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Prenatal stress and models explaining risk for psychopathology revisited: Generic vulnerability and divergent pathways

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Abstract

The present review revisits three hypothesized models that potentially could explain how prenatal maternal stress influences fetal development, birth outcomes, and subsequent developmental psychopathology. These models were mostly based on animal models, and new evidence for these models from human studies is evaluated. Furthermore, divergent trajectories from prenatal exposure to adversities to offspring affected outcomes are reviewed, including the comparison of studies on prenatal maternal stress with research on maternal substance use and maternal malnutrition during pregnancy. Finally, new directions in research on the mechanism underlying prenatal stress effects on human offspring is summarized. While it is concluded that there is abundant evidence for the negative associations between prenatal maternal stress and offspring behavioral, brain, and psychopathological outcomes in humans, there is no consistent evidence for specific mechanisms or specific outcomes in relation to stress exposure in utero. Rather, principles of multifinality and equifinality best describe the consequences for the offspring, suggesting a generic vulnerability and different pathways from prenatal adversities to developmental psychopathology, which complicates the search for underlying mechanisms. New and promising directions for research are provided to get a better understanding of how prenatal stress gets under the skin to affect fetal development.

It is now widely accepted that prenatal stress is a risk factor for a range of adverse developmental outcomes, starting from birth (e.g., low birth weight and premature birth; Bolten et al., 2011; Mulder et al., 2002), progressing into infancy behavior and development (e.g., negative emotional reactivity and delayed motor and mental development; Davis & Sandman, 2010; Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002, 2003), child behaviors (e.g., impulsivity, hyperactivity, or anxiety; O'Connor et al., 2005; Van den Bergh, Mulder, Mennes, & Glover, 2005), problems with learning, memory, and executive functioning (e.g., Buss, Davis, Hobel, & Sandman, 2011; Mennes, Van den Bergh, Lagae, & Stiers, 2009; Plamondon, O'Reilly, Remi, & Duval, 2013), and eventually, adolescent emotional and behavioral problems (e.g., depression and aggression; Betts, Williams, Najman, & Alati, 2015; Huizink et al., 2007). Despite the accumulating evidence that prenatal stress, experienced by the (expecting) mother, is linked to this wide variety of adverse outcomes, for the most part the question still remains which putative mechanisms are underlying these associations. Multifinality, referring to the principle that one specific factor (here prenatal stress) may have differential effects on developmental psychopathology (Cicchetti & Rogosch, 1996; Nolen-Hoeksema & Watkins, 2011), may complicate the search for these mechanisms. One could even argue that prenatal stress is not a specific risk factor for this range of developmental adverse outcomes, as similar results have been found after other types of prenatal exposure, including maternal substance use (most commonly referring to nicotine and alcohol use) or malnutrition. Thus, besides the observed multifinality, the principle of equifinality (Cicchetti & Rogosch, 1996) may also be involved. In the field of prenatal stress research, equifinality, or divergent trajectories (Nolen-Hoeksema & Watkins, 2011), pertains to the idea that a diversity of prenatal-onset pathways may lead to the same outcome. The combination of both principles (equifinality and multifinality) makes it complicated, if not impossible, to precisely describe how prenatal stress may impact fetal and child development on an individual level. In the end, that is what clinicians, patients, parents, and teachers, who all may have to deal with the consequences of prenatal stress exposure in the offspring, are mostly interested in. Researchers in the field of developmental psychopathology also have shown a growing interest in underlying, possibly person-oriented, pathways from early life exposure to adversities, from pregnancy onward, toward psychopathology (Insel et al., 2010). Most of this current research interest has been embedded in the framework of prenatal or fetal programming, also known as the developmental origins of (mental) health and disease hypothesis (see, for a recent overview, O'Donnell & Meaney, 2017). The basic idea underlying this hypothesis is that the fetal environment and the associated quality of fetal development, in the broadest sense, shapes or programs individual vulnerability to a range of adverse (mental) health outcomes. More evidence-based insight into such prenatal "programming" pathways would not only provide a solid

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ground for the appreciation of the prenatal period as a highly sensitive time for adverse environmental exposures but also guide more effective preventive intervention programs. Perhaps, these programs may prove to be in need of a generic instead of a specific approach, targeting shared underlying mechanisms or pathways toward psychopathology.

The idea of applying the multifinality principle in the field of prenatal stress research is not new. More than a decade ago, we published a now highly cited review in *Psychological Bulletin* (Huizink, Mulder, & Buitelaar, 2004), in which we concluded that, until that point in time, the empirical evidence supported the view that "exposure to prenatal stress may result in a general susceptibility to psychopathology, rather than exerting a direct effect on a specific form of psychopathology" (p. 115). At that time, the evidence from mostly animal studies and some human studies was not pointing to specific outcomes after prenatal stress exposure, but to a diversity of affected behaviors.

In this earlier review, a first model was hypothesized describing the mechanisms through which stress in the pregnant woman could lead to adaptations in the developing (fetal) hypothalamic–pituitary–adrenal (HPA) axis. This model was mostly based on findings from animal studies and consisted of the following possible mechanisms that could be responsible for transducing stress from the pregnant mother to her developing fetus: (a) transplacental transport of maternal cortisol to the fetus; (b) maternal stress-induced release of placental corticotropin-releasing hormone (pCRH), which in turn could enter the fetal circulation; and (c) maternal stress-induced effects on the sympathetic nervous system, yielding vasoconstriction and thereby reduced uteroplacental blood flow.

Next, a second model was postulated, suggesting that during sensitive periods, repeated exposure to high levels of glucocorticoids (GCs), such as cortisol, could lead to abnormalities in brain development. There is evidence for the critical role of GCs in normal brain development and neuronal maturation, and particularly the hippocampus appears vulnerable to early developmental insults and alterations in GCs levels (Henry, Kabbaj, Simon, Le Moal, & Maccari, 1994; Welberg & Seckl, 2001) at least in animal studies. In addition, fetal hippocampal ontogeny could also be altered through prenatal stress exposure in such a way that glucocorticoid receptors are downregulated, resulting in altered offspring HPA axis regulation. At the same time, development of the amygdala could be affected by increased levels of corticotropin-releasing hormone (CRH).

Finally, a third model was suggested that hypothesized how prenatal maternal stress could also alter the opioid and neurotransmitter systems, including the serotonergic, noradrenergic, dopaminergic, and cholinergic systems. Alterations in the serotonergic system could explain heightened risk for mood disorders, including depression and anxiety, in the prenatally stressed offspring, and increased activation of the HPA axis (Huizink, Mulder, & Buitelaar, 2004; Peters, 1990). The noradrenergic system is involved in attentional processes and stress responses of the sympathetic–adrenal stress system, and hence, alterations in this system due to prenatal stress exposure could be linked to inattention, memory problems (Vermetten & Bremner, 2002), and enhanced sympathetic stress responses in the offspring, but for the latter hypothesis, no evidence was found in rodent studies (Weinstock, Poltyrev, Schorer-Apelbaum, Men, & McCarty, 1998). The dopaminergic system was hypothesized to be affected by prenatal stress exposure, potentially resulting in delayed motor development (Barlow, Knight, & Sullivan, 1978), increased fearfulness in stressful situations (Alonso, Navarro, & Rodriguez, 1994; Fride & Weinstock, 1988), which could eventually lead to anxiety and depression disorders, and memory dysfunction (Jaber, Robinson, Missale, & Caron, 1996). Finally, prenatal stress effects in the cholinergic system could affect learning and memory (e.g., Messer, 2002), and may also be related to mood and sleep disorders (Janowsky, Overstreet, & Nurnberger, 1994) and increased responsivity of the HPA axis (Day, Koehl, Deroche, Le Moal, & Maccari, 1998).

These three proposed models were mostly based on animal studies when the review of Huizink, Mulder, and Buitelaar (2004) was published and are not mutually exclusive, but each could elucidate a piece of the puzzle that was created by the multifinality observed after prenatal stress exposure. The three separate models already imply multifinality in potentially adverse outcomes of exposure to prenatal maternal stress. The first model points to a generic effect of prenatal stress exposure to altered, or more specifically, hyperactive fetal and subsequent offspring HPA axis functioning. Offspring hyperactive HPA axis functioning has been hypothesized to result in a generic susceptibility for developmental psychopathology. For instance, an overactive HPA axis was implicated in inhibited behavior during infancy (Schmidt et al., 1997) and depression and anxiety in adult life (Gold & Chrousos, 2002), but has also been related to reactive aggression in children (Lopez-Duran, Olson, Hajal, Felt, & Vazquez, 2009). Furthermore, HPA axis hyperactivity has been associated with memory deficits and cognitive dysfunction, possibly through neurotoxic effects of HPA axis hormones on hippocampal neurons (O'Brien, Lloyd, McKeith, Gholkar, & Ferrier, 2004). From the literature in this field, one can deduce that alterations in HPA axis functioning could reflect an increased vulnerability to environmental challenges of any kind, resulting in a wide array of possible adverse outcomes, suggesting a generic effect on risk for psychopathology.

The second model holds more promise for specificity, encompassing explicit brain areas (i.e., hippocampus and amygdala) that may be disturbed in their normal developmental trajectories during the fetal period. Nonetheless, these regions are also related to a wide array of emotional and cognitive disturbances that may differ according to the level of (increased or decreased) activity in these regions due to prenatal stress exposure. For instance, disruptive behavior and callous–unemotional traits have been linked to low amygdala responses to fearful emotional expressions of children (Marsh et al., 2008), whereas highly fearful children show much more activity in the amygdala to emotional threatening stim-

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uli (e.g., Thomas et al., 2001). Alterations in hippocampal functioning have similarly been related to affected emotional regulation (Buss et al., 2012) and also with learning problems (DeLong, 1992; Gómez & Edgin, 2016), memory disorders (Nosarti & Froudist-Walsh, 2016), and severe forms of psychopathology such as psychotic disorder (Pruessner et al., 2015) and autism spectrum disorder (Groen, Teluij, Buitelaar, & Tendolkar, 2010).

The third model again points to a diversity of neurotransmitter systems that may be altered through prenatal stress exposure, each of them linked to different behavioral, emotional, or cognitive disorders, such as impulsivity and aggression (5-HT), locomotion and cognitive problems (dopamine), or inattention, learning, and memory disorder (NE; Huizink, Mulder, & Buitelaar, 2004).

