholamines, which are released during periods of anxiety and distress, causing subsequent oxygen and nutrition reduction to the fetus, and thereby affecting fetal growth (Copper et al., 1996; McCubbin et al., 1996) and nervous system development (Sjöström et al., 1997). An important goal of future research should be the determination of possible mechanisms by which maternal psychological functioning during pregnancy may affect maternal ANS function (Braeken et al., 2015), and how the combined action of maternal psychology and ANS function may affect the developing child's ANS function. For instance, one study administered a

mental arithmetic stress task to pregnant women twice: once in the first trimester and again in the third. In non-anxious women, stress reactivity was reduced between the first and third trimesters, whereas anxious women showed less dampened stress reactivity in the third trimester; this may pose long-term risks for the offspring of the anxious women (Braeken et al., 2015). To obtain greater insight into the daily, continuous interaction between maternal and fetal autonomic function, more research should focus on using 24 hours ambulatory monitoring of maternal biological-physiological factors (such as HR, HRV, pre-ejection period, cortisol) in combination with maternal distress and/or positive emotional factors (such as mindfulness) as has been done by Braeken et al. (2017) or in combination with fetal autonomic and behavioral measures (Doyle et al., 2015). Another important aim is to study the developmental trajectory and alteration of autonomic function in longitudinal studies into adulthood (e.g.,von Leupoldt et al, 2017). While or review did not include studies examining the effect of proximal risk on ANS since the focus of this review is on ANS effects of maternal distress, results of these studies bear conclusions that are relevant for our review. For instance, the authors of a recent review article (Propper and Holochwost, 2013) concluded that infants and children exposed to proximal risk (including substance use, disruption in parenting, domestic violence in prenatal or early postnatal life) show a pattern of ANS activity characterized by reduced PNS activity during rest (i.e., lower resting vagal tone/RSA) as well as during times of environmental challenge or stress (i.e., reduced vagal withdrawal); this pattern was sometimes combined with an increase in SNS activity when confronted with challenges or stress (e.g., Suurland et al, 2016). Such an ANS pattern would support increased vigilance and active defense responses, which, when confronted with high proximal risk may be adaptive in the short-term, but in the long-tern maintaining this pattern may impose high allostatic load (McEwen et al., 2015; Propper & Holochwost, 2013) and lead to

dampening or blunting of the SNS response (e.g., Alkon et al., 2014; McLaughlin et al., 2015) which in turn may induce physical and mental health problems (McEwen et al., 2015).

2.5. Associations between maternal stress, its biological correlates, and offspring behavior and mental health

As highlighted in this section, maternal stress during pregnancy predicts a large number of unfavorable outcomes in the offspring, including more severe behavioral problems, motor problems and poorer cognitive development, psychopathology and alterations in brain development, HPA-axis and ANS function. For many of these outcomes, there does not appear to be any evolutionary advantage, that is, there is little evidence that the consequences of maternal stress in pregnancy enhance the unborn child's chances of immediate survival or long-term health, as might be predicted from some fetal programming theories (Del Giudice, 2014; Glover, 2011; Nederhof and Schmidt, 2012). There are a handful of studies, however, that do suggest that a moderate degree of maternal stress infers slight advantages to infant and child outcomes, whether that stress is maternal psychological distress (DiPietro et al., 2010; DiPietro et al., 2006; Kantonen et al., 2015; Lin et al., 2014; Rothenberger et al., 2011b) or maternal objective exposure from a natural disaster (Laplante et al., 2008; Simcock et al., 2016a). Maternal cortisol in the third trimester also has been shown to promote fetal neurdevelopment (Glynn and Sandman, 2012) and infant cognitive development at 12 months (Davis and Sandman, 2012) and at 6 to 9 years (Davis et al., 2017)(see section 3.1.), although the curvilinear results in the studies of DiPietro et al. (2006) and of Laplante et al.(2008) still find that high levels of stress predict poorer outcomes than low levels of stress. Sandman et al. (2012), however, observed increased motor and mental development during the 1st year of life among infants whose mothers experienced congruent levels of depressive symptoms during and after

pregnancy, even when the levels of symptoms were relatively high and the prenatal and postnatal environments were unfavorable.

At this stage in the development of the field, it is becoming increasingly important to publish studies demonstrating how biological correlates mediate the link between prenatal stress and offspring behavior and mental health - either by a mediational analysis (e.g., Buss et al., 2012; Monk et al., 2016; Räikkönen et al., 2015; Rouse and Goodman, 2014; Van den Bergh et al., 2008) or a structural equation model (e.g., Baibazarova et al., 2013a; Monk et al., 2016; Suurland et al., 2016); this analytic approach will help us to understand and substantiate the mechanisms by which in utero stress exposure may have a lasting effect on offspring outcomes. Similar increases in knowledge can also be gained from studies showing significant moderation effects, that is, by finding a statistical significant interaction effect between a predictor and a biological correlate. For example, some studies demonstrate specific vulnerability in offspring according to a biological correlate (i.e., an interaction between the predictor and biological correlate, e.g., Chen et al., 2015; Conradt et al., 2013; Gao et al, 2016; Lambertini et al., 2015; Peltola et al., 2017; Qiu et al., 2015b). Vineis and Perera (2007) have proposed the use of complementary study designs to establish new biomarkers, such as DNA methylation changes, that lie on the causal pathway between exposure and disease. According to Demetriou et al. (2015, p.328) this approach, termed ‘Meet-in-the Middle’ may open up new possibilities for strengthening causal inference. For example methylation markers that in prospective studies are shown to be associated with the exposure of interest and are also shown to be predictive of disease risk can be classified as biomarkers of the mechanistic pathway linking exposure to disease, and the association between exposure and disease can be regarded as causal evidence. In a similar way, enhanced risk for neurodevelopmental disorders is predicted from prenatal

exposure to maternal stress in several of the studies reviewed (e.g., Braeken et al., 2013; Braeken et al., 2017; Rifkin-Graboi et al., 2015; Soe et al., 2016). Finally, joint modeling is a powerful new tool developed to simultaneously integrate multiple brain imaging neural measures (e.g. fMRI and EEG) and behavioral data. It allows to make simultaneous inferences about both behavior and brain measures in all directions (Turner et al., 2017). The latter is interesting, e.g, to study how the bi-directional interactions between the brain (adapted to early adversity) and behavior may shape an atypical developmental trajectory (cf. Johnson et al., 2015 or whether changes in parental caregiving behaviors expressing enhanced reflective functioning (e.g. Smaling et al., 2016) lead to changes in children's brain function (e.g., in frontal asymmetry as assessed with EEG, Peltola et al., 2014).

Although there has long been an interest in finding "the" period in gestation that is most vulnerable to prenatal stress, effects of prenatal maternal stress on offspring outcomes have been found at all periods of gestation. A few examples of the timing effects noted in this review are reproduced here. Timing of stress in the peri-conceptional period predicts some outcomes in the offspring (Bloomfield et al., 2004; Tobi et al., 2015), while other studies find that first trimester gestational stress has particular effects on attention (de Groot et al., 2011; Ronald et al., 2011), internalizing problems (Kingsbury et al., 2016; Robinson et al., 2011; Tearne et al., 2015; Wang et al., 2016), as well as on more difficult temperament and other behavior problems (Jennings et al., 1999; Laplante et al., 2016; Loomans et al., 2011; St-Hilaire et al., 2015; Walder et al., 2014). Both first and second trimester gestational stress has effects on cognitive development (Laplante et al., 2004; Mennes et al., 2009; Otte et al., 2015; Van den Bergh et al., 2005a; Van den Bergh et al., 2005b; Velders et al., 2011). Some studies have found some outcomes that are specific to second trimester exposure (Field et al., 2003; Huizink et al., 2008; Stroustrup et al.,

2016; Van den Bergh and Marcoen, 2004) and others find effects specific to third trimester stress (Cao et al., 2014; Class et al., 2014; Fernández et al., 2013; McMahon et al., 2013; Simcock et al., 2016a). Similarly and as stated above, it appears that both male and female fetuses are susceptible to the effects of prenatal stress, although the patterns of effects of different kinds of prenatal stress, timed at different moments in gestation, for different outcomes, may differ. Multiple examples of sex-specific effects are evident in this review.

As such, it appears that there is no period of gestation, nor gender, which is impervious to the effects of prenatal stress on child development. Thus, all women and their unborn children, in any stage of pregnancy, can be considered members of a vulnerable population. On the other hand, there is always variance in the levels of poor outcomes in children, with some children appearing to be more susceptible to the same level of maternal stress than others. What maternal or child characteristics might infer resilience against stress in pregnancy? In Section 3.1 we provide an answer to this important question.

3. Maternal stress and offspring behavior and mental health in early and later life: changes in underlying biological systems

The association between maternal stress during pregnancy and offspring behavior and mental health disorders (Gluckman et al., 2008; Hanson and Gluckman, 2015) may be due to a different trajectory of (i) brain development and altered function of neuronal systems, (ii) HPA-axis development and (iii) autonomic nervous system in early and in later life; reviews of research on these systems these are presented in sections 2.2 to 2.4. However, we still know relatively little about the changes in offspring biological systems that may reflect which mechanisms underlie these changes in developmental trajectory effects especially in the human situation. The

available evidence – for the stress system, immune system, gut microbiome, and telomore biology - is described in the following sections.

3.1. Stress system

Maternal stress exposure produces activation of two branches of the maternal stress axis : the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic division of the autonomic nervous system (Chrousos and Gold, 1992; Elenkov and Chrousos, 1999). However, the relation between maternal stress during pregnancy and maternal cortisol levels is inconsistent, with some studies reporting a significant association (e.g., Giesbrecht et al., 2012; Kane et al., 2014; Kivlighan et al., 2008; Pluess et al., 2010), while others report only minor associations (Voegtline et al., 2013), or non-significant associations (Baibazarova et al., 2013a; Bergman et al., 2010a; Davis et al., 2007; Davis et al., 2011; Davis et al., 2017; Davis and Sandman, 2010; Harville et al., 2009; Hompes et al., 2012; Salacz et al., 2012; Voegtline et al., 2013; Werner et al., 2013). Some studies have found significant positive associations between basal maternal cortisol levels during pregnancy (either during one specific or during several trimesters) and suboptimal outcomes in the offspring including the following: difficult temperament in infancy (e.g., infant negative affectivity (Davis et al., 2007; de Weerth et al., 2003; Rouse and Goodman, 2014), infant emotional reactivity (Davis and Sandman, 2010), observer rating of infant high distress to novelty (Werner et al., 2013), child anxiety (Davis and Sandman, 2012), child cortisol concentrations (Davis et al., 2011), and altered child brain structure (Buss et al., 2012; Davis et al., 2013). On the other hand, some studies have found that maternal cortisol level in the third trimester actually promoted better outcomes including the following: fetal neurodevelopment (Franke et al., this issue; Glynn and Sandman, 2012), and cognitive development at age 1 year (Davis and Sandman, 2012) and at 6 to 9 years (Davis et al., 2017). However, most studies have

not found significant associations between maternal cortisol during pregnancy and child outcomes; for example, no associations were found with temperament (Davis and Sandman, 2010; Gutteling et al., 2005; Rothenberger et al., 2011a) nor with mother ratings of infant distress to novelty (Werner et al., 2013). In fact in a recent review, Zijlmans et al. (2015b) concluded that 76% of statistical analyses performed in the papers they reviewed did not reveal a significant association between maternal cortisol in pregnancy and poorer offspring birth outcomes, lower cognitive/motor development, or more behavioral problems in infancy and childhood. Zijlmans et al. (2015a) concluded that maternal cortisol during pregnancy may not be the sole, or even the main, underlying mechanism in the association between maternal stress during pregnancy and offspring child outcomes. Rather, the evidence suggests that maternal psychosocial stress and maternal cortisol may each exert their influence through different pathways (Baibazarova et al., 2013b; Zijlmans et al., 2015a).