Nevertheless, the evidence for these three models, describing potential mechanisms through which prenatal stress in humans could exert its effects on a variety of outcomes in the offspring, was limited. The first aim of this review is therefore to revisit the various elements of these three models and look for new empirical evidence in recent years that either fits or conflicts with them. This would address the question of why multifinality, or generic susceptibility for psychopathology, may be a consequence of being exposed to high levels of prenatal maternal stress.

A second aim of this review is to describe the evidence for equifinality, or divergent prenatal trajectories leading to developmental psychopathology. To address this aim, we will summarize findings from studies focusing on maternal substance use during pregnancy, particularly nicotine and alcohol use, and on prenatal nutritional factors that have proven to be related to offspring outcomes very similar to the ones observed after prenatal stress exposure. We will particularly focus on overlap or specificity in mechanisms underlying associations between these prenatal factors and offspring outcomes, as compared to mechanisms used to describe prenatal stress effects.

A third aim of this review is to identify novel directions in research that focus on potential underlying mechanisms explaining how prenatal stress in mothers could affect human offspring outcomes, to gain a better understanding of how prenatal stress could lead to developmental psychopathology in human offspring. For example, the field of epigenetics has emerged since the publication of the review paper in 2004, and holds much promise for a better understanding of how prenatal stress, as an environmental factor, can alter or program, for example, the set point of the HPA axis from early life onward. In addition, brain imaging techniques have advanced in high speed and can illuminate early brain development after prenatal stress exposure. New research methods further include the application of intervention studies to manipulate and change prenatal stress in a positive way (by reducing it) and subsequently investigate the effect of this manipulation on offspring behavioral outcomes, with a detailed focus on alterations in potentially underlying mechanisms as well (Huizink & Bögels, 2013).

Prenatal Stress Definitions

Before we start reviewing new findings in prenatal stress research, it is important to attain clarity in terminology that is and has been used over the years to describe and measure prenatal stress in human studies. Prenatal stress is described more precisely as *maternal prenatal psychosocial stress*, which implies that the expecting mother is exposed to a stressful situation that causes feelings of stress or physiological or neuroendocrine stress responses in her body. The perceived feelings of stress are related to the appraisal of a certain event or challenge, which is considered to be beyond one's control or ability to cope. Thus, an individual's evaluation of the situation results in feelings of stress. In research, this is often reported in questionnaires, such as the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983) or similar instruments. The bodily response to a challenging situation is not necessarily highly correlated with these self-reported feelings of stress. This is also true in pregnancy, when maternal psychosocial stress levels are at most only weakly related to maternal cortisol levels (Beijers, Jansen, Riksen-Walraven, & de Weerth, 2010; Bleker, Roseboom, Vrijkotte, Reynolds, & de Rooij, 2017). Detailed studies showed no association between maternal stress or anxiety with maternal cortisol, measured in saliva, plasma, or amniotic fluid (Baibazarova et al., 2013; Kramer et al., 2009; Sarkar, Bergman, O'Connor, & Glover, 2008), or a weak correlation between maternal anxiety and plasma cortisol in early pregnancy only (Sarkar et al., 2008). Part of this lack of association may have to do with the difference in timing of the emotional and neuroendocrine response. For instance, cortisol in saliva, as an index of HPA axis reactivity to an acute stressful situation, shows elevated levels 20–30 min after the actual stress exposure. In addition, chronic exposure to relatively mild daily stress that results in relatively moderate levels of self-reported perceived stress could still lead to heightened HPA axis basal activity and heightened cortisol stress responses (Viena, Banks, Barbu, Schulman, & Tartar, 2012). A different picture emerges for pregnant women who suffer from depression or from comorbid depression and anxiety. These women show a significant elevated diurnal cortisol output (Evans, Myers, & Monk, 2008; O'Connor et al., 2014), as compared to nonaffected pregnant controls. This implies that effects of prenatal maternal depression on offspring outcomes may be explained by a different pathway than prenatal stress. It is likely that for prenatal depression, a pathway exists in which prenatal GCs exposure plays a more prominent role.

For maternal stress, however, a distinction should be made between "psychosocial stress" and "maternal cortisol" levels when prenatal stress is used as a predictor of offspring outcomes. Independent predictive effects of these two aspects of maternal stress have been found (see, e.g., Davis & Sandman, 2010). Both psychosocial stress and maternal cortisol may thus operate through different pathways, and we currently lack insight into potential mediating mechanisms for psychosocial stress effects in particular.

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The stressful situation itself is sometimes also used as a conceptualization of prenatal maternal stress exposure, particularly when it is related to extreme stressors or adversities, such as being exposed to a disaster or experiencing a severe traumatic experience (e.g., death of a first-degree relative; Class et al., 2014). Thus, prenatal stress is not a single construct consistently used throughout different studies, but rather a heterogeneous concept of an adverse situation that could yield an emotional or bodily response of the pregnant mother.

Moreover, it is important to note that other aspects of maternal emotions or maternal adversities are often used under the umbrella term "prenatal distress," collectively referring to a negative psychological state of well-being, including perceived stress, maternal trait and state anxiety, pregnancy-specific anxiety, and even symptoms of depression. Most studies have assessed these aspects of maternal mood with general instruments, not specifically sensitive for pregnancy-related factors, with the exception of pregnancy-specific anxiety or stress questionnaires. This broad range of symptoms of affected maternal mental health, so to speak, seems to assume common underlying mechanisms that could affect optimal fetal development. One mechanism that is often referred to, when trying to explain any associations between prenatal maternal distress and offspring outcomes, is a heightened level of glucocorticoids in utero, due to elevated maternal HPA axis activity. There is little evidence thus far to support this assumption for each maternal mood factor separately. For instance, only some women with high levels of depression have associated high levels of cortisol (Voegtline et al., 2013). Similarly, there is no consistent proof that women with anxiety have consistently high levels of cortisol either (O'Donnell, O'Connor, & Glover, 2009; Sarkar et al., 2008). When reviewing the literature on prenatal stress, we will therefore clearly mention (if possible) which of the different aspects of "maternal mood," encompassing general depression or anxiety, or "prenatal stress" was used as a predictor in a study, as the evidence to date suggests that it is uncertain that they share an underlying mechanism related to adverse offspring outcomes.

On a side note, it is of interest that particularly pregnancy-specific anxiety, also referred to as pregnancy-specific stress (Alderdice, Lynn, & Lobel, 2012), is emerging as a topic of interest to researchers. This interest may arise from the observation that pregnancy-specific anxiety (or stress) seems to be a robust predictor of a variety of fetal (e.g., DiPietro, Costigan, & Gurewitsch, 2003), birth (e.g., DiPietro, Ghera, Costigan, & Hawkins, 2004; Roesch, Schetter, Woo, & Hobel, 2004), and infant and child outcomes (e.g., Davis & Sandman, 2010; Huizink et al., 2003; Nolvi et al., 2016), in comparison with more general anxiety or stress measures during pregnancy. These general measures of maternal distress may not sufficiently detect feelings of anxiety and stress that are unique during pregnancy. Examples of pregnancy-specific anxiety include worries about the health of one's (unborn) baby, and concerns and fears about the upcoming delivery and the pain and loss of control it may cause (Huizink et al., 2016; Huizink, Mulder, de Medina, Visser, & Buitelaar, 2004). These types of anxieties or feelings of stress are specifically related to pregnancy itself and are more contextually bound. It appears that pregnancy-specific anxiety and pregnancy-specific stress measures are more sensitive to capture subtle but relevant changes in feelings of anxiety and stress during the course of pregnancy, and hence, they could have more predictive value. It must be noted, however, that there is still a paucity in studies examining the underlying mechanisms that could be responsible for the consistently reported associations of pregnancy-specific anxiety or stress with birth and child outcomes. We are aware of only two studies that examined the association between pregnancy-specific anxiety or stress and maternal cortisol levels. The first study, by Davis and Sandman (2010), reported no significant cross-sectional associations between pregnancy-related anxiety and maternal cortisol levels at five different time points, implying independent predictive effects on infant developmental outcomes they examined as well. In contrast, the more recent second study, by Kane, Schetter, Glynn, Hobel, and Sandman (2014), used longitudinal analyses of a much larger sample and found that women with higher mean levels of pregnancy-specific anxiety across the prenatal period more often had steeper increases in cortisol, as compared to women with low levels of pregnancy-specific anxiety. This study implies that using repeated measures of both pregnancy-specific anxiety and cortisol during pregnancy may be needed to examine their longitudinal association in detail. Moreover, these authors once again showed the potential of using pregnancy-specific anxiety measures to capture the changes in maternal anxiety throughout pregnancy, which according to their findings, may have an impact on prenatal GCs exposure to the fetus. Thus, there is some first evidence explaining how pregnancy-specific anxiety can exert its influence on the developing fetus and, subsequently, on birth and child outcomes. In contrast, for more general anxiety or stress measures during pregnancy, there is no clear evidence to support the hypothesis that maternal cortisol could mediate their association with adverse birth and offspring outcomes thus far (see, for a recent review, Zijlmans, Korpela, Riksen-Walraven, de Vos, & de Weerth, 2015).

Model 1 Revisited: Evidence for Transduction of Maternal Stress to Fetus

Already during fetal development, the HPA axis becomes responsive to environmental stimuli, including biological signals from the mother when she is stressed (Gitau, Fisk, & Glover, 2001; Kempná & Flück, 2008). This could generate physiological and epigenetic changes with potentially long-lasting consequences for the offspring (e.g., Sandman, Davis, Buss, & Glynn, 2011), as described in more detail below (novel directions).