Nevertheless, in DOHaD models that are based on preclinical research, maternal-fetal transfer of cortisol is thought to be the key pathway through which maternal stress is transferred to the fetus (O'Donnell and Meaney, 2016). Placental cortisol transfer is regulated by the activity of placental 11β-hydroxysteroid dehydrogenase enzyme type 2 (11β -HSD2) that converts about 80-90 % of maternal cortisol to the inactive form: cortisone (Harris and Seckl, 2011). Maternal-fetal cortisol transfer is facilitated by two mechanisms: via placental 11β-HSD2, and placental CRH (Rakers et al., this issue). First, increased levels of maternal cortisol down-regulate the activity of the 11β-HSD2 in experimental animal studies and, thus, increase fetal exposure to maternal cortisol. Results in humans are inconsistent, however. O'Donnell et al. (2012) showed that higher maternal anxiety, but not depression, on the day prior to elective caesarean section was associated with down-regulation of placental 11β-HSD2 expression. Similarly, in another

study, a history of maternal depressed mood during pregnancy, irrespective of any maternal antidepressant medication use, was not associated with a lower 11β-HSD2 level (Ponder et al., 2011). As the second mechanism, increased levels of maternal cortisol also stimulate synthesis of corticotrophin-releasing hormone (CRH) production in the primate placenta which is released in large amounts into the fetal and maternal circulations (Chrousos and Gold, 1992).
Several experimental studies in rodents and sheep have shown that the resulting exposure of the fetus to inappropriately high levels of glucocorticoids (cortisol in sheep, corticosterone in rodents) induces a long-lasting increase in the sensitivity of the HPA axis (Harris and Seckl, 2011; Weaver et al., 2004; Weinstock, 2005, 2008). The increased stress sensitivity is associated with major depression, among other problems, due to a cortisol-mediated suppression of noradrenaline and serotonin, and changes in immune activity (Dinan, 1996; Makhija and Karunakaran, 2013).

Rouse and Goodman (2014), in a mediation study in which maternal cortisol was measured (in urine samples) at each of the monthly pregnancy visits, did not find evidence for elevated maternal cortisol mediating the link between maternal depression during pregnancy and infant negative affectivity. At least three studies examined associations between amniotic cortisol and outcomes in the offspring. Amniotic fluid cortisol, which is presumed to affect fetal brain development (Baibazarova et al., 2013a), has different sources, such as maternal cortisol, fetal membranes (Baibazarova et al., 2013a), but also fetal cortisol. There is functional feedback in the HPA-axis from mid-gestation onwards (Gitau et al., 1998; Pang et al., 1980). In the study of Salaria et al. (2006) increased amniotic fluid cortisol was found to influence the expression of genes in fetal brain cells. Bergman et al. (2010b) showed that greater amniotic fluid cortisol predicted lower cognitive scores at 17 months; however, in a second paper (Bergman et al.,

2010a) no relationship was found with child temperament (i.e., fear reactivity) at 17 months. In the study of Baibazarova et al. (2013a) (Baibazarova et al., 2013a) the amniotic fluid cortisol was measured simultaneously with maternal psychological distress and maternal blood plasma cortisol. Structural equation modelling found evidence for an indirect effect of maternal cortisol on infant temperament: greater maternal cortisol was associated with greater amniotic cortisol, which then predicted lower birth weight which, in turn, was associated with greater fear and distress to limitations in the infant at age 3 months as assessed by maternal report; there was no direct effect of maternal anxiety or maternal cortisol in pregnancy on infant temperament.

It is well known that the activity of the HPA axis is influenced by genetic factors (Wüst et al., 2004). At least one study has shown that, also in humans, the effect of maternal psychological distress during pregnancy is moderated by genetic variance in the offspring glucocorticoid receptor (GR) gene (Velders et al., 2012). A common variant in GR at rs41423247 (BclI) was associated with increased risk for emotional and behavioral problems in preschool children, with attenuated cortisol reactivity in response to stress, but only in children of mothers who experienced psychological distress during pregnancy; no moderation effects were found for maternal genotype at rs41423247 (Velders et al., 2012). Clearly, in future research more studies should focus on genetic differences in HPA axis activity of both mother and offspring.

The role of epigenetics in prenatal maternal stress is reviewed in detail in another paper in this issue (Cao-Lei et al., this issue), however, we highlight several recent studies here. Several studies in humans have shown that the effects of maternal stress and psychophysiological function during pregnancy on offspring behavior are mediated by epigenetic changes of gene transcription of, amongst others, the glucocorticoid receptor gene *NR3C1* both in the placenta

and the fetus (Devlin et al., 2010; Garfield et al., 2016). Conradt et al. (2013) showed that higher maternal self-reported depression during pregnancy and higher placental methylation of the *NR3C1* were associated with poorer self-regulation, more hypotonia and more lethargy in the infant. Another study demonstrated that maternal depressive symptoms in second and third trimester of pregnancy predicted up-regulation of the *NR3C1* (third trimester depression only) and the mineralocorticoid receptor gene *NR3C2* expression in the placenta (Räikkönen et al., 2015; Reynolds et al., 2015); placental *NR3C1* expression partly mediated the link between maternal depression in third trimester and regulatory behavior problems with regard to crying, sleeping, feeding, spitting or elimination in the 2-week-old offspring (Räikkönen et al., 2015). In Monk et al. (Monk et al., 2016), perceived stress (but not cortisol levels) was found to be associated with elevated methylation of 11β-HSD2 which, in turn, was associated with lower fetal coupling, a measure of the relationship between fetal movements and fetal heart rate. In addition, regulation of other genes seems to be involved in the relation between maternal mood or stress and offspring behavior. A recent study showed that depression during pregnancy was related to decreased placental expression of the imprinted gene *PEG3* which was co-incident with decreased expression of human placental lactogen (*hPL*) (Janssen et al., 2016). The study of Lambertini et al. (2015) showed that gene expression of the protein-coding mitochondrial-encoded *MT-ND2* gene was associated with both maternal stress during pregnancy and infant temperament at 6 months of age.

On the fetal side, gene expression changes or epigenetic changes of DNA methylation patterns of the *NR3C1* by maternal stress are thought to be responsible for the increase of the sensitivity of the fetal HPA axis (Harris and Seckl, 2011; Weaver et al., 2004) and, at least in part, for the subsequent mental health disorders in the offspring. Thus, studies have shown associations

between maternal depression and anxiety during pregnancy and epigenetic changes in the methylation of *NR3C1* in cord blood and infant salivary samples (Braithwaite et al., 2015; Hompes et al., 2013; Nemoda et al., 2015; Oberlander et al., 2008; Palma-Gudiel et al., 2015b). These changes in *NR3C1* methylation in blood and saliva samples have also been associated with risk of psychiatric problems in childhood and adulthood (Dadds et al., 2015; Heinrich et al., 2015; Palma-Gudiel et al., 2015a; Parade et al., 2016; Tyrka et al., 2016; Van Der Knaap et al., 2015). The study of Nemoda et al. (2015) tested associations between maternal depression, and genome-wide methylation signatures in the mothers and their neonates, in one sample, and in post-mortem hippocampal samples in men in a second sample. Although there was no association between maternal depression and their own DNA methylation, maternal depression was associated with methylation levels in cord blood, and in the postmortem hippocampi. There was also an overlap in these results involving 33 genes with changes in DNA methylation in T lymphocytes of neonates and (postmortem) hippocampal samples of adult male offspring of mothers with a history of depression. Project Ice Storm has found that the objective severity of maternal exposure to the ice storm (Cao-Lei et al., 2014), and mothers' cognitive appraisal of the event (Cao-Lei et al., 2015) (but not maternal subjective distress) were highly correlated with genome-wide methylation levels in the offspring at age 13 years (Cao-Lei et al., 2016). These studies show that there is a growing body of clinical and epidemiological evidence for the role of epigenetic factors in mediating the link between maternal distress during pregnancy and behavior and mental health problems in the offspring (Vaiserman, 2015).

Besides the maternal-fetal stress transfer by cortisol, increased maternal catecholamine levels may have indirect effects on the fetus by diminishing placental perfusion although catecholamines do not cross the placenta in relevant concentrations (Rakers et al., this issue).

Catecholamines have also been shown to down-regulate 11β-HSD2 gene expression in isolated human placental trophoblastic cells via α-adrenergic signaling (Sarkar et al., 2001). Importantly, a case-control study (Braeken et al., 2013) measured HRV in pregnant women during a stress-relaxation task and showed that pregnant women with previous, but not current, anxiety had lower HRV that was later found in their infants as well. In this study, children with low HRV tended to show more fearfulness. The authors concluded that it remains unclear whether the altered maternal ANS function, reflected by lower HRV, was an important causative factor for infants' lower HRV, or simply the result of other underlying processes (Braeken et al., 2013). Other studies also found evidence for a role of offspring ANS in mediating (e.g., Suurland et al., 2016) or moderating (e.g., Gao et al, 2016; Peltola et al., 2017) the link between prenatal exposure to adversity and offspring temperament and psychopathology.

Reduced HRV is associated with dysregulation of various allostatic systems, including glucose regulation, HPA axis function, and inflammatory processes (Thayer and Sternberg, 2006), all of which may program fetal brain development (Leff-Gelman et al., 2016; Matthews and Phillips, 2010; Meyer et al., 2006; McEwen, 2015; Young, 2002). It is also important to appreciate that stress hormones play an essential and obligatory role in orchestrating key events underlying cellular growth, replication and differentiation in the brain (Cole et al., 1995; Garbrecht et al., 2006; Matthews, 2002; Merrill, 1992; Trejo et al., 2000; Zhao and Schwartz, 1998) as well as in the maturation of many other organs (Moisiadis and Matthews, 2014). Thus, perturbations in the level and/or time of exposure of these biologic effectors are likely to produce alterations of normal structure and function.

3.2. Immune system

In the non-pregnant state, stress-related states (e.g., depressive symptoms) are associated with dysregulation of inflammatory processes including elevations in circulating proinflammatory cytokines, exaggerated inflammatory responses to in vivo biologic challenges, and more robust inflammatory responses to psychological challenges; these processes likely also play a role during pregnancy (Christian, 2014; Leff-Gelman et al., 2016). It has been reported that psychosocial stress in pregnant women is associated with higher circulating levels of pro-inflammatory cytokines IL-1b, IL-6 and TNF and lower circulating levels of the anti-inflammatory cytokine IL-10. In addition, *ex vivo* endotoxin (LPS)-stimulated levels of proinflammatory IL-1b and IL-6 were higher in stressed pregnant women (Christian et al., 2009; Coussons-Read et al., 2005). Another study of pro-inflammatory responses to an *in vivo* antigen challenge (influenza virus vaccination) in pregnant women reported an association between depressive symptoms and sensitization of the inflammatory cytokine responses (Christian et al., 2010).

There is good evidence that maternal stress during pregnancy also has effects on the immune function of the fetus, as reviewed in the animal literature (Veru et al., 2014), possibly by transfer of maternal cortisol or cytokines to the fetus (Rakers et al., this issue). Maternal immune activation in pregnancy and prenatal immune challenges have been associated with CNS-dysfunction and related behavioral and mental health disorders, including autism and schizophrenia (Knuesel et al., 2014). Prenatal immune challenges may also precipitate the development of Alzheimer and Parkinson diseases (Knuesel et al., 2014). In Project Ice Storm, the relative effects of maternal objective exposure and maternal subjective stress were compared for their effects on immune function in the offspring at the age of 13 years (Veru et al., 2015). Results showed that more severe objective maternal exposure to the ice storm, but not subjective

stress as reflected in PTSD symptom severity, was associated with multiple long-lasting effects on the immune system: CD4+ lymphocytes were decreased, cytokines derived from the innate immune system (TNF-α, IL-1β and IL-6) were increased, and a Th2 shift occurred. This shift to a proinflammatory state affects glucocorticoid gene expression and function (Pariante and Miller, 2001), stimulates activity of the HPA axis (Tsigos and Chrousos, 2002), and attenuates the noradrenaline and serotonin content in the brain (Leonard, 2001) and may, thus, have an pathophysiological role in the mental health problems observed in offspring prenatally exposed to severe maternal stress in Project Ice Storm (Veru et al., 2015).

Recent research focuses on the role of resident immune cells of the brain (i.e., microglia), and their role in neuroimflammation during development and later in life (Bilbo, 2013; Hanamsagar and Bilbo, 2016). Prenatal immune challenges also seem to induce peripheral changes such as, accumulation of adipose tissue, increased body weight, insulin resistance, altered myeloid lineage development and increased gut permeability (Labouesse et al., 2015). Importantly, preclinical studies have shown that normalization of at least some of the peripheral dysfunctions lead to changes in the behavioral deficits, which points to the fact that CNS-dysfunction and peripheral dysfunctions could share interrelated pathological mechanisms induced by a common prenatal stressor (Labouesse et al., 2015).

The effects of maternal stress during pregnancy on immune function in the offspring seem to be, at least in part, mediated by epigenetic changes. Maternal depression-associated changes in the levels of DNA methylation have been observed in neonatal T-lymphocytes; those alterations have also been found in adulthood in post-mortem hippocampal tissues, suggesting life-long persistence in maternal depression-associated epigenetic changes (Nemoda et al., 2015). In Project Ice Storm, the effects of maternal objective exposure on offspring immune function at

age 13 was also mediated by DNA methylation (Cao-Lei et al., 2016). It is worth noting that changes in the maternal immune state may also affect fetal brain development since the immune system plays a critical role in orchestrating key events underlying cellular growth, replication and differentiation in the brain (Merrill, 1992; Zhao and Schwartz, 1998).

3.3. Gut microbiome

The microbiota (or microflora) refers to the bacteria, fungi, archaea, viruses and protozoans that co-exist within mammalian bodies, and influence (both positively and negatively) risk for a range of diseases including inflammatory bowel disease, metabolic diseases, and allergies, but also neurodevelopment (Jandhyala et al., 2015). As reviewed and summarized by (Jašarević et al., 2015b) stress in pregnancy alters vaginal host immunity and resident bacteria composition. During vaginal parturition, the newborn ingests this maternal ecosystem, communicating information about the maternal environment, and establishing the infant's initial microbial population, which then appears to influence risk for a host of immune, metabolic, and neurodevelopmental outcomes; infants born by C-section have significantly less of their mothers' microbiota. In research with non-human primates, one study found that randomly-assigned stress in either early or late pregnancy predicted significant changes in the offspring's microflora as found in fecal samples over the first six months of life: specifically, lower numbers of "good" bifidobacteria and lactobacilli (Bailey et al., 2004). The differences in total anaerobes, bifidobacteria and lactobacilli between unstressed controls and those stressed in late pregnancy had large effect sizes, on the order of .56 to .83. A study of 56 vaginally-delivered Dutch babies found that infants of mothers with either high reported levels of stress or high cortisol concentrations, or both, in pregnancy had higher levels of "bad" proteobacterial groups, and lower levels of "good" bifidobacteria and lactobacilli (Zijlmans et al., 2015a), as in the non-

human primate study; this aberrant colonization pattern was related to more maternally-reported infant gastrointestinal symptoms and allergic reactions. In addition to the infant gut microbiome, recent research also studies the maternal milk and gastrointestinal microbiome as systems mediating the effects of prenatal stress on neurodevelopment in the perinatal period (Bale et al., 2010; Fernández et al., 2013; Grönlund et al., 2011; Jašarević et al., 2015a; Jašarević et al., 2015b; Logan, 2015; O'Mahony et al.; Palagini et al., 2015; Rogers et al., 2016; Stokholm et al., 2016; Zijlmans et al., 2015a). Thus, the microbiome may mediate the effects of maternal stress during pregnancy on the offspring's mental health, neurodevelopment, and immune function in later life.

3.4. Telomere biology

A recent review paper indicated that several psychiatric illnesses (such as major depressive disorder, anxiety disorders, posttraumatic stress disorder) have been associated with accelerated aging as indexed by shorter leucocyte telomere length (Lindqvist et al., 2015). Although conflicting results exist, and no firm conclusions can yet be made about causality (Lindqvist et al., 2015), there are some studies linking prenatal stress to shorter leucocyte telomere length (Entringer et al., 2012; Marchetto et al., 2016).

Telomeres are non-coding double-stranded repeats of guanine-rich tandem DNA sequences and shelter in protein structures that cap the ends of linear chromosomes (Blackburn and Gall, 1978; Moyzis et al., 1988). Telomeres protect chromosomes from recognition by the DNA damage-repair system as DNA breaks. Telomerase is the reverse transcriptase enzyme that adds telomeric DNA to existing telomeres (Blackburn et al., 1989). Telomerase not only maintains telomere length but also preserves healthy cell function.

It has been proposed that telomere biology may represent a common underlying mechanism connecting fetal programming and subsequent health outcomes (Entringer et al., 2012). It appears that the initial setting of the telomere system may be plastic and receptive to the influence of intrauterine conditions (Aviv, 2012). There is evidence that various forms of stress during the intrauterine period of development may alter or program the telomere biology system in a manner that accelerates cellular dysfunction, aging, and disease susceptibility over the lifespan (Entringer et al., 2012; Entringer et al., 2011; Entringer et al., 2013; Haussmann et al., 2011).

The early life setting of telomere length represents a critically important characteristic of an individual's telomere biology system. A reduction in the newborn telomere length could confer greater susceptibility in later life for pathophysiological outcomes, highlighting the importance of understanding factors that determine an individual's newborn telomere length (Aviv, 2012; Entringer et al., 2012; Heidinger et al., 2012). The first human study that addressed the question of an association between maternal psychosocial stress exposure during pregnancy and offspring telomere length employed a retrospective case-control design in a sample of young adults. There was a significant association between prenatal stress exposure and leukocyte telomere length in young adult offspring (Entringer et al., 2011). The effect equated to an additional ~3.5 years of cell aging in prenatally stressed offspring. In another human study in which telomere length was assessed in cord blood samples from a prospective, longitudinal pregnancy cohort, the effects of maternal pregnancy-specific stress (e.g., worries about the health of the unborn child) assessed in early pregnancy (week 10) on offspring telomere length were already evident at birth (Entringer, 2013). Very similar findings were recently reported by a different research group in an independent cohort (Marchetto et al., 2016). Newborns whose

mothers experienced a high exposure to life events during pregnancy had significantly shorter telomere length compared to newborns of mothers with low exposure (Marchetto et al., 2016).

It is well-established in the non-pregnant state that three major, inter-related biological pathways link stress and life-style factors with telomere biology: stress hormones, oxidative state and inflammation. For example, telomere length has been linked in several studies to *in vivo* elevated levels of cortisol and catecholamines, larger cortisol responses to acute stress and dysregulation of the diurnal cortisol rhythm (Epel, 2009; Parks et al., 2009; Tomiyama et al., 2011). *In vitro* treatment of stimulated human T-cells with cortisol causes decreases in cell proliferation, decreased telomerase activity and lower telomerase activity after cell activation (Choi et al., 2008). Furthermore, depression and many unhealthy stress-related behaviors (smoking, alcohol, high fat diet) increase oxidative stress (summarized in Epel, 2009; Lin et al., 2012). Oxidative stress is known to decrease TERT (telomerase protein) activity and to preferentially damage telomeric, as opposed to other, genomic DNA regions (Epel, 2009; Lin et al., 2012). Several studies have demonstrated that markers of inflammation, such as IL-6 and CRP, are linked to telomere length shortening (Carrero et al., 2008; Fitzpatrick et al., 2007), and reduced telomerase activity via NFkB-mediated pathways (Bu et al., 2010). As summarized in sections 3.1 - 3.3 psychological stressors during pregnancy have the potential to increase maternal and fetal cortisol, placental CRH, and inflammatory mediators. Thus, maternal psychological distress stress from exposure to stressful life events or natural disasters, through activation of endocrine stress-related, inflammatory- and oxidative stress-related pathways in the maternal and placental compartment could either directly or indirectly (through changing placental function) impact fetal stress physiology and thereby program the fetal telomere system already during intrauterine life.

4. Conclusion

Early alterations of biological systems may have an adaptive value and may reflect anticipatory adaptations to projected demands (Gluckman and Hanson, 2004). Early life exposure to stress may have beneficial effects on resilience to stress in later life, but the benefits likely depend on the adult environment (Monaghan and Haussmann, 2015). These benefits have a price, namely: atypical brain development (Johnson et al., 2015). An understanding of the adaptive responses of the nervous system provides insight into consistently shown inter-individual variation or uniqueness of brain organization (Xu et al., 2016), and is vital for gaining insights into the structure and function of the atypically developed brain (Miller, 2006).

Development of the mammalian brain is a protracted process that relies on complex mechanisms and intense interaction between genetic, epigenetic and environmental factors (Brown et al., 2016; Dubois et al., 2014). Brain developmental processes are critical for behavior (neurodevelopment including state-regulation in the newborn and motor development, cognitive development and temperament) and early- or late-onset mental health disorders (Di Martino et al., 2014; Richmond et al., 2016; Walhovd et al., 2016) and neurodegenerative diseases disease (Ben-Ari, 2008; Faa et al., 2014; Piras et al., 2014). Our review showed that prenatal exposure to maternal subjective stress, general and pregnancy-related anxiety, depressive symptoms, life events stress, and exposure to a disaster can have long-lasting effects on the behavior and mental health of the offspring, and that several biological systems are involved. The ways and extent to which the offspring are affected depends on a range of mediating and moderating factors.

The results of this review on the effects of prenatal exposure to maternal stress suggest that pregnant women and their unborn children ought to be recognized as vulnerable populations, and protected accordingly from undue hardship and distress. In addition to studying the

particular effects and mechanisms of prenatal stress, researchers are also called to translate this knowledge to women, their spouses, and diverse care providers including psychologists, nurses, general practitioners, obstetricians, pediatricians and other medical professionals who are in a position to provide advice about avoiding avoidable stressors, and taking steps to reduce the effects of unavoidable hardships and mental health conditions.

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Figure 1.

Overview of variables and study design in studies reviewed in section 2.

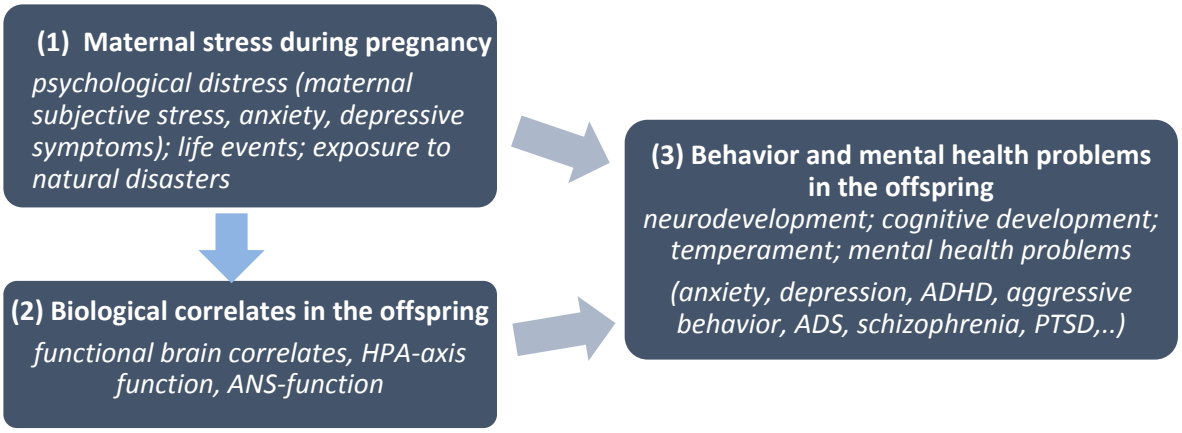

Table 1

Maternal Stress During Pregnancy and Offspring Neurodevelopment: Prospective Studies Since 2010. The articles are sorted by offspring age at follow-up.