In the last decade, most interest of researchers has focused on GCs, indexed by cortisol in humans, which have been

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proposed as the most important candidate for the transduction of signals of maternal stress to the fetus. GCs play a critical role in normal fetal (brain) development and are the end product of the HPA axis. For example, GCs shape the development of brain structures involved in emotion regulation and cognitive function, including the hippocampus and amygdala (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006; Lee et al., 2011), in animal studies. In humans, the effects of alterations in GCs exposure on offspring outcomes have been examined in a handful of studies, evaluating the impact of treatment with a high dose of synthetic GCs in pregnant women at risk for preterm delivery to enhance fetal lung maturation. Findings suggested that exposure to excessive levels of exogenous GCs in utero was related to dysregulated stress responses shortly after birth, with suppressed baseline levels of cortisol and a similarly suppressed cortisol response to a painful heel-stick procedure (Schäffer et al., 2009), a persisting blunted stress response in infancy (Davis et al., 2006), and neurodevelopmental delays in toddlers (Spinillo et al., 2004; Wapner et al., 2007). For studies among prematurely born children who received prenatal synthetic GC treatment for lung maturation, we must consider the limitation that prematurity is associated with more medical complications and painful medical procedures, which could have an impact on both offspring HPA axis functioning and infant behavior (Grunau et al., 2005, 2007, 2009). Therefore, Davis, Waffarn, and Sandman (2011) conducted a study among infants born at term, who were exposed to a single course of exogenous GCs (betamethasone) prenatally. These infants showed no difference in baseline cortisol levels, when compared to nonexposed controls, but did exhibit a stronger cortisol response to the heel-stick procedure shortly after birth.

Other human studies reported high levels of maternal cortisol during pregnancy in relation to infant behavior (e.g., more fussiness and fearfulness; Davis et al., 2007) and enhanced childhood stress reactivity (Davis et al., 2011; Gutteling, de Weerth, & Buitelaar, 2005). This indicates that changes in GCs exposure due to maternal stress or due to exogenous administration of synthetic GCs during the prenatal period may underlie part of the effects found in the offspring (Welberg & Seckl, 2001). In contrast, one study reported that cortisol levels in amniotic fluid, measured as part of an amniocentesis procedure in 108 pregnant women early in pregnancy (on average at 17 weeks of gestation), were unrelated to observed fear reactivity in 17-month-old infants (Bergman, Glover, Sarkar, Abbott, & O'Connor, 2010). Despite this more direct measure of exposure to cortisol in utero, some methodological limitations of this study may have yielded the nonsignificant association, including the nonrepresentativeness of the study population and the single measure of cortisol exposure in early pregnancy only.

The regulation of the HPA axis changes considerably during human pregnancy, as the placenta also starts producing and releasing CRH from 8 to 10 weeks of gestation (Majzoub & Karalis, 1999). Maternal cortisol stimulates placental CRH production, and through a positive feedback loop, simultaneously increasing CRH, ACTH, and cortisol in the maternal and fetal system follows throughout gestation (e.g., King, Smith, & Nicholson, 2001). Through this positive feedback loop, maternal cortisol henceforth increases two- to fourfold in pregnancy (Sandman et al., 2006). However, in contrast to most other mammals, particularly in early pregnancy, the human fetus is protected from excessive levels of maternal cortisol by 11-β-hydroxysteroid dehydrogenase-type 2 (11β-HSD2), an enzyme that converts maternal cortisol into its inactive form, cortisone (Kajantie et al., 2003; Seckl & Chapman, 1997). The enzyme 11β-HSD2 can be considered as a partial barrier, implying that to some extent maternal cortisol passes through the placenta. Fetal cortisol levels are correlated with maternal levels during pregnancy (Gitau et al., 2001), but cortisol levels in the maternal circulation are much higher than in the fetus (Cottrell, Holmes, Livingstone, Kenyon, & Seckl, 2012). The activity of 11β-HSD2 increases during the course of pregnancy (Schoof et al., 2001), but declines near the end of pregnancy (Murphy & Clinton, 2003), to ensure that enough cortisol reaches the fetus when lung maturation is at a critical phase and is facilitated by cortisol exposure. In addition, the fetus is prepared for delivery through high levels of maternal cortisol (Murphy, Smith, Giles, & Clifton, 2006), referred to as a normal hypercortisolaemic status (Jung et al., 2011). Therefore, this process of regulating maternal cortisol transduction to the fetus by altering 11β-HSD2 enzyme activity seems to be of adaptive significance (Majzoub & Karalis, 1999) and critical for the developing fetus, particularly for maturation of the lungs (Murphy et al., 2006). In line with this normative change in the protective effect of the 11β-HSD2 enzyme, Davis and Sandman (2010) reported that early in pregnancy, exposure to significant elevations of maternal cortisol were related to lower infant cognitive scores, whereas in late pregnancy, close to delivery, high levels of cortisol predicted enhanced cognitive scores. Some recent evidence summarized in a systematic review (Carpenter, Grecian, & Reynolds, 2017) suggests that particularly female offspring may be mostly affected by these changes in 11β-HSD2 enzyme activity in response to exposure to maternal exogenous GCs, showing increased HPA axis reactivity early in life. A similar sex-specific pattern for exposure to high levels of endogenous GCs in utero has not been reported thus far.

Recent studies reported that placental 11β-HSD2 is dynamically regulated by several factors, including maternal stress or anxiety (Chapman, Holmes, & Seckl, 2013; Togher et al., 2014). Moreover, a recent study by Monk et al. (2016) showed that particularly high levels of maternal self-reported perceived stress were related to changes in 11β-HSD2 gene methylation, and exposure to high levels of GC in utero and malnutrition was also found to be related to 11β-HSD2 gene methylation (Alikhani-Koopaei, Fouladkou, Frey, & Frey, 2004). New studies also indicate that epigenetic regulation of genes related to 11β-HSD2 enzyme functioning may play an important role in explaining preterm birth and neonatal neurodevelopmental alterations (e.g., Green et al., 2015;

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Lester et al., 2015). Furthermore, recent studies have shown that genetic variants exist that are linked to hypofunctional 11β-HSD2, which implies that some fetuses could be exposed to higher levels of maternal cortisol and, consequently, exhibit more adverse outcomes (e.g., risk for psychopathology) than others. In addition, these genetic variants could perhaps account for individual differences in neurodevelopment (Chapman et al., 2013; O'Donnell et al., 2012). These studies need replication in larger human samples, but show a promising direction in getting a better understanding of how maternal distress levels may impact offspring outcomes.

A final aspect of the first proposed model relates to the maternal stress-induced effects on the sympathetic nervous system, yielding vasoconstriction and thereby reduced uteroplacental blood flow, which could negatively impact offspring outcome. Since 2004, relatively few human studies have been conducted specifically on these so-called maternal–fetal hemodynamics, because the main interest of researchers has been on the first two parts of the model, particularly in relation to prenatal maternal stress. Significant hemodynamic changes arise in pregnancy to facilitate fetal growth (e.g., Duvekot & Peeters, 1994). For instance, maternal cardiac output steadily increases during pregnancy, with a small decline in the last phase. Meanwhile, blood pressure decreases in early pregnancy, reaching a minimum in middle pregnancy, only to return to baseline levels at term. Consequently, peripheral vascular resistance is reduced throughout pregnancy. These normative changes are related to placental blood flow. During pregnancy, Doppler ultrasound can be used to noninvasively measure placental blood flow (Harville et al., 2008) and to assess information about both maternal and fetal circulation. Resistance in blood flow is an important measure and found to be increased in the uterine artery (UtA) and umbilical artery (UA) when poor placentation occurs, resulting in a higher resistance index. Increased resistance in the UtA has been associated with preeclampsia, fetal growth restriction (Hollis, Prefumo, Bhide, Rao, & Thilaganathan, 2003), and poor pregnancy outcomes (Aardema et al., 2004). Similarly, increased resistance in the UA has been found to predict not only fetal growth restriction but also fetal distress (Bartha, Comino-Delgado, Gonzalez-Mena, Lopez, & Arrabal, 1998).

Although these parameters have been studied extensively in relation to a range of birth outcomes from an obstetric perspective, only a few studies looked at their association with prenatal stress. Nonetheless, a recent systematic review was able to identify 12 human studies using Doppler ultrasound to measure maternal–fetal hemodynamics in relation to prenatal stress, all of which were published in the period of 1999 to 2015 (Levine, Alderdice, Grunau, & McAuliffe, 2016). Of these 12 studies, three studies addressed pregnancy-specific stress (Helbig, Kaasen, Malt, & Haugen, 2011, 2013; Mendelson, DiPietro, Costigan, Chen, & Henderson, 2011). The findings were inconsistent: half of the 12 studies in the review reported an association between maternal stress during pregnancy and some maternal or fetal hemodynamics parameters, including, for example, the UtA resistance index, with only 1 out of 5 studies showing a significant association, and the UA resistance index, for which only 1 out of 6 studies reported a significant relation. Levine et al. (2016) therefore concluded that, until now, there is limited evidence that prenatal maternal stress affects maternal–fetal hemodynamics systematically. More promise for future research can be found in the first two parts of the model, focusing on HPA axis aspects in the maternal–placental–fetal unit, and particular in the function and adaption of the 11β-HSD2 barrier to high levels of maternal cortisol.

Model 2 Revisited: Evidence for Specific Effects of Prenatal Stress on Offspring Hippocampus and Amygdala

The rapid developments in magnetic resonance imaging technology over the last decade have fueled research into brain-related mechanisms underlying the effects of prenatal stress on the development of psychopathology. One of the first neuroimaging studies to demonstrate effects of prenatal stress on brain morphology was performed by Buss, Davis, Muftuler, Head, and Sandman (2010). This group showed that the 6- to 9-year-old offspring of mothers with high levels of pregnancy anxiety during middle gestation had smaller gray matter volumes in large parts of the brain, including volume reductions in the prefrontal cortex, the premotor cortex, the medial temporal lobe, the lateral temporal cortex, the postcentral gyrus, and the cerebellum. These associations were not present for anxiety later in pregnancy, and therefore, they seem to reflect a time-specific effect of pregnancy anxiety on specific changes in brain morphology. The brain regions that were found to be affected by maternal anxiety in middle gestation are areas specifically associated with cognitive performance, motor learning, and stress regulation, emphasizing the relevance of these findings in the context of development of cognitive problems and mood disorders (Buss et al., 2010).

Later on, Buss et al. (2012) also showed that high maternal cortisol levels in early, but not late, pregnancy were associated with a larger right amygdala volume in girls, but not in boys, at the age of 7. The higher cortisol levels were also associated with more affective problems in girls, and this association was partly mediated by amygdala volume. Studies on the long-term sequelae of trauma exposure in childhood have also shown that amygdala volume as well as hippocampal volume, both key players in cognition and mood regulation, seem to be sensitive to stress exposure during early developmental periods (Ahmed-Leitao, Spies, van den Heuvel, & Seedat, 2016).

Recent imaging studies shortly after birth confirm these findings. Two studies used diffusion tensor magnetic resonance imaging (DT-MRI) to examine developmental disruption to corticolimbic systems in the brain of infants (Rifkin-Graboi et al., 2015) or children (Sarkar et al., 2014) after prenatal exposure to anxiety or stressful life events, respectively. Rifkin-Graboi et al. (2015) applied a whole-brain

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DT-MRI to examine neural microstructure in newborns after exposure to prenatal maternal anxiety. The authors were particularly interested in whether prenatal anxiety levels of the mother would predict differences in the insula and amygdala structures already in infancy, as part of the corticolimbic system, because these parts have been consistently linked to a variety of anxiety disorders in adults (Etkin & Wager, 2007). They did not observe differences in the newborn amygdala in relation to prenatal anxiety, but significant associations with fractional anisotropy in the right insular cortex were present. Fractional anistropy is regarded as a highly sensitive but rather nonspecific biomarker of microstructural architecture, and hence, it is difficult to interpret the findings of this study beyond the observation that prenatal maternal anxiety is related to altered neonatal brain microstructures in an interesting area. The insula is widely connected to other relevant areas involved in social–emotional responses to, for instance, stress, such as the amygdala, nucleus accumbens, and orbitofrontal cortex (Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006). Another study among young infants reported that maternal anxiety during pregnancy was related to a slower bilateral hippocampal growth over the first 6 months of life (Qiu et al., 2013).

In addition, Sarkar et al. (2014) reported a significant relationship between stressful life events in pregnancy and white matter microstructural organization of a small sample of 6- to 9-year-old children, using DT-MRI, in a brain area connecting the prefrontal cortex with the amygdala: the right uncinate fasciculus. The authors indicate that their findings support the hypothesis that prenatal stress exposure modifies this particular connecting white matter, although the underlying biological mechanism explaining how this modification can occur is still unknown.

It is important to conduct long-term follow-up studies of these infants and children, to test the hypothesis that prenatal stress, through changes in early brain development, may be related to heightened risk for specific developmental psychopathology as well.

Model 3 Revisited: Evidence for Prenatal Stress Effects on Neurotransmitters

Several neurotransmitters have been proposed to play an important role in accounting for altered neurobehavioral outcomes in prenatally stress-exposed human offspring. Special attention may be directed to serotonin, or 5-hydroxytryptamine (5-HT), as it appears to be important for different phases in brain development, from fetal life onward (for an overview, see Oberlander, 2012), at least in rodents. For example, during early fetal development, 5-HT regulates its own development and that of closely related neural systems, such as the dopamine system (Whitaker-Azmitia, Druse, Walker, & Lauder, 1996). Furthermore, it acts as a trophic factor by regulating important brain developmental processes, including differentiation, migration, and myelination (Gaspar, Cases, & Maroteaux, 2003). Moreover, 5-HT is also critically involved in the development and function of the HPA axis, and various components of serotonergic systems in the brain are sensitive to stressors (Chaouloff, Berton, & Mormède, 1999). Therefore, alterations in 5-HT functioning could in theory act as an important underlying mechanism between prenatal stress exposure and offspring behavior (Way & Taylor, 2010), particularly in the internalizing spectrum. Some human studies have examined the direct impact of prenatal exposure to serotonin reuptake inhibitor (SRI) antidepressants, used by depressed pregnant women, on fetal neurobehavioral development, and found disrupted sleep patterns, increased motor movements (Mulder, Ververs, de Heus, & Visser, 2011), or reduced fetal breathing and reduced fetal heart rate variability, as an index of enhanced arousal (Rurak et al., 2011).

New research into individual genetic variation suggests that particularly carriers of the short allele of the gene encoding the serotonin transporter (5-HTT) protein, *SLC6A4*, may experience adverse outcomes of prenatal SRI exposure. *SLC6A4* codes for a serotonin reuptake transporter, which is a key factor in the regulation of serotoninergic neurotransmission. The short allele is linked to reduced 5-HTT protein availability and function (Talge, Neal, Glover, & Early Stress, Translation Research and Prevention Science Network, 2007), yielding a stronger prenatal serotonin exposure during fetal brain development. In addition, individuals with the short allele show increased stress reactivity and more emotional problems as compared to carriers of the long allele. Already in the neonatal period, higher cortisol responses to the heel-stick procedure have been observed in short allele carriers (Mueller, Brocke, Fries, Lesch, & Kirschbaum, 2010). Oberlander (2012) suggested that children with the short allele may be more vulnerable to prenatal adverse exposures, including SRIs or maternal stress, implying a moderating role of the gene variants of 5-HT functioning. Some studies point to the differential susceptibility hypothesis that could apply to this specific genetic variant, in which carriers of the short allele are more susceptible to both negative and positive environmental stimuli, and may therefore be either more affected by a negative environment or benefit more from a stimulating environment than carriers of the long allele (e.g., Taylor, Freemantle, Geddes, & Bhagwagar, 2006).

Finally, epigenetic mechanisms could be involved as well in elucidating how prenatal stress first impacts the serotonergic system through which it exerts an effect on offspring behavior. There is some first evidence for epigenetic modifications of *SLC6A4* after prenatal maternal depression (Devlin, Brain, Austin, & Oberlander, 2010), but as of yet, no evidence for similar prenatal stress epigenetic effects on this serotonergic gene has been reported. In contrast, a recent study among offspring of mothers exposed to life events or trauma during pregnancy found no association with *SLC6A4* methylation (Wankerl et al., 2014). In rodents, however, GCs exposure during pregnancy was related to gene expression of an enzyme related to 5-HT synthesis, tryptophan hydroxylase-3 (TpH2), and more anxiety-like behavior in an experimental setting in female offspring only (Hiroi, Carbone,

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Zuloaga, Bimonte-Nelson, & Handa, 2016). This implies a potential sex-specific mechanism of the developing serotonin system underlying prenatal GCs exposure effects on anxious and depressed behavior in the rodent offspring, which may be an interesting topic of research for prenatal GCs exposure studies in humans as well.

Much less interest can be noticed when it comes to examining the potential prenatal stress influence on the development of other neurotransmitter systems, including (but not limited to) dopamine, noradrenaline, and acetylcholine. We limit ourselves here to discuss some recent work on dopamine, as this seems to be the only neurotransmitter system besides 5-HT that has been related to prenatal stress exposure, albeit in animal studies only thus far. Dopamine has an important function in the developing brain, regulating neuronal differentiation, migration, and axonal and dendritic growth (Frederick & Stanwood, 2009). Alternations in this neurotransmitter system have further been associated with severe neurological disorders, such as Parkinson disease, but also with attention-deficit/hyperactivity disorder, schizophrenia, and substance abuse (Valenzuela, Puglia, & Zucca, 2011). Particularly the midbrain dopamine system seems to be of importance, regulating behavioral and cognitive functions that are essential for integrating stimuli and responses to adapt to the environment (Baier, Katunar, Adrover, Pallarés, & Antonelli, 2012). Therefore, it can be expected that any impact of prenatal stress on the dopaminergic system may be critical. Baier et al. (2012) recently summarized the rodent literature on prenatal stress effects on the dopaminergic system, showing some support for increases in dopamine D2 receptors in limbic areas and the nucleus accumbens, while dopamine-stimulated release in cortical areas was reduced after prenatal stress exposure. Furthermore, the dopamine–glutamate balance was disrupted and some transcription factors were also affected. Particularly the limbic area seemed to be vulnerable to prenatal stress insults, and the authors imply that alterations in this area, along with affected mesocorticolimbic pathways, may underlie prenatal stress impact on emotion, cognition, and decision making in humans as well. However, we are not aware of any human studies thus far focusing on dopaminergic neurotransmitter functioning in relation to prenatal stress exposure, though these animal studies provide some interesting hypotheses to be tested among human offspring as well.

Specificity of Prenatal Stress: Shared Mechanisms With Maternal Substance Use?

Remarkably, the long-term effects of exposure to prenatal maternal stress show many similarities with the long-term effects of prenatal maternal substance use or maternal malnutrition. All these prenatal adversities may lead to similar adaptations and alterations during fetal development, yielding potentially overlapping offspring outcomes. Moreover, these adversities often co-occur. In this section, we first want to consider the correlation between prenatal maternal psychosocial stress and substance use of these women, before we turn to their possible overlap in underlying mechanisms and offspring outcomes. In the next section, we will discuss overlap between prenatal stress and malnutrition, and any shared mechanisms of these two prenatal adversities.

Particularly nicotine use during pregnancy may be associated with heightened feelings of stress. Smokers report using nicotine to cope with stress (e.g., Greaves et al., 2011), to alleviate feelings of tension (Wood, France, Hunt, Eades, & Slack-Smith, 2008). While many female smokers try to quit when they (try to) become pregnant, women in disadvantaged circumstances are less likely to quit nicotine use in pregnancy (Flemming, Graham, Heirs, Fox, & Sowden, 2013). These disadvantaged circumstances include financial problems, unemployment, and relational conflicts, all sources of stress (e.g., McCormick et al., 1990) and related to anxiety and depression during pregnancy (e.g., Linares Scott, Heil, Higgins, Badger, & Bernstein, 2009). The same appears to be true for experiencing severe life events in pregnancy. Pregnant women who reported three or more stressful life events were only half as likely to quit using nicotine as compared to women who reported no stressful events in the previous year (Gyllstrom, Hellerstedt, & Hennrikus, 2012). Thus, nicotine use and stress may co-occur during pregnancy, and chronic stress due to socially disadvantaged circumstances or repeated life events could be an important maintaining factor when it comes to continued nicotine use habits during pregnancy.

The association between prenatal maternal stress and substance use may further be confounded by other shared unhealthy lifestyle habits, such as poor nutrition, less physical activity, and health problems related to these habits (e.g., obesity, high blood pressure, and high blood sugar), and the frequently occurring poor living conditions among pregnant women who use nicotine (Meschke, Hellerstedt, Holl, & Messelt, 2008), each of which may significantly add to a less optimal fetal development (Rubio, Kraemer, Farrell, & Day, 2008). Therefore, when examining the relationship between nicotine use in pregnancy and fetal and offspring outcomes, stress needs to be taken into account as an additional prenatal risk factor. Conversely, in highly stressed pregnant women, lifestyle habits may need to be assessed as well, as they may be partly responsible for hampered offspring outcomes.