Authors, Year	**Offspring age**	**Sample Size**	**Prenatal exposure or measure of maternal stress**	**Prenatal Timing**	**Offspring Outcome(s)**	**Main Findings**
Gerardin et al. (2011)	3 days	205	Antenatal depression (Montgomery-Asberg Depression Rating Scale ≥ 15 and DSM-IV criteria for major depressive episode confirmed by the Mini-International Neuropsychiatric Interview	3rd pregnancy trimester	NBAS, neurobehavioral characteristics: habituation, orientation, motor skills, range of states and regulation of states)	- Poorer regulation of states in all participants - Poorer motor skills and regulation of states in boys.
Pacheco & Figueirido, 2012	1-5 days	110	EPDS depressive symptoms (n= 55 depressed with EPDS >= 10; n=55 EPDS < 10)	3rd pregnancy trimester (28th-37th pregnancy week); during first 5 days after birth	NBAS	- Poorer regulation of states - Lower neurobehavioral maturity (lower total NBAS score)
Figueirido et al. (2017)	1-5 days	104	EPDS depressive symptoms (n= 52 depressed with EPDS >= 9; n=52 EPDS < 9)	3rd pregnancy trimester (28th-33th pregnancy week)	NBAS	- Poorer autonomic stability - Lower neurobehavioral maturity (lower total NBAS score) - link between depression and total NBAS mediated by fetal heart rate variability
Räikkönen et al. (2015)	2 weeks	54	CES-D depressive symptoms	Mean of biweekly assessments from 12th-13th pregnancy weeks onwards until delivery or 38th-39th pregnancy week	Mother-rated infant regulatory behaviors with the Neonatal Perception Inventory	- More behavioral regulatory challenges in the infant, and these changes were mediated by changes in placental glucocorticoid receptor gene expression.
Simcock et al. (2016a)	2, 6, and 16 months	191	QFOSS Queensland Flood Objective Stress Scale, Impact of Event Scale – Revised, Peritraumatic Distress Inventory, Peritraumatic Dissociative Experiences Questionnaire, maternal cognitive appraisal of the flood	Flood was timed at any point in pregnancy. Maternal stress was assessed within 12 months of the flood.	Fine and gross motor function by maternal report on the Ages and Stages Questionnaire	- Better infant motor development at 2 months, yet at 6 and 16 months of age there was a negative association, particularly if flood exposure occurred later in pregnancy and if mothers had negative cognitive appraisals of the event.
Moss (2017)	16 months	145	Objective severity of flood exposure assessed with Queensland Flood Objective	Flood exposure occurred while mother was pregnant: questionnaires	Bayley-III fine and gross motor development	- Objective severity of flood exposure did not predict gross or fine motor development.

			Stress Scale; The Impact of Event Scale – Revised, Peritraumatic Distress Inventory, Peritraumatic Dissociative Experiences Questionnaire, and cognitive appraisal of flood consequences.	were completed at recruitment within 1 year of the flood		- Maternal negative cognitive appraisal of the overall flood consequences predicted poorer child gross motor development. - Higher maternal post-traumatic stress symptoms predicted poorer fine motor development. The effects were independent of maternal mental health after pregnancy.
Lin et al. (2017)	24-36 months	225	The Global Severity Index on maternal emotional stress and depressive and anxiety symptoms of the Symptom Checklist-90-Revised; The Life Event Stress Scale for Pregnant Women on maternal life events	28th to 3ls6th week of gestation	The Gesell Developmental scale on child gross motor, fine motor skills, adaptive behavior, language, and social behavior	Independently of maternal mood at the time of the follow-up, maternal general emotional distress during pregnancy and maternal depressive symptoms during pregnancy predicted lower development quotient scores in gross motor skills, adaptive behavior, and social behavior. - Maternal depressive symptoms during pregnancy also independently predicted lower language development quotients, while the association of maternal general emotional distress was marginal. - Maternal anxiety during pregnancy had no independent effects on child cognitive development.
Cao et al. (2014)	5.5 years	89	Severity of maternal objective exposure to an ice storm with power loss up to 45 days; and maternal PTSD symptoms.	Across pregnancy and during 1st 2nd and 3rd pregnancy trimesters	Bruininks-Oseretsky Tests of Motor Development: Bilateral Coordination, Balance, Visual-Motor Integration	-Higher subjective distress and objective hardship predicted poorer bilateral co-ordination of the child. - Higher objective hardship predicted poorer visual motor integration. - No effects on balance were found.
Grace et al. (2016)	10, 14 and 17 years	2900	Life Stress Inventory on Stressful Life Events	Assessed at 18th and 34th weeks of gestation; comprising life events from 0 to 18 and from 18 to 34 gestation weeks	McCarron Assessment of Neuromuscular Development on Motor Development	- Poorer motor development in children across ages 10-17 years. The associations were independent of perinatal and sociodemographic covariates.

CCEI=Crown-Crisp Experiential Index EPDS=Edinburgh Postnatal Depression Scale; CES-D= Center for Epidemiologic Studies Depression Scale; NBAS= Neonatal Behavioral Assessment Scale

Table 2

Maternal Stress During Pregnancy and Offspring Cognitive Development: Prospective Studies Since 2010. The articles are sorted by offspring age at follow-up.

Authors, Year	**Offspring age**	**Sample Size**	**Prenatal exposure or measure of maternal stress**	**Prenatal Timing**	**Offspring Outcome(s)**	**Main Findings**
Figueiredo et al, 2010	1-5 days	100	EPDS: depressive symptoms (cut-off score EPDS >= 10) STAI: anxiety symptoms (cut-off score STAI >= 45) Socio-demographic questionnaires	3rd pregnancy trimester (30th-34th pregnancy week); during first 5 days after birth	Mother versus stranger's face/voice visual preference paradigm	-neonates of anxious/depressed mothers compared to neonates of non anxious/depressed mothers: do not show visual preference for the mother, require more trials for habituoation and show greater preference for the stranger after habituoation
Pacheco & Figueiredo, 2012	1-5 days	110	EPDS depressive symptoms (n= 55 depressed with EPDS >= 10; n=55 EPDS < 10)	3rd pregnancy trimester (28th-37th pregnancy week); during first 5 days after birth	Mother versus stranger's face/voice visual preference paradigm	-effects of face/voice preference similar to Figueirido et al, 2010 -effects of maternal depression in 3th trimester on infant cognition were not mediated nor moderated by depression at birth.
Tarabulsy et al. (2014)	0-60 months	5903	Meta-analysis on the effects of different stressors: Life events or exposure to catastrophic life events; pregnancy-specific and other stress and anxiety	At different stages of gestation: comparing retrospective and prospective studies	Combination of different tests on cognitive development (Bayley, WISC, WPPSI, MacArthur, Prechtl)	- Maternal stress during pregnancy predicted significantly poorer cognitive development in 0-5-year-old children. Maternal stressful life events or exposure to objective stressors had stronger effects on cognitive development than maternal subjective stress or anxiety symptoms.
Sandman et al. (2012)	3, 6 and 12 months	221	CES-D Depressive symptoms Perceived Stress Scale Cortisol (blood plasma) in afternoon	14 -16 weeks; 24 to 26 weeks, 30 to 32 week, 36 or more weeks gestation and 3, 6, 12 months after birth	Bayley Scales of Infant Development; Mental and Psychomotor Index	- Infants in the two concordant groups had higher scores than in two discrepant groups; at 3 months for Psychomotor Index, at 6 months for both Mental and

				4 groups formed based on scores pre-and postnatal: high-high and low-low (concordant) versus high-low and low-high ‘		Psychomotor index and at 12 months for Mental index; - No such effects were found for Perceived stress; - Depression at any gestational time alone had no effect -Congruence between pre-and postnatal environment was not related to maternal cortisol level
Simcock et al. (2016b)	6 months	115	Disaster-related maternal objective hardship (Queensland Flood Objective Stress Scale); subjective distress (Impact of Events Scale – Revised, Peritraumatic Dissociative Experiences Questionnaire, Peritraumatic Distress Inventory); and cognitive appraisal of the flood.	During the 1st, 2nd, or 3rd trimester of pregnancy	Ages and Stages – III: Communication, Problem Solving and Personal-Social scales.	- High levels of subjective distress was associated with lower problem solving abilities in girls. - Early in utero exposure to the flood was associated with poorer personal-social abilities. - Higher levels of objective hardship were associated with lower personal-social abilities.
Plamondon et al. (2015)	18 months (48 months: see Table 4)	236	Stressful life events; EPDS depressive symptoms; STAI anxiety symptoms	12-24 weeks of pregnancy	Mother-rated Early Childhood Behavior Questionnaire on attention shifting and attention focusing	Maternal stressful life events during pregnancy predicted poorer attentional shifting at 18 months of age, but only in the context of low maternal anxiety during pregnancy. - Maternal anxiety during pregnancy did not have any main effects on child neurocognition, and no significant predictors emerged for attention focusing.
Koutra et al. (2013)	18 months	223	EPDS depressive symptoms	28th-32nd weeks of gestation	Bayley Scales of Infant and Toddler Neurodevelopment	-Poorer infant cognitive development, independently of postpartum depression. - No associations for motor, communication or socio-emotional development.
King et al. (2012)	2, 5, 8 and 11 years	58, 89, 95, 89 respectively	Disaster-related objective hardship (STORM32) and subjective distress (Impact of Events Scale – Revised)	During the 1st, 2nd, or 3rd trimester of pregnancy or up to 3 month preconception.	Bayley Scales of Infant Development, WPPSI, WISC, MacArthur Communicative Development Inventory, and Peabody Picture Vocabulary Test.	Higher levels of objective hardship, but not subjective distress, were associated with lower cognitive abilities. Child sex moderate this relationship when the children were 11 with objective hardship associated with lower cognitive abilities in boys

						only. For language, higher objective hardship, but not subjective distress, was associated with lower language performance. However, when the children were 11 years of age, objective hardship was associated with lower abilities in boys but better performance in girls.
Schechter et al. (2016)	2.5-5 years	162	Psychological distress: a combined index of clinician assigned Clinical Global Impression Score, interviewer-administered Hamilton Rating Scale for Depression and self-completed Perceived Stress Scale and Beck Depression Inventory	Mean measure of assessments on average each 4 weeks from 20th gestation week onwards	Differential Ability Scales, 2nd Edition, Early Years, a neuropsychological assessment tool on general cognitive abilities	Maternal psychological distress during pregnancy predicted poorer cognitive development scores in the children. These effects occurred independently of maternal mood after pregnancy at the time of the follow-up and of sociodemographic and perinatal covariates. Mother's positive engagement with the child emerged as a protective factor such that the effects of prenatal distress were only evident at low levels of maternal engagement.
Nulman et al. (2012)	3-6 years	220	Visual Analogue Scale on depressive symptoms	During pregnancy: timing not specified	WPPSI verbal, performance, and total Intelligence Quotient	- No significant associations with child intelligence quotient scores. in regression models that also adjusted for maternal depression at follow-up.
Evans et al. (2012)	8 years	6735 (5029 with complete data)	EPDS depressive symptoms	18th and 32nd week of gestation	Intelligence quotient measured with WISC	High maternal depressive symptoms during pregnancy predicted significantly - Lower IQ scores in the children, independently of maternal depression after pregnancy. However, adjustments for sociodemographic and prenatal covariates attenuated the association somewhat.
Pearson et al. (2016)	8 and 16 years	5801	CCEI anxiety symptoms	Not specified: measurements in the cohort available at 18th and 32th weeks of gestation	Executive Functioning (working memory; attentional switching and control, verbal and motor processing speed, selective attention) at age 8 in neuropsychological	Poorer working memory at 8 years of age and poorer math grades at 16 years of age, independently of postpartum depression.

					assessment tasks (Math and English Grades at age 16	- The effects on math grades at 16 years of age were partially mediated by changes in working memory at 8 years of age.
Li et al. (2013)	10 years	1038; 964 with data on maternal stressful life events	Stressful life events during pregnancy	Assessed at 18th and 34th weeks of gestation; comprising life events from 0 to 18 and from 18 to 34 gestation weeks	Mathematics, reading, writing, and spelling tests of numeracy and literacy skills	-Poorer reading performance in girls. - In boys, better scores on reading and mathematics tasks. -The effects were independent of maternal stressful life events after pregnancy.
Whitehouse et al. (2010)	10.5 years	1309	Stressful life events during pregnancy	Assessed at 18th and 34th weeks of gestation; comprising life events from 0 to 18 and from 18 to 34 gestation weeks	Vocabulary ability measured with the Peabody Picture Vocabulary Test	- No association with vocabulary development.

CCEI=Crown-Crisp Experiential Index; EPDS=Edinburgh Postnatal Depression Scale; STAI=Spielberger State and Trait Anxiety Inventory; CES-D= Center for Epidemiologic Studies Depression Scale; WISC=Wechsler Intelligence Scale for Children; WPPSI= Wechsler Preschool and Primary Scale of Intelligence

Table 3.

Maternal Stress During Pregnancy and Offspring Temperament: Prospective Studies Since 2010. The articles are sorted by offspring age at follow-up.