When fetal and offspring outcomes are studied in relation to prenatal adversity, such as high levels of maternal stress or maternal substance use, many investigators have focused on birth outcomes, most typically birth weight and sometimes also related indices like gestational age at birth, length at birth, and head circumference (Schlotz & Phillips, 2009). The basic assumption is that these birth outcomes may be regarded as a proxy of hampered fetal development due to prenatal adversity (Bussières et al., 2015). The pathways toward reduced fetal growth can be very different though, and hence, the associations of birth weight with later mental health outcomes in longitudinal studies do not illuminate which specific or generic prenatal mechanism played a pivotal role. Still, these measures of fetal growth have been used in

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many epidemiological studies for mostly pragmatic reasons, as it is easier to obtain reliable data on these birth outcomes than on detailed prenatal adversity factors or fetal growth and developmental parameters in large-scale studies. In their review, Scholtz and Phillips (2009) report how these relatively crude and summary birth outcome measures have subsequently been related to a variety of behavioral and mental health outcomes in childhood and adolescence, including negative affectivity, harm avoidance, inattention, hyperactivity, and stress reactivity (e.g., Phillips & Jones, 2006). Later in life, suboptimal birth outcomes were moderately related to risk for psychotic disorders (e.g., St. Clair et al., 2005; Wahlbeck, Forsen, Osmond, Barker, & Eriksson, 2001), and more inconsistent associations with mood disorders were reported (e.g., Costello, Worthman, Erkanli, & Angold, 2007; Gale, O'Callaghan, Godfrey, Law, & Martyn, 2004; Osler, Nordentoft, & Andersen, 2005).

Prenatal stress in human studies, indexed by high levels of maternal cortisol in early to middle pregnancy, has been related to low birth weight (Bolten et al., 2011; Goedhart et al., 2010). Exposure to maternal psychosocial stress is also consistently reported to be related to adverse birth outcomes, including preterm delivery and reduced birth weight (Bussières et al., 2015; Ding et al., 2014; Mulder et al., 2002). Similarly, a recent meta-analysis and systematic review reported a clear relationship between maternal nicotine use during pregnancy and low birth weight, defined as <2500 g (Pereira, Da Mata, Figueiredo, de Andrade, & Pereira, 2017).

Although the pathways from prenatal maternal substance use and from prenatal maternal stress to reduced birth weight may differ, it is striking that both these prenatal maternal adversity factors have been related to a significant reduction in birth weight, premature birth, or reduction in gestational age at birth. This could be due to changes in health behaviors of prenatally stressed women and women who use nicotine alike. For instance, Lobel et al. (2008) showed that particularly pregnancy-specific stress was related to nicotine use, more caffeine consumption, lower exercise, and unhealthy eating during pregnancy. In addition, in a large-scale study Westerneng et al. (2017) recently reported that pregnancy-specific anxiety was related to high weight gain and nicotine use during pregnancy.

Perhaps reduced birth weight and other related suboptimal birth measures reflect a shared intermediate outcome of prenatal stress and maternal substance use exposure and set the stage for a less than optimal developmental trajectory starting with a suboptimal intrauterine environment (Schotz & Philips, 2009). It is unlikely that affected birth outcome measures, as an index of hampered fetal development (Barker, Eriksson, Forsén, & Osmond, 2002) and fetal adaptation to adverse exposures in utero, is the sole cause of subsequent suboptimal development, including psychopathology in offspring.

To get a better understanding of how both stress and maternal substance use during pregnancy gets "under the skin" to affect fetal and offspring brain and behavior, there is increasing interest in studying whether both could lead to dysregulation of the fetal, infant, and child HPA axis. This could be a shared underlying mechanism, or common pathway, leading to long-term adverse outcomes, because prenatal stress-induced or nicotine-induced dysregulation of the HPA axis' functional maturation may provide a basis for the altered stress susceptibility later in life, which in turn could heighten the risk for a variety of psychopathological problems. Thus, alterations in HPA axis functioning, as a result of either prenatal stress or prenatal substance use exposure, may explain the overlap in other shared, more distal offspring outcomes as well, including impulsive and hyperactive behavior and inattention problems that were also observed in the offspring (e.g., Huizink & Mulder, 2006; Jacobson & Jacobson, 1999). After exposure to prenatal stress, multiple studies have shown that offspring HPA axis functioning is altered, even beyond childhood (see, e.g., Carpenter et al., 2017; de Weerth, Buitelaar, & Beijers, 2013; Su et al., 2015; Vedhara et al., 2012). Several studies are now also available reporting on maternal nicotine use or other forms of substance use in relation to offspring HPA axis. For instance, Stroud et al. (2014) found attenuated basal and reactive cortisol levels in the first month of life of infants prenatally exposed to maternal nicotine use. In contrast, other studies observed more heightened cortisol levels in infants and children after prenatal exposure to maternal nicotine (e.g., Eiden et al., 2015; Saridjan et al., 2010) or alcohol use (Keiver, Bertram, Orr, & Clarren, 2015; McLachlan et al., 2016; Ouellet-Morin et al., 2011). Even though the direction of effects in HPA axis functioning (i.e, attenuated or heightened cortisol) differs across studies, it appears that HPA axis functioning is dysregulated in most of them.

Sullivan and Gratton (2002) suggested that the (right) prefrontal cortex, linked to stress-regulatory systems, may be affected by different prenatal adversities, and therefore, may be the focus of future studies trying to understand the overlap in some offspring outcomes after a variety of prenatal exposures. The prefrontal cortex is regarded as a key to stress coping and emotion regulation (Arnsten, 2009) through its inhibitory connections to both the amygdala (Banks, Eddy, Angstadt, Nathan, & Phan, 2007) and the paraventricular nucleus, inhibiting CRH release (Radley, Arias, & Sawchenko, 2006). Thus, the HPA axis interacts with these particular brain areas to regulate emotional and bodily responses to stressors (Lupien, McEwen, Gunnar, & Heim, 2009).

A recent review of rodent studies shows clear evidence for this suggestion (van Bodegom, Homberg, & Henckens, 2017), but thus far, few studies have been conducted, examining this particular brain area in relation to either prenatal maternal stress or substance use exposure in human studies. The handful of human prenatal stress studies that are available were already discussed as part of new evidence for Model 2 above (Qiu et al., 2013; Rikfin-Graboi et al., 2015; Sarkar et al., 2014). With regard to maternal substance use, including nicotine and alcohol use, similar and related parts of the brain have been examined in the exposed offspring as well. For instance, Toro et al. (2008) reported differences in the

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orbitofrontal, middle frontal, and parahippocampal cortices, which were thinner in particularly female adolescents who were exposed to prenatal maternal nicotine use, as compared to nonexposed. Kühn et al. (2016) evaluated differences in mean curvature in the left orbitofrontal cortex of adolescents in relation to prenatal nicotine and alcohol exposure, and found that only prenatal alcohol exposure was related to lower gyrification in the left orbitofrontal cortex. Other studies have examined a variety of brain areas in relation to prenatal exposure to nicotine and adolescent behaviors, such as inhibitory control (Holz et al., 2014) and reward processing (Müller et al., 2013), but these studies did not focus on stress-regulatory systems. The limitation of these studies, conducted among adolescent offspring of pregnant mothers who used nicotine, is the possibility that other postnatal (environmental) factors may partially obscure any associations between prenatal exposure and adolescent brain outcomes. With regard to prenatal alcohol effects on brain development, much has been published on clear overall damage to the central nervous system in fetal alcohol syndrome offspring (e.g., Thompson, Levitt, & Stanwood, 2009). However, specific associations of more moderate levels of prenatal maternal alcohol use and HPA axis-related brain areas have not been reported in humans thus far. A recent rodent study suggested differential effects of prenatal alcohol exposure and prenatal stress exposure on glucocorticoid signaling in the placenta and fetal brain (Lan, Chiu, Ellis, & Weinberg, 2017), which could indicate that prenatal stress effects may not overlap with prenatal alcohol effects on the fetus, but more human studies are needed to confirm these findings.

A final explanation for a shared HPA axis dysregulation found in offspring after both prenatal maternal stress and maternal substance use may be conveyed by results from an exploratory analysis of Stroud et al. (2014), suggesting that epigenetic regulation of placental glucocorticoid receptor functioning may alter as a consequence of prenatal nicotine exposure. This epigenetic modification may underlie the observed dysregulation of the offspring HPA axis functioning after prenatal nicotine exposure, and similar epigenetic changes may also result from prenatal stress exposure. As reported above, when discussing the new evidence for Model 1, Togher, Treacy, O'Keeffe, and Kenny (2017) demonstrated that a composite score of prenatal distress (encompassing stress, general anxiety, and depression scores of pregnant women) was related to a significant reduction in the expression of placental 11β-HSD2 mRNA, but also with elevated levels of the placental *NR3C1* receptor mRNA. These placental genes have been associated with birthweight (Green et al., 2015; Mulligan, D'Errico, Stees, & Hughes, 2012) and infant neurodevelopment (Appleton, Lester, Armstrong, Lesseur, & Marsit, 2015; Sheinkopf, Righi, Marsit, & Lester, 2016), suggesting that both prenatal stress and prenatal nicotine exposure effects on offspring may be (partly) mediated through dysregulation of the expression of these genes by means of epigenetic modification. As we are aware of just a few human studies reporting these findings, replication and longer term follow-up of the offspring is needed to gain more evidence for the potential involvement of epigenetic modification of placental glucocorticoid signaling in explaining how prenatal stress and other prenatal adversities, including maternal nicotine use, may result in common adverse offspring outcomes. Nonetheless, this line of research is a promising one.

In sum, dysregulation of the HPA axis in offspring after being exposed in utero to either prenatal stress or prenatal substance use, in particular maternal nicotine use, could explain part of the overlap in offspring behavioral outcomes. Nonetheless, more developmental neuroimaging work is needed to further understand the interaction between HPA axis and brain functioning involved in offspring behavioral outcomes. In addition, investigating epigenetic modification of the placental GR functioning after prenatal stress or substance abuse offers an exciting new avenue for researchers aiming at a better understanding of prenatal biobehavioral mechanisms implicated in shaping the HPA axis in the offspring.