Authors, Year	**0ffspring age**	**Sample Size**	**Prenatal exposure or measure of maternal stress**	**Prenatal Timing**	**Offspring Outcome(s)**	**Main Findings**
Hill et al. (2013)	5 weeks	209	The Life History Calendar of life events; STAI state anxiety	32nd week of gestation	Observer-rated The Neonatal Behavioural Assessment-Measure of Negative Emotionality	- Both maternal state anxiety and life events during 3rd pregnancy trimester were associated with higher negative emotionality in the infant. - Postpartum depressive symptoms were not associated with child temperament. In multivariate models, the effect of life events was significant and state anxiety marginal. - The effects were more evident among children with MAOA-

						LPR low activity variants genotype.
Stapleton et al., 2012	6 to 8 weeks	272	The Marital Adjustment Test; Social Support Effectiveness interview; STAI state anxiety; CES-D	18-20th and 24th-26th weeks of gestation	IBQ modified scale on infant distress to novelty	Increased prenatal partner support predicted lower infant distress to novelty. Infant distress to novelty was not associated with antenatal anxiety or depression.
Bhat et al. (2015)	1-4 months	100	General Health Questionnaire psychological distress (somatic symptoms, anxiety, insomnia, social dysfunction and depression)	3rd pregnancy trimester	EITQ Activity, Rhythmicity, Adaptability, Approach, Intensity, Mood, Persistence, Distractibility, Threshold scales	- No continuous associations between maternal psychological distress and infant temperament. Categorically defined high maternal psychological distress during pregnancy predicted significantly lower Adaptability and Approach scores of the infant.
Lin et al. (2014)	6 and 12 weeks	257 for questionnaires; 58-78 for observational assessments	Hispanic Stress Inventory Family Stressors	Between 21st and 40th week of gestation	IBQ-R Negative Affectivity and Extraversion/Surgency at 6 weeks, Observer rating of Self-Comforting and Orienting Behaviors at 12 weeks	- Higher infant Negative Affectivity and Extraversion/Surgency scores as well as more Orienting behaviors in the infant. - No significant associations with self-comforting were found.
Chong et al. (2016)	3 months	594	EPDS depression and STAI state and trait anxiety above clinical cutoffs (13, 45 and 45 points)	26 weeks of gestation	EITQ temperament difficultness and 3 factors of Negative Affectivity and Attentional Regulation, Sensory Reactivity and Regularity and Motor Expression	-Significant associations between maternal anxiety and infant difficult temperament and with higher scores on a temperament factor combining high negative affectivity with poor attentional regulation. These effects were independent of maternal anxiety postpartum. -No significant associations with temperament traits sensory reactivity or regularity and motor expression were found - Maternal depression during pregnancy was not significantly associated with infant temperament.
Rode and Kiel (2016)	3 months	168	EPDS depressive symptoms	3rd trimester	Infant Characteristic Questionnaire fussy/difficult temperament	Marginally significant associations with infant difficult

						temperament/temperamental fussiness.
Baibazarova et al. (2013)	3 months	158	PSS Maternal Perceived Stress, Pregnancy-Related Anxieties-Revised or pregnancy-specific stress, STAI on State Anxiety	2nd trimester	Mother-Rated IBQ-R Fear and Distress to Limitations subscales	Maternal perceived stress during pregnancy was associated with higher infant distress to limitations. - Maternal anxiety levels during pregnancy were not associated with infant temperament.
Nomura et al. (2014)	3 months	141	SCID-I diagnosed depression during pregnancy	Between first prenatal visit and 3rd pregnancy trimester	IBQ-3 14 Temperament Scales	- Higher pleasure seeking, lower soothability and falling reactivity and higher sadness of the infant. - These effects were independent of maternal postpartum depression. -Temperamental differences were strongest if the mother had both depression during pregnancy and pre-eclampsia.
Della Vedova (2014)	3 months	107	CES-D depressive symptoms; STAI state and trait anxiety, The 20-Toronto Alexithymia Scale on alexithymia	3rd pregnancy trimester	EITQ temperamental difficulty	- Maternal depressive symptoms during pregnancy, but not maternal prenatal state or trait anxiety on alexithymia was associated with a more difficult infant temperament., independently of maternal mood postpartum and of perinatal and sociodemographic covariates and life events.
Rouse and Goodman (2014)	3 months	77	Cortisol Levels, Beck Depression Inventory-II depressive Symptoms, SCID-I diagnosis of major depressive episode and anxiety disorders	Assessed monthly from 3rd or 4th pregnancy month onwards	Mother-rated IBQ-R Negative Affectivity	- Higher maternal depressive symptoms during pregnancy predicted higher infant negative affectivity. These effects were independent of postpartum depression.
Zande and Sebre (2014)	3 and 6 months	258	Depressive Symptoms (EPDS and GMDS); Perceived Social Support	3rd pregnancy trimester	Mean score of biparental ratings of IBQ-R negative affectivity, orienting/regulation, extraversion/surgency	- Maternal depressive symptoms during pregnancy predicted higher infant negative affectivity at 3 months of age. - N significant associations with orienting/regulation or surgency/extraversion were found.

						- Social support during pregnancy did not predict infant temperament. For negative affectivity at 6 months of age, negative affectivity at 3 months and maternal depressive symptoms and social support at 3 months postpartum were the significant predictors.
Green et al. (2016)	3, 6, 18 and 36 months	179	CES-D depressive symptoms	24^{th} to 36^{th} weeks of gestation	Negative emotionality assessed with IBQ-R at 3 and 6 months and Early Child Behavior Questionnaire at 18 and 36 months of age	- Prenatal maternal depressive symptoms interacted with a genetic risk score derived from serotonin- and dopamine receptor gene genotypes in predicting child negative emotionality such that among individuals with a high-risk genotype, prenatal maternal depressive symptoms predicted higher negative emotionality across ages 3 to 36 months independently of postpartum depression. Among children with low-risk genotype, no effects of maternal prenatal depression were found.
McMahon et al. (2013)	4 months	512	EPDS depressive symptoms: STAI trait and state anxiety, Baby Schema questionnaire; Anxiety concerning Health and Defects in the Child–subscale on pregnancy-specific anxiety	3^{rd} pregnancy trimester	Short Temperament Scale for Infants on difficult temperament	- Maternal depressive, trait- and state and pregnancy-specific anxiety were associated with more difficult temperament. However in multivariate models including all the (highly multicollinear) maternal psychological distress measures during pregnancy together with postpartum state anxiety and depressive symptoms, only prenatal trait anxiety and postpartum state anxiety were independently associated with a more difficult temperament.
Werner et al. (2013)	4 months	103	Salivary Cortisol, STAI state anxiety, CES-D depressive	36^{th}-38^{th} week of gestation	The Harvard Infant Behavioral Reactivity Protocol on Temperamental Reactivity; IBQ	- Higher maternal cortisol levels during pregnancy predicted high reactivity of the infant.

			symptoms and PSS perceived stress		scales on Negative and Positive Reactivity	- No significant associations with maternal prenatal psychological distress with child reactivity were found. - Cortisol levels were not associated with mother-rated reactivity.
Braeken et al. (2016)	4 months	109	The Freiburg Mindfulness Inventory – short form mindfulness; EPDS depressive symptoms during pregnancy	Before 15th week of gestation and at 31st to 37th week of gestation	Socio-emotional development assessed with the Ages and Stages Questionnaire subscales of self-regulation, communication, affect, interaction with people and adaptive functioning	- Maternal mindfulness during pregnancy predicted better adaptive functioning in 4-months old infants, independently of maternal mood postpartum. - Mindfulness was not associated with the other subscales; - Maternal depressive symptoms during pregnancy did not predict adaptive functioning.
Rothernberger et al. (2011)	5 months	104	Edinburgh Postnatal Depression Scale, Perceived Stress Questionnaire; Overall Objective Stress Scale	During 1st, 2nd and 3rd pregnancy trimesters	Laboratory-based assessment of infant affective reactivity	Higher perceived stress was associated with less infant affective reactivity. No continuous associations with antenatal depression or objective stress emerged. -Assessed categorically, infants with high emotional reactivity had mothers with less perceived stress, depressive symptoms and objective stress during pregnancy.
Braithwaite et al. (2013)	6 months	3946	Crown Crisp Index anxiety symptoms	18th and 32nd weeks of gestation	IBQ temperamental reactivity	-Maternal anxiety symptoms during pregnancy predicted higher infant temperamental reactivity, independently of maternal depressive symptoms postpartum. No moderating effect of serotonin transporter gene 5-HTTLLPR were found.

Pluess et al. (2011)	6 months	1513	Brief Symptom Inventory anxiety symptoms	20 weeks of gestation	IBQ-R Negative Emotionality	- Higher antenatal anxiety predicted higher negative emotionality. - The effects were independent of sociodemographic and perinatal covariates and maternal anxiety and depressive symptoms after pregnancy. -The effects of antenatal anxiety were particularly evident in the infants carrying one or two short alleles of the serotonin transporter polymorphism gene *5HTTLPR*. -No significant effects emerged among those homozygous for the gene's long allele.
Kantonen et al. (2015)	6 months	102	Maternal alexithymia assessed with Toronto Alexithymia Scale, depression (EPDS), Pregnancy-Related Anxiety-Revised questionnaire on pregnancy-related anxiety	EPDS and alexithymia at 18-22 and 32-34 weeks, EPDS and Pregnancy-Related anxiety at 32-34 weeks	Mother-rated IBQ temperament traits activity level, smiling and laughter, fear, distress to limitations, soothability & duration of orienting	-Higher maternal alexithymia and higher maternal depressive symptoms were correlated with higher infant duration of orienting. -The effects of alexithymia were independent of maternal depression. -No significant effects on other temperamental traits were found.
Huynh (2014)	6 months	135	Family History Screen Questionnaire on Mental Disorders in the mother and her partner: Major depression was the assessed exposure here	3rd pregnancy trimester	Mother-rated IBQ-R 14 subscales	-Maternal depression predicted lower smiling and laughter, soothability, and vocal reactivity and higher sadness of the infant. -No main effects of paternal depression emerged, but maternal and paternal depression occurring together predicted lower smiling and laughter, high pleasure seeking, soothability, cuddliness, and vocal reactivity.
Laplante et al. (2016)	6 months	121	Severity of maternal objective exposure to an ice storm with power loss up to 45 days; and maternal PTSD symptoms.	Across pregnancy and during 1st, 2nd or 3rd pregnancy trimesters	Infant Characteristic Questionnaire traits difficult/fussy temperament, low responsiveness, needs attention, and unadaptable	- Higher maternal subjective distress during pregnancy predicted higher scores on temperament traits needs attention and difficult/fussy temperament and lower scores

						on temperamental responsiveness in the offspring. - - Early exposure to the ice storm during pregnancy combined with high subjective distress also predicted a more difficult temperament, as well as objectively rated hardship.
Simcock et al. (2017, in press)	6 months	126	Disaster-related maternal objective hardship (Queensland Flood Objective Stress Scale); subjective distress (Impact of Events Scale – Revised, Peritraumatic Dissociative Experiences Questionnaire, Peritraumatic Distress Inventory); and cognitive appraisal of the flood	During 1st, 2nd or 3rd trimester of pregnancy	Short Temperament Scale for Infants: approach, rhythmicity, cooperation-manageability, activity-reactivity, irritability, easy-difficult	- Maternal subjective distress and cognitive appraisal were associated with easier temperaments. - Boys exposed to higher objective exposure levels were rated as more irritable. - Higher objective exposure in early pregnancy was associated with more arrhythmic temperaments. Mothers whose subjective distress levels exceeded their level of objective exposure rated their children as being more active-reactive.
Peltola et al, (2016)	8 to 10 months	173	Maternal anxiety (short version of State Trait Anxiety Inventory); other questionnaires	Third trimester; postnatally	Respiratory sinus arrhythmia (RSA; electrocardiography); negative affectivity (IBQ-R; short version)	-interaction effect: no association between anxiety on negative affectivity in infants with low RSA whereas a positive association in infants with high RSA
van den Heuvel et al. (2015b)	10 months	90	Maternal mindfulness (assessed with Freiburgh Mindfulness Inventory-Short Form) and maternal anxiety symptoms (assessed with Symptom Checklist-90)	Between 15th and 22nd week of gestation	Ages and Stages Questionnaire Neurocognitive and Social-Emotional Development: IBQ-R Negative affectivity surgency/extraversion, and orienting/regulation	- Higher maternal anxiety and lower maternal mindfulness during pregnancy predicted higher infant negative affectivity. - Higher maternal anxiety during pregnancy predicted higher extraversion/surgency and higher mindfulness predicted higher orienting/regulation. - Maternal anxiety mediated the effects of low maternal mindfulness on child negative affectivity.

Stroustrup et al. (2016)	24 months	500	EPDS depressive symptoms	2nd pregnancy trimester	Mother-Rated Difficult Temperament with the Toddler Temperament Scale	- Maternal depression during pregnancy predicted higher risk of infant difficult temperament and its subscales, independently of postpartum depression.
Blair et al. (2011)	24 months	120	STAI state anxiety and Pregnancy-Related Anxiety Scale on pregnancy-specific anxiety	16th. 20th, 26th, 32th and 37th gestation week	Early Child Behavior Questionnaire Negative Affectivity	- Maternal pregnancy-specific anxiety predicted significantly higher infant negative affectivity, independently of maternal concurrent anxiety. - Maternal general state anxiety had no effects on child temperament.
Lin et al. (2017)	24-36 months	225	The Global Severity Index and Symptom Checklist-90-Revised depressive and anxiety symptoms and emotional distress; The Life Event Stress Scale for Pregnant Women on life events	28th to 36th week of gestation	Toddler Temperament Scale on temperament traits of activity level, regularity, phobotaxis, adaptability, reaction intensity, mood, persistence, attention, reaction threshold	- Maternal anxiety and global severity of emotional distress during pregnancy were associated with higher reaction intensity in children, independently of maternal mood after pregnancy concurrently to rating the child. - No other independent associations of maternal depressive, anxiety, or general emotional distress severity during pregnancy with child temperament traits were found.
Bekkhus et al. (2011)	3 years	24259	Hopkins Checklist 5 items on maternal anxiety and depressive symptoms, 10-item questionnaire on family disharmony	17th and 30th gestation weeks	Crying and aggressive behaviour of the Child, assessed based on selected items from The Emotionality Activity, Sociability temperament questionnaire and Child Behavior Checklist	-Maternal depressive or anxiety symptoms during pregnancy were not associated with child crying or aggressive behavior. -Family disharmony predicted less crying behavior of the child. -Consistently high depressive and anxiety during and after pregnancy predicted higher child crying behavior and postpartum depressive/anxiety symptoms and family disharmony predicted higher crying and aggressive behavior in the child.

EITQ=Early Infancy Temperament Questionnaire; EPDS=Edinburgh Postnatal Depression Scale; IBQ=Infant Behavior Questionnaire; IBQ-R: Infant Behavior-Questionnaire Revised; STAI= Spielberger State and Trait Anxiety Inventory; CES-D=Center for Epidemiologic Studies Depression Scale PSS=Perceived Stress Scale; SCID=Structured Clinical Interview for DSM disorders

Table 4

Maternal Stress During Pregnancy and Offspring Mental Health Problems: Prospective Studies Since 2010. The studies are sorted by offspring age at follow-up.

Authors, Year	**Offspring Age**	**Sample Size**	**Prenatal exposure or measure of maternal prenatal distress**	**Prenatal Timing**	**Offspring Outcome(s)**	**Main Findings**
Su et al. (2015)	0 to 3 years	5102034	Maternal loss of a relative prenatally or before conception. Bereavement stress was divided to close (father or older child) and further relatives (other).	Throughout pregnancy	Diagnosis of eating disorder leading to hospitalization or outpatient care.	- Maternal death of a close relative (spouse or an elderly child) 6 months prior to pregnancy predicted an increased risk of eating disorders in the offspring. - Prenatal exposure showed nonsignificant associations of similar effect size. - Death of other relatives had no effects on offspring eating disorders.
Gerardin et al. (2011)	1 year	101	Prenatal depression diagnosis based on Montgomery-Asberg Depression Rating Scale score≥15 and DSM-IV criteria of major depressive episode in Mini-International Neuropsychiatric Interview	3rd pregnancy trimester	Infant-Toddler Social and Emotional Assessments Scale	- Infants exposed to antenatal but not postpartum maternal depression had significantly higher scores on activity/impulsivity, dispositional and oppositional aggression, generalized anxiety and sleep problems.
Ronald et al. (2011)	2 years	2868	Maternal stressful life events during pregnancy	Between 0 and 18 weeks and between 18 and 34 weeks of gestation, assessed at 18th and 34th gestation weeks	ADHD and autism symptoms in CBCL (ADHD, pervasive developmental problems)	-Higher risk of ADHD symptoms in boys and girls and of autism symptoms in boys. All effects were independent of maternal mood postpartum.
Edwards and Hans (2016)	2 years	196	CES-D depressive symptoms	27.6 weeks	Brief Infant-Toddler Social and Emotional Assessment Social and Emotional Problems	- Increased toddler behavior problems. -This association was partially mediated by maternal depressive symptoms after pregnancy concurrently to rating the child and by maternal sensitivity towards the child.

Robinson et al. (2011)	2-14 years	1744	Maternal stressful life events during pregnancy	Between 0 and 18 and 18 and 34 gestational weeks, assessed at 18th and 34th weeks of gestation	CBCL internalizing, externalizing, and total psychiatric problems	- Higher internalizing, externalizing, and total psychiatric problems in children across ages 2-14 years, independently of maternal life events and mental health postpartum.
Tearne et al. (2015)	2-14 years	2459	Maternal stressful life events during pregnancy	Life events at 0-18 weeks of gestation assessed at 18th weeks of gestation	CBCL internalizing, externalizing, and total psychiatric problems	- Higher internalizing, externalizing and total problems in 2-14 years old children and increases in internalizing and total problems between 2 and 14 years.
Sharp et al. (2015)	2.5 years	243	STAI state anxiety	32nd week of gestation	CBCL Internalizing, Externalizing, Anxious/Depressed, and Attention Problems	- Higher Internalizing, Anxious/Depressed and Attention Problems in children independently of maternal mood concurrently to rating the child. Effects on externalizing problems were non-significant after this adjustment, although not among girls. - Effects were moderated by maternal stroking behavior in child's infancy, particularly among girls. - Maternal prenatal anxiety predicted higher psychiatric problems especially if maternal stroking behavior was low.
Cents et al. (2013)	3 years	4167	Brief Symptom Inventory depressive symptoms	20th week of gestation	CBCL Internalizing and Externalizing Problems	- Consistently high maternal depressive symptoms during and after pregnancy predicted highest levels of child internalizing and externalizing psychiatric problems.
Velders et al. (2011)	3 years	2698	Brief Symptom Inventory depressive symptoms and hostility, General Functioning of the Family Assessment Device on family functioning	20th week of gestation	CBCL Internalizing and Externalizing Problems	- Maternal and paternal prenatal depressive symptoms, prenatal hostility and poorer family functioning were associated with increased internalizing and externalizing problems in children. -However, all associations were non-significant after adjustment for maternal and paternal hostility 3 years postpartum.

Velders et al. (2012)	3 years	1727	Brief Symptom Inventory Global Severity Index on General Psychological Symptoms	20th week of gestation	CBCL Total Problems	-Maternal depressive symptoms during pregnancy predicted increased child total emotional and behavioral problems, independently of maternal mood postpartum. -This association was particularly evident among carriers of the CC alleles of the rs41423247 glucocorticoid receptor gene.
Pickles et al. (2016)	3.5 years	813	STAI state anxiety; The Pregnancy-Specific Anxiety on pregnancy-specific anxiety	20th week of gestation	CBCL Internalizing, Externalizing, Anxious/Depressed, and Attention Problems and Aggressive Behavior	- Maternal general and pregnancy-specific anxiety during pregnancy were associated with significantly higher psychiatric problems of all types in children. - After adjustment for confounders including maternal postpartum anxiety and depressive symptoms concurrently to rating the child, the effects of general state anxiety were completely non-significant. - Maternal pregnancy-specific anxiety still predicted significantly higher externalizing, aggressive behavior and attention problems and marginally significantly higher internalizing problems in children. - The effects on child internalizing externalizing and aggressive problems were moderated by maternal stroking behavior such that maternal pregnancy-specific anxiety predicted these types of problems particularly at low levels of maternal stroking behavior.
Van Batenburg-Eddes et al. (2013)	3-4 years	2280 in Generation R; 3442 in ALSPAC	Generation R: Brief Symptom Inventory ALSPAC: EPDS depressive symptoms, CCEI anxiety symptoms	Generation R: 20th gestational week ALSPAC: 18the gestational week	Generation R: CBCL attention problems ALSPAC: SDQ hyperactivity/inattention scale	- Generation R: Maternal depression/anxiety during pregnancy were associated with higher child attention problems, but not after adjusting for maternal concurrent mood. - ALSPAC: Maternal depressive and anxiety symptoms predicted higher attention problems in

						children, independently of maternal mood after pregnancy.
Nulman et al. (2012a)	3-6 years	220	Visual Analogue Scale on depressive symptoms	During pregnancy: not specified	CBCL and Conner's Parent Rating Scale on total psychiatric problems	-Antenatal depressive symptoms predicted total psychiatric problems in the children, independently of maternal depressive symptoms at follow-up.
Li et al. (2010)	From 3 years of age to Late Adolescence	1015912	Bereavement stress (death of a close relative during pregnancy)	Across pregnancy and during each pregnancy trimester	Hospital discharge register diagnosis of, or purchase of, prescribed medication for ADHD	Maternal bereavement stress predicted increased ADHD risk in boys but not girls, independently of prenatal and sociodemographic covariates and maternal history of mental disorders.
O'Donnell et al. (2014a)	4,7,9,11.5, and 13 years	7944	CCEI anxiety and depressive symptoms and EPDS depressive symptoms	18th weeks of gestation	SDQ scales on ADHD, conduct and emotional problems and total psychiatric problems: SDQ-rated presence of psychiatric disorder	- Maternal anxiety and depressive symptoms predicted higher internalizing and externalizing problems in the offspring throughout ages 4-13 years, independently of maternal symptoms after pregnancy.
Braithwaite et al. (2013)	4,7,9,11.5, and 13 years	3946	Crown Crisp Index anxiety symptoms	18th and 32nd weeks of gestation	SDQ total, emotional, conduct and hyperactivity scales	- Increased total, emotional, conduct and hyperactivity in the child, independently of maternal symptoms postpartum. - There was no moderating effect of serotonin transporter gene genotype.
O'Donnell et al. (2014b)	4,7,9,11.5, 13,and 15 years	4-13 years: 8584 15 years: 4704	Crown Crisp Index anxiety symptoms	32nd week of gestation	SDQ emotional problems on internalizing symptoms; Development and Well-Being Assessment interview on internalizing (depressive or anxiety disorder) symptoms	- Maternal antenatal anxiety predicted higher child internalizing problems across childhood and adolescence and anxiety/ depressive internalizing symptoms at age 15 years. - These effects were independent of maternal anxiety and depressive symptoms postpartum and sociodemographic and perinatal covariates. Some effects were moderated by BDNF genotype.
Zhu et al. (2015)	4-4.5 years	1765	Stressful Life Events with Prenatal Life Events Checklist. Social Support and Trait Coping Style Questionnaire on avoidance coping	Life events during 1st, 2nd and 3rd trimesters; assessed at 30-34th weeks gestation when social	Conner's Hyperactivity Index ADHD symptoms	- Maternal stressful life events during 2nd and 3rd pregnancy trimesters predicted higher child ADHD symptoms.

				support and avoidance coping were also assessed		- The effect of 2nd trimester life events was more evident among boys, and found also for clinically significant ADHD symptoms. - The effect of life events during 3rd pregnancy trimester was present only in girls and only on continuously assessed symptoms. - Particularly among boys, lower social support and higher avoidance coping also predicted higher ADHD symptoms. - No effects of 1st trimester life events were found.
King et al. (2012)	4 – 11.5 years		Disaster-related maternal objective hardship (STORM32) and subjective Distress (Impact of Events Scale – Revised)	During 1st, 2nd, 3rd trimester of pregnancy or 3-months preconception	Child Behavior Checklist	- Higher levels of maternal objective hardship, subjective distress, and the interaction term predicted higher levels of internalizing and externalizing behaviors in children from 4 to 11.5 years of age.
Loomans et al. (2011)	5 years	3758 children; 3446 for maternal assessments, 3520 for teacher assessment	STAI state anxiety	16th week of gestation	Teacher- and mother rated SDQ scales on total psychiatric problems, hyperactivity/inattention, conduct problems, peer problems emotional symptoms and pro-social behavior	- Higher mother and teacher-rated total psychiatric problems and lower prosocial behavior, independently of maternal mood concurrently to rating the child, - Independent effects on mother-rated conduct problems, peer problems and emotional symptoms were also found. - In boys, maternal antenatal state anxiety independently predicted higher mother-rated hyperactivity/inattention. - In univariate analysis, maternal state anxiety was associated with higher scores on all mother-and teacher-rated psychiatric problem scores and significantly lower mother-and teacher-rated prosocial behavior.
Rijlaarsdam et al. (2016)	6 years	743	A cumulative stress measure based on self-reports on four stress domains: (1) life stress	During pregnancy: not specified but Generation R	Autistic traits measured with Social Responsiveness Scale	- Higher levels of prenatal stress independently predicted higher autistic traits in the offspring.