Specificity of Prenatal Stress: Shared Mechanism With Maternal Malnutrition?

Not unlike the association between prenatal maternal stress and maternal substance use, the long-term effects of exposure to prenatal maternal stress show many similarities with the long-term effects of prenatal maternal malnutrition (undernutrition or overnutrition; Monk, Georgieff, & Osterholm, 2013). These factors are also highly likely to mutually influence each other. Although psychological stress is generally well known to affect eating behavior, and this is probably no different for pregnant women, few studies have investigated whether this is actually the case. An observational study in 134 women with low-risk, normal pregnancies demonstrated that at 28 weeks of gestation, women who were more fatigued, stressed, and anxious consumed more foods, as evidenced by their increased macronutrient intakes, while appearing to have decreased intakes of some micronutrients (Hurley, Caulfield, Sacco, Costigan, & DiPietro, 2005). Further studies into the interplay between psychological stress and nutrition during pregnancy are important, especially considering the ongoing obesity epidemic that also affects women in child bearing age. Stress exposure in pregnancy may play a major role in overeating with subsequent effects on fetal development. This may particularly be the case in pregnant women with a poor economic background who have been shown to suffer from high levels of chronic stress. A focus group study showed that up to 80% of these women were indicated to experience significant stress and recognized that this influenced their eating behavior (Thomas, Burr, Spieker, Lee, & Chen, 2014).

It is important to realize that stress and nutrition both play important roles in gestation and can have similar profound effects on brain development and mental health in later life. Prenatal malnutrition has been shown to be associated with decreased cognitive function and a range of psychopathological disorders, including depression and schizophrenia (Black,

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Perez-Escamilla, & Rao, 2015; Monk et al., 2013; Susser, Hoek, & Brown, 1998). Malnutrition is in essence also a physical stress condition, and as stated above, stress and malnutrition are closely interrelated. The question arises whether common pathways exist by which both prenatal stress and prenatal malnutrition program the brain and, subsequently, influence mental health. The most important pathway is probably constituted by the HPA axis. As discussed above, the hypothalamus is the key regulator of the stress response, with the HPA axis triggered by physical as well as psychological stressors. Traditionally, the HPA axis output hormone cortisol has received much attention as a key player in developmental programming of later life (mental) health by prenatal adverse conditions (Fowden, Valenzuela, Vaughan, Jellyman, & Forhead, 2016). However, the hypothalamus is also a key regulator of energy metabolism and food intake, with leptin being a key hormone. Leptin, also called the satiety hormone, is released by fat cells and causes a loss of appetite and increase in energy expenditure (Kelesidis & Mantzoros, 2006). In addition, leptin plays a critical role in development. Although largely based on animal studies with little evidence in humans as yet, leptin has been shown to be related to growth of the fetus and also to play a role in brain development (Briffa, McAinch, Romano, Wlodek, & Hryciw, 2015). A rise (surge) in leptin levels occurs during pregnancy in humans, and postnatally in other mammals, and this rise plays a role in organ maturation and development (Briffa et al., 2015). In rodents, it has been shown that the leptin surge during a sensitive period of brain development is necessary to form connections within the HPA axis. Further, it has been shown in mice that absence of the leptin surge during this specific postnatal developmental period leads to lasting alterations in feeding behavior as well as in stress responses (Ahima, Prabakaran, & Flier, 1998). It has been proposed that stress and undernutrition may interfere with the leptin surge and thereby influence the developmental trajectory of the hypothalamus, ultimately affecting neuroendocrine and eating behavior regulating centers (Bouret & Simerly, 2006; Yam, Naninck, Schmidt, Lucassen, & Korosi, 2015). This may in due course affect the risk for development of mental disorders and cognitive dysfunction. High as well as low leptin levels in adults have been associated with psychopathology, including schizophrenia (Valleau & Sullivan, 2014).

A likely pathway via which maternal malnutrition as well as maternal stress may cause programming effects on functioning of the hypothalamus and HPA axis is through epigenetic mechanisms (see also the Novel Directions in Underlying Mechanisms to Explain Prenatal Stress Effects on Offspring section). Shortages of specific nutrients important for neurodevelopment, such as choline, iron, and folate, may cause epigenetic alterations affecting neurodevelopment with subsequent effects on functioning of specific areas/organs including the hypothalamus, hippocampus, and amygdala. Evidence that specific micronutrients can be linked to epigenetic alterations was demonstrated by a study investigating epigenome-wide DNA methylation changes in relation to maternal folate status during pregnancy. Maternal folate status was associated with methylation levels in a large number of genes with many of these genes implicated in neurodevelopment (Joubert et al., 2016).

In addition, as already discussed in the section on Model 1 revisited, both maternal malnutrition and maternal stress seem to affect methylation in the 11β-HSD2 gene thereby influencing the level of cortisol passing the placental barrier (Monk et al., 2016; Alikhani-Koopaei et al., 2004).

In conclusion, there is evidence that both undernutrition and stress during pregnancy induce developmental programming of mental health and may share similar underlying mechanisms, although most evidence thus far comes from animal studies. As undernutrition and stress are also highly interrelated, it is important to take both factors into consideration when studying long-term effects of these adverse prenatal circumstances. Monk et al. (2013) have even proposed that the one exposure is serving as a proxy for the other and recommends always studying both prenatal malnutrition and prenatal distress, in the context of one another.

Novel Directions in Underlying Mechanisms to Explain Prenatal Stress Effects on Offspring

New lines of research have emerged in the last couple of years, adding to a better understanding of the mechanisms underlying prenatal stress effects on fetal and offspring outcomes. These novel directions in research are summarized below.

As already discussed above, long-term alterations in the epigenome have received wide attention over the last decade as a potential mechanism by which prenatal stress may cause the development of psychopathology in later life. Epigenetic patterns are generated during development and can be affected in response to environmental factors. Of the three major epigenetic mechanisms, histone modification, microRNA, and DNA methylation, the latter received the most attention in human research. DNA methylation is involved in gene regulation, and alterations in DNA methylation can result in long-term changes in gene function. Prenatal stress in relation to methylation in glucocorticoid pathway related genes has been investigated in numerous studies (see, for a review, Cao-Lei et al., in press), with the study by Oberlander et al. (2008) as its hallmark. This study showed that prenatal maternal (general) anxiety and depression were associated with increased DNA methylation in the exon 1F of NR3C1 (the gene encoding for GR) in infants at 3 months of age. The methylation levels were also associated with increased salivary cortisol response to stress of these infants, demonstrating the mechanistic link between prenatal stress and subsequent offspring outcomes, here observed as altered HPA axis functioning. Methylation alterations after prenatal stress have also been shown in other glucocorticoid pathway related genes, such as 11β-HSD2, as described above in the section reporting new evidence for Model 1.

Effects of prenatal stress on DNA methylation of genes in other pathways implicated in the development of psychopathology, such as the serotonin pathway, have also been

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investigated, as described under Model 3 earlier, although the few studies among humans did not report consistent results (Cao-Lei et al., in press). A recent epigenome-wide association meta-analysis in human offspring of prenatally stressed mothers showed no clear association with neonatal differential DNA methylation (Rijlaarsdam et al., 2016). In this meta-analysis, however, prenatal maternal stress exposure was defined by a cumulative adversity score, including a broad range of factors such as life events, substance abuse, and family conflict, which may have been too heterogeneous and broad to find any association with (specific) alterations in methylation in the offspring.

In recent years, the use of such epigenome-wide studies has become available, and results of these studies often confirm the mechanistic role of DNA methylation in the relationship between prenatal stress and adverse (mental) health in the offspring, despite the lack of findings in the Rijlaarsdam et al. (2016). In Project Ice Storm, children of women who were pregnant during the 1998 Quebec ice storm were followed. The ice storm led to 45 days without electricity in the coldest month of the year and probably led to high levels of stress for pregnant women living in that area at the time of the storm. In a genome-wide methylation study, it was found that a large number of genes in the in utero exposed children were differentially methylated according to levels of perceived maternal stress during the ice storm. These methylation differences were related to differences in health outcomes, such as body mass index and adiposity, as well as to differences in levels of cytokines (Cao-Lei et al., 2015). This latter finding is of interest as another potential prenatal pathway has attracted increased attention recently: the prenatal stress programming of immune function. Maternal stress induces secretion of stress-related hormones, such as cortisol, but it generates immunological changes as well. Maternal cortisol as well as immunological factors may impact the development of the fetal immune system, in addition to the direct effects of maternal immunological changes on fetal brain development that are expected. The subsequent alterations in the immune system and the brain may both heighten the risk for developing psychopathology (Entringer, Buss, & Wadhwa, 2010; Marques, Bjorke-Monsen, Teixeira, & Silverman, 2015). Most evidence for this hypothesis results from animal work, which currently also concentrates on pre- and perinatal effects of stress on neuroinflammation. Studies in this field showed effects on increased microglial activity in the hippocampus after stress exposure (Calcia et al., 2016). Microglia are cells in the brain and spinal cord that are responsible for the main active immune defense, but recent research has also demonstrated their role in synaptic pruning during development (Frick, Williams, & Pittenger, 2013). Altered microglial activity has been found to be associated with diverse psychopathological disorders, including depression and autism, suggesting that microglial activity could be one of the mechanisms underlying prenatal stress-induced psychopathology (Frick et al., 2013).