			(death in family, illness, work problems), (2) contextual stress (financial difficulties, housing problems), (3) personal stress (psychopathology, substance abuse), and (4) interpersonal stress (relationship difficulties, arguments with friends).	measurements took place at 20th week of gestation	and CBCL Pervasive Developmental Problems Scale	
Walder et al. (2014)	6.5 years	89	Severity of maternal objective exposure to an ice storm with power loss up to 45 days; and maternal PTSD symptoms.	Across pregnancy and during 1st, 2nd or 3rd pregnancy trimesters	Autism Spectrum Screening Questionnaire autistic symptoms	- Severity of maternal stress exposure during pregnancy predicted higher autism spectrum disorder symptoms in the offspring.
Davis and Sandman (2012)	6-10 years	178	Maternal salivary cortisol, depressive symptoms (CES-D), perceived stress (PSS), state anxiety (STAI) pregnancy-specific anxiety (Pregnancy-Related Anxiety Scale)	Cortisol, CES-D, PSS and pregnancy-Related Anxiety Scale at :20th, 25th and 30th gestational week; STAI at 20th and 30th weeks of gestation	Mother-rated CBCL Anxiety Problems Scale	- Higher maternal cortisol, state- and pregnancy-specific anxiety, depressive symptoms and perceived stress during pregnancy each predicted significantly higher anxiety problems in children, independently of maternal mood after pregnancy concurrently to rating the child. -The effects of pregnancy-specific anxiety and maternal cortisol were independent of other measures of prenatal psychological distress.
Buss et al. (2012)	7.5 years	65	Maternal salivary cortisol, measured most often in afternoon	15, 19, 25, 31, 37 weeks of gestation	Mother-rated CBCL affective problems	- Higher maternal cortisol levels at 15 weeks of gestation predicted higher risk of affective problems among girls, independently of maternal concurrent depressive symptoms when rating the child. - This effect was mediated by changes in child amygdala volume. - No significant associations were observed in boys, and changes in cortisol levels later in pregnancy did not independently predict child problems.
Isaksson et al. (2015)	9 years	70	Maternal salivary cortisol, The Self Reporting Questionnaire on psychological distress during last four weeks, and a self-report	2nd or 3rd pregnancy trimester (Mean week=29)	Mother-rated CBCL internalizing, externalizing and total psychiatric problems	- Higher maternal morning cortisol levels during pregnancy were associated with significantly higher internalizing, externalizing and total psychiatric problems in

			questionnaire on maternal exposure to abuse			children, independently of maternal concurrent mood and other covariates. - Higher maternal afternoon cortisol during pregnancy was associated with higher child externalizing problems. - Maternal psychological distress or exposure to abuse were not associated with child psychiatric problems.
Leis et al. (2014)	10-11 years	2891	EPDS Prenatal Depressive Symptoms; CCEI anxiety symptoms	18th and 32nd weeks of gestation	Mother- and teacher-rated SDQ Total Difficulties, Prosocial Behavior, Peer and Conduct Problems, Emotional Symptoms and Hyperactivity	-Maternal depressive symptoms during pregnancy were independently associated with higher mother-and teacher-rated hyperactivity and mother-rated total difficulties, emotional symptoms and conduct problems, --Anxiety symptoms during pregnancy were independently associated with higher mother-rated total difficulties, and emotional symptoms.
Kingsbury et al. (2016)	10-18 years	10569	Stressful Life events assessed with a 42-item questionnaire	18th week of gestation and 8th week postpartum	Self-reported depressive symptoms assessed with Clinical Interview Schedule-Revised and with Short Mood and Feelings Questionnaire d	- Higher depressive symptoms in the offspring across ages 10-18 years. -The effects were particularly evident for life events occurring during the first 18 weeks of gestation.
Winsper et al. (2015)	11-12 years	6050	CCEI Maternal Anxiety and Depressive Symptoms: EPDS Depressive Symptoms	18th and 32 pregnancy weeks	UK Childhood Interview for DSM-IV Borderline Personality Disorder	- Maternal depressive symptoms in pregnancy predicted higher risk of borderline personality disorder in the offspring, independently of maternal mood postpartum.
Pawlby et al. (2011)	11 and 16 years	120	Maternal ICD-9 diagnosis of depression during pregnancy assessed with the Clinical Interview Schedule Interview	36th week of gestation	Child and Adolescent Psychiatric Assessment ICD-9 diagnosis of depression and conduct disorder: a combination of these two diagnoses were used as an outcome	- Increased risk of offspring psychiatric disorder in the offspring of antenatally depressed mothers, independently of offspring exposure to childhood maltreatment. - There were accumulative effects such that offspring risk of psychiatric disorder was

						particularly increased if the mother had depression during pregnancy and if the offspring was exposed to childhood maltreatment.
Plant et al. (2013)	11 and 16 years	125	Maternal ICD-9 diagnosis of depression during pregnancy assessed with the Clinical Interview Schedule Interview	36th week of gestation	Child and Adolescent Psychiatric Assessment interview symptoms of depression and antisocial behavior(Disruptive Behavior Disorder) (mean score of symptoms at 11 and 16 years)	-Maternal depression during pregnancy combined with maternal exposure to childhood maltreatment predicted a significantly higher risk of antisocial behavior in the offspring. - Exposure to only one of these stressors did not predict antisocial behavior, and no accumulative effects of maternal childhood maltreatment and maternal antenatal depression on offspring risk of depression were found.
St-Hilaire et al. (2015)	13 years	54	Subjective and objective stressfulness of exposure to "Ice Storm", timing of exposure	Across pregnancy and during 1st, 2nd or 3rd pregnancy trimesters	Eating Attitudes Test on eating attitudes and behaviors, on eating disorder symptoms	- Maternal stress exposure during 3rd pregnancy trimester predicted higher eating disorder symptoms in the offspring.
Betts et al. (2014)	14 years	3925	Delusions-States-Symptoms Inventory on depressive and anxiety symptoms; Reeder Stress Inventory on stress symptoms	First antenatal clinic visit	Achenbach Youth Self-Report Internalizing and Externalizing problems	- Higher maternal emotional distress during pregnancy (stress, anxiety and depressive symptoms) predicted higher internalizing problems in the offspring, independently of maternal mood after pregnancy. - No significant effects of externalizing problems were found.
Glasheen et al. (2013)	16 years	577	CES-D depressive symptoms; STAI trait scale on trait anxiety	1st, 2nd and 3rd pregnancy trimesters	Diagnostic Interview Schedule diagnosis of major depressive disorder, conduct disorder, post-traumatic stress disorder, separation anxiety disorder and generalized anxiety disorder	-Trajectories of pre- and postnatal depressive symptoms or trait anxiety were not associated with offspring depressive or anxiety disorders. - Girls of mothers with high pre- and postnatal anxiety symptoms had significantly lower risk of conduct disorder, -Boys born to mothers with high trait anxiety pre-and postnatally had significantly higher risk of conduct disorder.

						- In boys, high pre- and postnatal depressive symptoms were associated with lower depression risk in the offspring.
Korhonen et al. (2014)	16 years	192	EPDS depressive symptoms	3rd pregnancy trimester	Mother (CBCL) and self (Young Adult Self Report)–rated internalizing and externalizing problems	-Higher offspring externalizing Problems in the CBCL and marginally higher externalizing scores in the YSR. - No significant effects on Internalizing Problems were found.
Capron et al. (2015)	18 years	4303	EPDS depressive symptoms	18th gestational week	CIS-R diagnostic interview diagnosis of anxiety disorder	Increased offspring risk of anxiety disorders, independently of maternal mood after pregnancy
Pearson et al. (2013)	18 years	2847, 8937 with imputations	EPDS depressive symptoms	32 weeks of gestation	CIS-R diagnostic interview diagnosis of major depression	Higher risk of major depression in the offspring of antenatally depressed mothers, independently of maternal mood after pregnancy
Plant et al. (2015)	18 to 25 years	103	Maternal ICD-9 diagnosis of depression during pregnancy assessed with the Clinical Interview Schedule Interview	36th week of gestation	SCID DSM-IV diagnosis of depression and continuously assessed severity of DSM-IV symptoms	- Maternal depression during pregnancy was associated with an over 3-fold, significantly increased risk of depression and with higher depressive symptoms in the offspring. - These associations were independent of maternal postpartum depression but mediated through offspring exposure to childhood maltreatment.
Rai et al. (2012)	Swedish Study: From Birth to Adolescence ALSPAC: Birth to 11 years of age	Swedish study: 4429 ASD cases and 43277 controls ALSPAC: 11554	Swedish study: Register-Diagnosis of Death, Life-threatening Illness, Accident or Injury of a Close Relative During Pregnancy ALSPAC: Maternal self-reported life events and their assessed severity	Swedish Study: Register-Information Across Pregnancy ALSPAC: Early and Late Pregnancy Life Events, assessed at 18th week of gestation and 8 weeks postpartum	Swedish Study: diagnosis of autism certified via a multidisciplinary approach combining information from health registers, diagnostic assessments including information, for example from parental life history interviews and child neuropsychiatric and neuropsychological assessments	- Maternal stressful life events during pregnancy showed no effect on offspring risk of autism in either cohort.

					ALSPAC: A register diagnosis of autism in the British National Health Records and the Pupil Level Annual Schools Census	
Class et al. (2014a)	From Birth to Early Adulthood	738144 in childhood; 2155221 in adulthood	Bereavement (death of a first-degree relative)	Across pregnancy and during each pregnancy trimester	Hospital Discharge Register diagnoses of autism, ADHD, bipolar disorder, schizophrenia, suicides, suicide attempts	-Higher risk of autism and ADHD but not of bipolar disorder, schizophrenia, suicides or suicide attempts in the offspring
Abel et al. (2014)	From Birth to Early Adulthood	1045336	Bereavement stress	Across pregnancy and during each pregnancy trimester	Hospital Discharge Register diagnosis of any, affective, and non-affective psychosis	No association with offspring risk of psychosis.
Betts et al. (2015)	21 years	3099	Delusions-States-Symptoms Inventory on depressive and anxiety symptoms and Reeder Stress Inventory on stress symptoms	First antenatal clinic visit	Achenbach Young Adult Self-Report Internalizing and Externalizing Problems; CES-D depressive symptoms	- Maternal emotional distress during pregnancy predicted higher internalizing and externalizing problems and depressive symptoms in the offspring.
Fineberg et al. (2016)	In adulthood	95 cases with schizophrenia and 206 controls	Negative affect, pregnancy-specific anxiety and traumatic and daily stressful life events identified from answers to an interview question "What kind of things have been worrying you recently?"	During pregnancy, on average at 16 weeks of gestation	Schizophrenia spectrum disorder diagnosed combining information from electronic health records and SCID interviews or with The Diagnostic Interview for Genetic Studies	In the whole cohort, none of the maternal prenatal psychosocial stress indices were associated with offspring schizophrenia risk. - However, among male offspring, increased maternal antenatal daily stressful life events predicted an increased risk of schizophrenia.

ADHD=Attention Deficit Hyperactivity Disorder; EPDS=Edinburgh Postnatal Depression Scale; CCEI=Crown-Crisp Experiential Index; STAI=Spielberger State and Trait Anxiety Inventory; PSS=Perceived Stress Scale; SDQ=Strength and Difficulties Questionnaire; CBCL=Child Behavior Checklist; ALSPAC=Avon Longitudinal Study of Parents and Children; DSM=Diagnostic and Statistical Manual for Mental Disorder; ICD=International Classification of Diseases; CIS-R=The Clinical Interview Schedule-Revised; SCID=Structured Clinical Interview for DSM disorders; CES-D: Center for Epidemiologic Studies Depression Scale

Table 5

Maternal Stress During Pregnancy and Offspring Functional Brain Correlates: Cerebral Information Processing and Functional Connectivity.

The studies are sorted by offspring age at follow-up.

Authors	Offspring Age	Sample Size (N)	Neuroimaging Technique	Prenatal exposure or measure of maternal stress	Prenatal Timing	Offspring Outcome(s)	Main Findings
Harvison et al. (2009)	Newborns	28	Event-Related Potentials (ERP)	BAI Anxiety	Late pregnancy	Electrophysiological brain responses (P150, P350, N450, and slow wave) to mother's versus strangers voice in an auditory paradigm.	Infants of high-anxious mothers displayed lower negative frontal slow wave amplitudes in response to their mother's voice compared to a female stranger's voice, while infants of low-anxious mothers displayed the opposite pattern.
Scheinost et al. (2016a)	Newborns	12 exteremely preterm newborns, no prenatal stress; 25 term born neonates, no prenatal stress; 10 extremely preterm newborns, with prenatal stress	Functional MRI	Prenatal Stress	Not specified	Amygdala functional connectivity	Maternal prenatal stress in preterm neonates (born < 28 weeks, without major brain injury) decreased amygdala-subcortical (e.g. thalamus) connectivity. The authors conclude that prenatal exposure to maternal distress during pregnancy seems to amplify the decrease in amygdala connectivity seen in very preterm born neonates.
Hunter et al. (2012)	6 months	242	Event-Related Potentials (ERP)	Anxiety Disorder (DSM-IV diagnosis) & antidepressant durg use	n.a.	Electrophysiological brain responses (P50) to auditory stimuli in a sensory gating paradigm.	Maternal anxiety disorder during pregnancy was associated with diminished infant P50 (i.e., less inhibition during sensory gating). Prenatal antidepressant exposure mitigated this effect.
Qiu et al. (2015a)	6 months	24	Functional MRI	EPDS Depression	26 weeks of gestation	Amygdala functional connectivity at 6 months of age.	Prenatal exposure to maternal depressive symptoms was associated with greater functional connectivity of the

							amygdala with the left temporal cortex, insula, bilateral anterior cingulate, medial orbitofrontal and ventromedial prefrontal cortices.
Soe et al. (2016)	6, 18, and 24 months	258	EEG	EDPS Depression	26 weeks of gestation	Frontal EEG power and frontal functional connectivity (phase synchronization) at 6 and 18 months of age; Internalizing and externalizing symptoms (CBCL) at 24 months of age	No association between prenatal exposure to maternal depression (or postnatal exposure) and frontal functional connectivity. The authors did found an increase in depressive symptoms from the prenatal to postnatal period predicted greater right frontal activity and relative right frontal asymmetry in 6-month-olds, but not in 18-month-olds. In addition, increasing maternal depressive symptoms predicted lower right frontal connectivity in 18-month-olds but not in 6-month-olds; Lower bilateral functional connectivity at 18 months predicted externalizing symptoms at 24 months; trend for lower right frontal functional connectivity to predict internalizing problems at 24 months
van den Heuvel et al. (2015a)	9 months	79	Event-Related Potentials (ERP)	SCL-90 Anxiety FMI Mindfulness	Beginning of second trimester	Electrophysiological brain responses (P150, N250, P3a) to auditory stimuli in an auditory oddball paradigm.	Prenatal exposure to maternal anxiety was associated with higher infant N250 amplitudes in response to standard sounds, while prenatal exposure to maternal mindfulness was associated

							with lower N250 amplitudes in response to standard sounds. In addition, maternal mindfulness during pregnancy was associated with higher infant P150 amplitudes in response to standard sounds.
Otte et al. (2015)	9 months	82	Event-Related Potentials (ERP)	SCL90- Anxiety STAI Anxiety	<15 weeks of gestation	Electrophysiological brain responses (P150, N250, P350, N450, and P650) to emotional vocalisations (happy/fearful) preceded by emotional facial expressions (happy/fearful).	Prenatal exposure to maternal anxiety was associated with larger P350 amplitudes in response to fearful vocalization, regardless of the type of visual prime.
Mennes et al. (2009b)	17 years	23 (only boys)	Event-Related Potentials (ERP)	STAI Anxiety	12-22, 23-31, 32-40 weeks of gestation	Behavioral measures during Go/Nogo paradigm (i.e., reaction time, number of correct responses) and gambling task (i.e., reaction time, total scores, distribution of gamble/inhibition responses); Electrophysiological brain responses during a Go/Nogo and Gambling task.	Boys of high-anxious mothers (12-22 weeks) showed a less efficient endogenous cognitive control in the Gambling task, complemented by a higher amplitude of the frontal P2a component during the Gambling task. No effects were found on the Go/Nogo paradigm.
Mennes et al. (2106)	20 years	18 (only boys)	fMRI	STAI Anxiety	12-22, 23-31, 32-40 weeks of gestation	Gamble paradigm (optimized for its use in fMRI; 4 decisions choices with two Go and two no Go trials	Boys of high-anxious mothers (12-22 weeks) showed less efficient endogenously decision making but not exogenously decision making; this was complemented by less modulation of brain regions (e.g. inferior frontal function)

							in brain regions typically involved in endogenous cognitive control and recruiting of extra areas not activated in boys of mother with low anxiety at 12-22 weeks of pregnancy
Favora et al. (2015)	15-40 years	35	fuctional connectivity fMRI and voxel based morphology	Retrospective Prenatal Stress Interview of participant and mother, using a life-chart method and revealing a Stressful life event score. Reviewing obstetric record	Not specified (whole pregnancy)	Resting state- fMRI, whole brain and in specific regions of interest (hippocampus and amygdala Hopkins Symptom Checklist Depressive symptoms STAI Anxiety Stress Interview about stressful life events	Prenatal stress shows positive linear association with decreased gray-matter volume in left medial temporal lobe and both amygdalae (i.e., latero-basal and superficial nuclei), but not with total amygdala volume nor with grey-matter or total hippocampal volume; prenatal stress shows positive association with connectivity between left medial temporal lobe and pregenual anterior cingulate cortex; both, variance in grey matter volumes and functional connectivity observed, partially explain variance in depressive symptoms in participants

Notes. BAI = Beck Anxiety Inventory; CBCL = Child Behavioral Checklist; EEG = electroencephalography; EPDS = Edison Postnatal Depression Scale; ERP = event-related potential; STAI = State-Trait Anxiety Inventory; SCL-90 = Symptom Checklist 90.

Table 6.

Maternal Stress During Pregnancy and Offspring Functional Brain Correlates: Cerebral Information Processing. The studies are sorted by offspring age at follow-up.

Authors	**Offspring Age**	**Sample Size (N)**	**Neuroimaging Technique**	**Prenatal exposure or measure of maternal stress**	**Prenatal Timing**	**Offspring Outcome(s)**	**Main Findings**
Harvison et al. (2009)	Newborns	28	Event-Related Potentials (ERP)	BAI Anxiety	Late pregnancy	Electrophysiological brain responses (P150, P350, N450, and slow wave) to mother's versus stranger's voice in an auditory	- Lower negative frontal slow- wave amplitudes in response to mother's voice versus stranger's voice (female) in newborns of
Hunter et al. (2012)	6 months	242	Event-Related Potentials (ERP)	Anxiety Disorder (DSM-IV diagnosis) & antidepressant drug use	Not available	Electrophysiological brain responses (P50) to auditory stimuli in a sensory gating paradigm.	- Maternal antenatal anxiety disorder was associated with diminished infant P50 (i.e., less inhibition during sensory gating). - Prenatal antidepressant
van den Heuvel et al. (2015a)	9 months	79	Event-Related Potentials (ERP)	SCL-90 Anxiety FMI Mindfulness	Beginning of second trimester	Electrophysiological brain responses (P150, N250, P3a) to auditory stimuli in an auditory oddball paradigm.	- Higher infant N250 amplitudes in response to standard sounds for higher maternal anxiety - Lower N250 amplitudes and higher P150 amplitudes in
Otte et al. (2015)	9 months	82	Event-Related Potentials (ERP)	SCL90- Anxiety STAI Anxiety	<15 weeks of gestation	Electrophysiological brain responses (P150, N250, P350, N450, and P650) to emotional vocalizations (happy/fearful) preceded by emotional facial expressions	- Larger P350 amplitudes in response to fearful vocalization, regardless of the visual prime type in children for higher maternal SCL90-Anxiety in pregnancy
Mennes et al. (2009b)	17 years	23 (only boys)	Event-Related Potentials (ERP)	STAI Anxiety	12-22, 23-31, 32-40 weeks of gestation	Behavioral measures during Go/No-go paradigm (i.e., reaction time, number of correct responses) and gambling task (i.e., reaction time, total scores, distribution of	- Less efficient endogenous cognitive control in the Gambling task, complemented by a higher amplitude of the frontal P2a component during the Gambling task in offspring of

						gamble/inhibition responses); Electrophysiological brain responses during a Go/No-go and Gambling task.	highly anxious pregnant women. - No effects of maternal anxiety in pregnancy in the Go/No-go paradigm.
Mennes et al. (2016)	20 years	18 (only boys)	fMRI	STAI Anxiety	12-22, 23-31, 32-40 weeks of gestation	Gamble paradigm (optimized for its use in fMRI; 4 decisions choices with two Go and two No-go trials	- Less efficient endogenous decision making but not exogenous decision making and less modulation of brain regions (e.g. inferior frontal function) in brain regions typically involved in endogenous cognitive control and recruiting of extra areas, in offspring of highly anxious pregnant women

Notes. BAI = Beck Anxiety Inventory; CBCL = Child Behavioral Checklist; EEG = electroencephalography; EPDS = Edison Postnatal Depression Scale; ERP = event-related potential; STAI = State-Trait Anxiety Inventory; SCL-90 = Symptom Checklist 90.

Table 7

Maternal Stress During Pregnancy and Offspring Functional Brain Correlates: Functional Connectivity. The studies are sorted by offspring age at follow-up.

Authors	**Offspring Age**	**Sample Size (N)**	**Neuroimaging Technique**	**Prenatal exposure or measure of maternal stress**	**Prenatal Timing**	**Offspring Outcome(s)**	**Main Findings**

Scheinost et al. (2016a)	Newborns	12 extremely preterm newborns and 25 term-born neonates with no prenatal stress; 10 extremely preterm newborns with prenatal stress	Functional MRI	Prenatal Stress	Not specified	Amygdala functional connectivity	- Decreased amygdala-subcorti (e.g. thalamus) connectivity
Qiu et al. (2015a)	6 months	24	Functional MRI	EPDS Depression	26 weeks of gestation	Amygdala functional connectivity at 6 months of age.	- Greater functional connectivit of the amygdala with the left temporal cortex, insula, bilatera anterior cingulate, medial orbitofrontal and ventromedial prefrontal cortices.
Soe et al. (2016)	6, 18, and 24 months	258	EEG	EDPS Depression	26 weeks of gestation	Frontal EEG power and frontal functional connectivity (phase synchronization) at 6 and 18 months of age;	- No association with frontal functional connectivity. - Increase in depressive sympto from the prenatal to postnatal period predicted greater right frontal activity and relative righ frontal asymmetry in 6-month-olds, but not in 18-month-olds. - Increasing maternal depressiv symptoms predicted lower right
Favora et al. (2015)	15-40 years	35	functional connectivity fMRI and voxel based morphology	Retrospective Prenatal Stress Interview of participant and mother, using a life-chart method and revealing a Stressful life event score. Reviewing obstetric records	Not specified (whole pregnancy)	Resting state- fMRI, whole brain and in specific regions of interest (hippocampus and amygdala Hopkins Symptom Checklist Depressive symptoms STAI Anxiety	- Decreased gray-matter volum in left medial temporal lobe and both amygdalae (i.e., latero-bas and superficial nuclei), but not with total amygdala volume no with grey-matter or total hippocampal volume; - Positive association with connectivity between left media

						Stress Interview about stressful life events	temporal lobe and pregenual anterior cingulate cortex. - Variance in grey matter volum and functional connectivity observed, partially explain variance in depressive sympton in participants.

Notes. BAI = Beck Anxiety Inventory; CBCL = Child Behavioral Checklist; EEG = electroencephalography; EPDS = Edison Postnatal Depression Scale; ERP = event-related potential; STAI = State-Trait Anxiety Inventory; SCL-90 = Symptom Checklist 90.