A third novel mechanism that could potentially underlie the association between prenatal stress and development of psychopathology is that of alterations in the intestinal microbiome, or the collective genome of microorganisms that inhabit the gut. The gut microbiome is a diverse and specialized ecosystem, with many different factors that can be responsible for alterations in its composition, such as diet and antibiotic use. It was long thought that infants were born with almost sterile intestines, but recently this assumption has been refuted. A number of recent small studies provided preliminary evidence that the infant gut may already be populated in utero, possibly in part through the consumption of amniotic fluid (see, for an overview, Walker, Clemente, Peter, & Loos, 2017). This opens up the possibility that exposure to prenatal stress influences the fetal intestinal microbiome, thereby setting the stage for an altered subsequent gut microbiome development. This could have implications for future health, including the development of psychopathology, as it is widely believed that the gastrointestinal microbiota contributes substantially to shaping the development of the central nervous system (Principi & Esposito, 2016). Studies in rats have shown that prenatal stress induced long lasting alterations in the intestinal microbiota composition, which also correlated with increased responsiveness of the HPA axis and elevated blood pressure after stress exposure (Golubeva et al., 2015). However, until now there is very little evidence for this hypothesis in humans. A study by Zijlmans et al. (2015) provided support in favor of the hypothesis: infants of mothers with high cumulative stress (i.e., high reported stress and high cortisol concentrations) during pregnancy had a significantly different microbial pattern with relatively higher and lower abundances of certain types of bacteria. Of course, this first study does not provide conclusive evidence on a causal link between maternal stress during pregnancy and altered fetal microbial composition. In addition, an additional next step in this line of research would be to study associations between an altered microbial pattern due to prenatal stress exposure, with subsequent structural and functional differences in neurodevelopment resulting in emotional and behavioral problems in the human offspring.

An interesting approach to study prenatal stress mechanisms can also be found in applying ultrasound techniques to observe fetal neurobehavior. Although strictly speaking studies that looked at fetal neurobehavior in relation to prenatal maternal stress are not new, there are a few interesting recent publications that may help in a better understanding of the putative mechanisms explaining the impact of maternal stress on the human offspring. One noteworthy new study focused on how daily negative mood and repeated measures of heart rate and cortisol during pregnancy were related to fetal heart rate (FHR) and fetal movement (Doyle et al., 2015), to gain a better understanding of how prenatal maternal stress has an impact on the fetus in utero. This is of interest as most offspring outcomes after prenatal stress exposure have been collected at birth or well after birth, with the possibility of confounding by postnatal environmental factors. Aspects of fetal neurobehavioral development can be assessed by FHR, fetal heart rate variability, and the cross correlation,

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or coupling, between fetal movements and FHR (Baser, Johnson, & Paine, 1992; DiPietro, 2005; Visser, Mulder, & Tessa Ververs, 2010), which provides an index of fetal autonomic nervous system and central nervous system (CNS) development (Doyle et al., 2015). During pregnancy, these fetal neurodevelopmental aspects show well-documented maturational changes, with increasing coupling reflecting CNS development (e.g., DiPietro et al., 2010). Several studies show that maternal stress during pregnancy was related to these so-called fetal behaviors (for a review, see van den Bergh et al., 2005), but they did not focus on how maternal stress potentially affected developmental changes during pregnancy, which was the focus of the study by Doyle et al. (2015). Their findings suggested that maternal distress, a composite measure of daily assessments of mood factors, including frustration, irritation, anger, and stress, was related to accelerated fetal development for boys. Higher prenatal maternal cortisol levels were independently related to accelerated fetal development as well, most clearly for males. As yet, it is unclear if and how accelerated fetal development as a consequence of mild maternal stress exposure is related to increased risk for developmental psychopathology. Nonetheless, these fetal observations are worthwhile to include in longer term follow-up studies from pregnancy onward, as they give a proximal measure of maternal stress and associated fetal neurodevelopmental changes, as a starting point of potentially adverse developmental trajectories throughout infancy and childhood.

A further interesting direction in research is focused on how prenatal maternal stress exposure also directly affects maternal behavior and cognition, from pregnancy onward, and how such altered maternal behavior may subsequently influence infant and child outcomes. Kataja et al. (2017) examined whether pregnant women with pregnancy-specific anxiety and depression showed cognitive deficits. Findings showed that aspects of visuospatial learning, error monitoring, and executive functioning were worse in women with high levels of pregnancy-anxiety and depression, as compared to women with few symptoms of anxiety or depression during pregnancy. These cognitive alternations due to maternal anxiety and depression may impact the transition of these women to parenthood and affect their parenting skills and, hence, their child's socioemotional development. Follow-up studies are required to adequately test for associations among prenatal maternal cognitive functioning, postnatal parenting behavior, and child development.

Strikingly few studies have investigated how prenatal stress and anxiety during pregnancy, including pregnancy-specific anxiety, transfers to high levels of postnatal parenting stress, which in turn could negatively impact mother–child interaction and child development. This line of research looks at how the early postnatal environment is of influence on offspring behavior, and which factors may induce a negative postnatal environment. One recent study of our own group (Huizink et al., 2017) reported that high levels of parenting stress were predicted by high levels of pregnancy-specific anxiety and trait anxiety during pregnancy, whereas prenatal maternal depression was not related to parenting stress. These findings may be understood from a transitional-stress viewpoint, implying that women who have difficulty dealing with the major life transitions experienced during pregnancy, and report feelings of anxiety that are specifically related to pregnancy itself, may also have difficulties in coping with the transition to parenthood. Thus, parenting skills may be affected by high levels of pregnancy-specific or trait anxiety directly, or through alterations in maternal cognitive functioning, setting off a pathway in which the mother–child interaction may be hampered early in life. Recent studies have also examined whether prenatal parental mentalizing, or reflective functioning, is related to postnatal parenting behavior. It is thought that highly reflective mothers are more aware of their own and their child's mental states, which would facilitate a more positive interaction with their child. Smaling et al. (2016) showed that women with better reflective functioning during pregnancy also were more sensitive and positive in engaging with their 6-month-old offspring. This is an important new direction in research, which also opens opportunities for early prenatal intervention. The relevance of such early prevention becomes clear when we notice that emerging research has shown that postnatal adversities, including hampered mother–child interaction, has an additive, or interactive, negative influence on child development after exposure to prenatal adversities (e.g., Fisher, 2016). Infants prenatally exposed to maternal stress with an insecure/resistant mother–infant attachment showed the highest level of fearfulness, as compared to prenatally stress exposed children with a more positive mother–infant attachment classification (Bergman, Sarkar, Glover, & O'Connor, 2008). Epigenetic modifications due to prenatal adversities could lead to heightened vulnerability to adverse postnatal environmental factors (Lester et al., 2011). Therefore, the social–emotional context of the child in early life, after being exposed to prenatal maternal stress or anxiety, needs more attention from researchers. The postnatal social–emotional context of the child also opens up opportunities for early interventions that may promote optimal child development, as some studies found that the early caregiving environment may compensate for harmful prenatal influences (Bada et al., 2012; D'Angiulli & Sullivan, 2010).

A final interesting new approach in research is to apply intervention studies, targeting either prenatal stress and pregnancy-specific anxiety or promoting early positive caregiving behavior. These intervention studies can manipulate maternal stress or anxiety through effective treatment, and should not only focus on reducing stress or anxiety in the mothers but also incorporate the assessment of change in the putative underlying stress-related mechanisms as an important indicator of treatment efficacy. This approach would allow for specification of mechanisms by which interventions achieve their effects on fetal and child development, and give more insight into the potentially causal factor in the pathways from prenatal maternal stress to offspring outcomes (Fisher, 2016; Huizink & Bögels, 2013). A few of these

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studies are now available. For instance, a recent study by Kusaka, Matsuzaki, Shiraishi, and Haruna (2016) showed that yoga exercises during pregnancy lead not only to a more positive mood and fewer symptoms of depression and anxiety (Davis, Goodman, Leiferman, Taylor, & Dimidjian, 2015) but also to lower levels of maternal cortisol and alpha amylase. This line of research is of interest and importance, for finding evidence for treatment efficacy as well as for elucidating potential causal prenatal pathways that can be redirected with adequately timed interventions. To test whether both maternal stress and substance use have a shared underlying mechanism (i.e., altered HPA functioning in both mother and offspring) leading to similar adverse outcomes, intervention studies aimed at, for instance, smoking cessation during pregnancy should also include measures of maternal and offspring HPA axis functioning. Thus far, this has not been examined, as most smoking cessation studies focus solely on smoking behavior and birth outcomes (e.g., see for a systematic review, Chamberlain et al., 2013). The same holds for intervention studies aimed at improving nutrition in pregnant women. These should include measures such as cortisol and leptin, but to the best of our knowledge, these have not yet been reported.

Discussion

There is now abundant evidence for a negative association between prenatal maternal stress, either indexed by psychosocial maternal stress or high levels of maternal cortisol, and offspring behavioral outcomes, potentially leading to psychopathological disorders. In this review, we summarized the recent evidence for assumed underlying mechanisms that could explain how prenatal stress experienced by a pregnant woman can have an impact on the development of the fetus she is carrying. The question was addressed whether prenatal stress is linked to specific disorders, or whether more generic adverse effects are found, and hence multifinality best describes the consequences for the offspring. Next, we described the evidence for equafinality, or divergent pathways, from prenatal adversities, including maternal stress, toward developmental psychopathology. Finally, we identified several promising new directions in research that provide a better or more complete understanding of the putative underlying mechanisms explaining how prenatal stress can affect fetal development and subsequent emotional and behavioral problems, potentially leading to developmental psychopathology in the human offspring.

What has become clear in recent years is that certain aspects of the models used to describe the way in which maternal stress is transduced to the fetus, mostly based on previous animal studies, may not hold in humans. An important observation is that perceived maternal stress or anxiety, measured with self-report questionnaires, is not consistently associated with high levels of maternal cortisol as index of heightened HPA axis activity (Beijers et al., 2010; Bleker et al., in press), which is supposed to be able to transduce signals of stress to the fetus (Gitau et al., 2001; Kempnå & Flück, 2008). There is some preliminary evidence for a positive relationship between more subtle and repeated measures of pregnancy-specific anxiety and steeper increase in cortisol levels across pregnancy (Kane et al., 2014), but this study needs replication to come to stronger conclusions about how measures of psychosocial stress or anxiety during pregnancy can actually impact fetal development. Kane et al.'s findings underscore the need to use repeated measures of both pregnancy-specific anxiety and cortisol during pregnancy to examine their longitudinal association in detail. Using a single measure of cortisol in a particular period of pregnancy does not validly reflect overall HPA axis functioning in pregnancy, and it will be difficult to find any meaningful association with offspring outcomes (e.g., Bergman et al., 2010). Despite the fact that multiple studies have replicated the association between prenatal psychosocial stress and adverse offspring outcome in humans, it is still puzzling that we have no clear idea or consistent evidence informing us about the underlying mechanism(s). It is striking to note that particularly pregnancy-specific anxiety or stress seems to be the most robust predictor of birth and child outcomes, while this particularly human emotional state, in which one worries about upcoming events (i.e., giving birth) and experiences fears regarding the health of the child one is carrying, cannot be modeled in animal studies. Therefore, if we want to get insight into the underlying mechanisms, we have to rely on inventive human research methods to elucidate how such fears and anxieties can impact fetal development. This will be quite a challenge for the field of prenatal (human) programming in the years to come. Some promising directions include epigenetic studies that until now have mostly focused on general stress or anxiety measures (Cao-Lei et al., in press; Oberlander et al., 2008) or even very broad measures of prenatal adversities during pregnancy (Rijlaarsdam et al., 2016) in relation to neonatal and child DNA methylation, rather than on the best predictor of offspring outcome thus far: pregnancy-specific anxiety or stress. In addition, it would be of interest to investigate whether high levels of pregnancy-specific anxiety throughout the prenatal period are associated with changes in 11β-HSD2 methylation, as has been found for general maternal stress and anxiety (Chapman et al., 2013; Monk et al., 2016; Togher et al., 2014). As 11β-HSD2 functions as a partial barrier against high levels of maternal cortisol, and both maternal cortisol and 11β-HSD2 activity naturally increase during the course of pregnancy, we could speculate that a hampered placental barrier may lead to more exposure to maternal cortisol in the fetus, which could explain affected birth and child outcomes. Thus, even in the absence of a direct link between pregnancy-specific anxiety and maternal cortisol, this process could explain how fetuses of mothers with high levels of these specific pregnancy anxieties may still be exposed to higher than average levels of maternal cortisol.

When we looked at the evidence for the three models that were previously proposed to explain the underlying

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mechanism of how prenatal stress affects the fetus, and we must be clear that this relates to high levels of maternal cortisol only, it became apparent that proof was found for certain but not all aspects of Model 1. Maternal cortisol levels during pregnancy may impact the fetus, most likely in a rather generic way, through transport of maternal cortisol to the fetus. In the last decade, numerous studies examined 11β-HSD in human pregnancy, and particularly the impact of prenatal stress or exogenous GC exposure on, or epigenetic modulation of, its function, and genetic variants explaining its hypofunction. However, in contrast to the importance of maternal cortisol and the barrier function of 11β-HSD in human pregnancy, there is little evidence for the third component of Model 1, in which the sympathetic nervous system would yield vasoconstriction and consequently reduced uteroplacental blood flow. Studies that have looked at maternal–fetal hemodynamics have not consistently found associations with prenatal stress (Levine et al., 2016), and therefore we conclude that this part of the model may not hold in human populations.

Due to new developments in brain imaging, several studies have examined the impact of prenatal stress on brain functioning in the human offspring in the last couple of years. In Model 2, it was assumed that particularly the amygdala and the hippocampus would suffer from exposure to maternal anxiety or stress in utero. There is some preliminary evidence suggesting that these structures in the brain are affected by prenatal stress, although the evidence is not consistent, and other connected areas, or microstructures in the brain, showed alterations in response to prenatal stress exposure as well. The handful of studies in this field used different definitions of stress exposure and studied its effect on brain functioning or brain development among different age groups; therefore, they cannot be compared easily. Nonetheless, more insight into what is going on in the brain of prenatally stress-exposed infants and children is certainly needed, and more brain research into this field should be supported, even though we still do not know how self-reported stress of pregnant women could eventually lead to altered brain development in their offspring: this missing link needs more attention as well. In addition, there appears to be a gap between fetal neurobehavioral research examining prenatal stress influences, using different indices of fetal heart rate (variability) and fetal movement to reflect CNS development, and studies focusing on postnatal brain development in relation to prenatal adversities with new imaging techniques. Bridging this gap by prospective, longitudinal studies from pregnancy onward will provide us with much needed insight into sensitive periods of early brain development and brain developmental trajectories from fetal life onward.

With regard to the involvement of neurotransmitter systems that could be affected by prenatal stress and underlie offspring behavioral outcomes, particularly serotonin has been examined, most likely because it appears to play an important role in (early) brain development. Moreover, studies among depressed pregnant women open up the opportunity to test for SRI medication effects on the developmental brain as well, although most studies until now either looked at behavioral outcomes in the offspring (e.g., Way & Taylor, 2010) or observed fetal neurobehavior as proxy of the prenatal impact of SRI use (e.g., Mulder et al., 2011; Rurak et al., 2011). Studies suggested that different genetic variants encoding for the 5-HTT protein may explain some of the individual differences in vulnerability to prenatal stress exposure, as observed in, for instance, increased cortisol responses to pain or more anxious behavior (e.g., Mueller et al., 2010; Oberlander, 2012). Dopamine seems a promising neurotransmitter system to investigate too, as this system is also heavily involved in brain development (Frederick & Stanwood, 2009). Recent rodent studies seem to suggest important alterations in dopamine functioning after prenatal stress in limbic areas and the nucleus accumbens (Baier et al., 2012), which may account for changes in emotion, cognition, and decision making in the offspring, but support from human studies is lacking thus far.

When taken together, the impact of prenatal stress (i.e., maternal cortisol) on the developing fetus has been partly explained by different underlying mechanisms, and each of them point to aspects of subsequent offspring behavior that varied from blunted to increased stress reactivity, from fearfulness to anxiety and perhaps hyperactive behavior (albeit based on animal studies only), and from lower to enhanced infant cognitive scores depending on the timing of exposure (and gender of the offspring). Most studies investigating more detailed aspects of Models 1–3 were recently conducted and, hence, have not included long-term follow-up measures of the offspring as yet, which would be needed to find out whether more specific pathways toward later developmental psychopathology can be described. For now, we can only conclude that multifinality is what may result from exposure to high levels of maternal cortisol in utero, with a generic vulnerability to "adverse behavioral outcomes" in the first years of life, most likely underpinned by a dysregulated HPA axis in the offspring. It also has become clear that many gaps in our knowledge of the underlying mechanisms still have to be filled and at the same time open up new opportunities for future research. So far, an overall model capturing the prenatal stress pathway(s) toward developmental psychopathology cannot be drafted completely as several intermediate steps are missing evidence.

A next aim of this review paper was to address the issue of equifinality. Particularly, we reviewed the potential overlap in occurrence of and mechanisms underlying prenatal maternal stress and maternal substance use, mostly focusing on nicotine use, and prenatal maternal stress and maternal malnutrition. We observed that both maternal stress and nicotine use or maternal stress and malnutrition may co-occur during pregnancy. Even though most studies have controlled for other lifestyle factors in their analyses, these particular combination of adversities may need more consideration, as they could not only confound associations with offspring behavior but also lead to additive or intensified effects. Each of these maternal adversity factors seems to predict lower birth weight (Bolten et al., 2011; Goedhart et al., 2010; Monk et al., 2013; Pereira et al., 2017), as a potential intermediate step

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toward predicting a wide range of later affected mental health outcomes (e.g., Costello et al., 2007; Scholtz & Philips, 2009; St Clair. et al., 2005). Additional intermediate outcomes include a dysregulated HPA axis function after prenatal stress or prenatal nicotine exposure (Carpenter et al., 2017; de Weert et al., 2013; Huizink & Mulder, 2006; Saridjan et al., 2010), epigenetic modulation of placental glucocorticoid receptor functioning (Stroud et al., 2014; Togher et al., 2017), and altered brain functioning (Kühn et al., 2016; Rifkin-Graboi et al., 2015; Sarkar et al., 2014; Toro et al., 2008). Malnutrition during pregnancy and maternal stress seem to share an altered HPA axis functioning in the offspring as well (Reynolds, 2013). Therefore, we can conclude based on the literature to date that besides multifinality, equifinality seems to be involved as well, and different but partly overlapping prenatal adversities, including maternal stress, maternal nicotine use, and maternal malnutrition during pregnancy, could lead to similar (intermediate) offspring outcomes.

Finally, we aimed to identify new promising directions of research that could further elucidate our search for an understanding of prenatal stress effects on developmental psychopathology in the exposed offspring. New technologies offer exciting opportunities to explore the epigenome, which will aid in more precise prediction of individual differences in vulnerability to prenatal stress exposure. In addition, the shift of interest toward the immune system, including microglial activity in the hippocampus after stress exposure, and the brain–gut axis, intestinal microbiota composition after stress, and its association with emotion regulation provide novel approaches in examining how stress impacts the fetus in multiple ways. More attention to measuring fetal neurobehavior directly in relation to pregnancy-specific anxiety would also help uncovering how such self-reported measures of maternal mood are related to fetal development, as a first proxy of later offspring development.

Finally, it cannot be emphasized enough that we should not disregard the impact of early postpartum mother–child interaction on future child development, and hence, we may need to pay much more attention to any factors influencing that earliest possible human relationship from pregnancy onward. Pregnancy-specific anxiety can predict affected maternal cognitive functioning, early parenting stress, and mother–child attachment. Intervention studies can be used to strengthen this relationship, even before birth, to promote a better developmental trajectory of the child. All efforts aimed at getting a better understanding of why and how prenatal stress is harmful to the developing child may need to be coupled with similar efforts in finding effective interventions aimed at reducing stress and anxiety in this particular sensitive first development period of human life. The interesting point of these interventions is that they can also be used to manipulate stress and anxiety during pregnancy and meanwhile observe the effects on putative underlying mechanisms and subsequently measure fetal, birth, and offspring outcomes, serving a double purpose: enhancing our insight into underlying mechanism and offering a protective tool for the future generation.

Concluding Remarks

The association between prenatal maternal psychosocial stress, maternal cortisol, and adverse biobehavioral outcomes, potentially leading to developmental psychopathology in human offspring, is now well established. In the past decade, many studies have focused on the mechanistic pathways underlying this association, and investigators have ventured into novel fields of research such as epigenetics and neuroimaging. However, the search for underlying mechanisms has turned out to be very complex, partly due to the multifinality as well as the equifinality observed in this field of research. More comprehensive, detailed studies encompassing different techniques and different research designs, such as intervention studies, may aid in further characterization of candidate mechanisms that have emerged from the research performed over the past 10 to 15 years.

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