Chapter 15
Early Life Influences on Cognition, Behavior, and Emotion in Humans: From Birth to Age 20

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Abstract The long-lasting effects of fetal exposure to early life influences (ELI) such as maternal anxiety, stress, and micronutrient deficiencies as well as mediating and moderating factors are quite well established in animal studies, but remain unclear in humans. Here, we report about effects on cognition, behavior, and emotion in offspring aged 5–20 years old in two prospective longitudinal birth cohorts.

The long-lasting effects of fetal exposure to early life influences (ELI) such as maternal anxiety, stress, and micronutrient deficiencies as well as mediating and moderating factors are quite well established in animal studies, but remain unclear in humans. Here, we report about effects on cognition, behavior, and emotion in offspring aged 5–20 years old in two prospective longitudinal birth cohorts.

Maternal anxiety in the first and second trimester of pregnancy was associated with more variable performance during a simple reaction time task at age 5–6. In addition, children of women who reported high levels of anxiety (state anxiety > 90th percentile) were slower and performed more variable on a choice reaction time task. Moreover, prenatal maternal anxiety was associated with problem behavior (e.g., hyperactivity/inattention problems, emotional symptoms) in 5–6-year-olds. Our findings suggest a heightened vulnerability to developmental modulation of programming effects of maternal anxiety during pregnancy in boys. Maternal caffeine intake during the first and second trimester of pregnancy was not associated with a higher risk for behavior problems in 5–6-year-olds. No evidence was found

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for mediation by fetal growth restriction or gestational age or for effect modification by the child's gender. Higher maternal concentrations of omega-3 fatty acids (docosahexaenoic acid, DHA, and eicosapentaenoic acid, EPA) during early pregnancy decreased the risk for overall problem behavior and emotional symptoms (mothers rating their child). In contrast, higher maternal concentrations of omega-6 fatty acid (archidonic acid, AA) and a higher omega-6 to omega-3 ratio during gestation increased the risk for overall problem behavior, hyperactivity/inattention problems, and peer relationship problems. Evidence was found neither for mediation by preterm birth, and being small for gestational age, nor for effect modification by the child's gender.

In 15-year-old offspring, hypothalamo–pituitary–adrenocortical (HPA) axis function was measured through establishing a saliva diurnal cortisol profile and depressive symptoms were measured with the Children's Depression Inventory. Maternal anxiety at 12–22 weeks of pregnancy was associated with an attenuated diurnal cortisol profile in both boys and girl due to elevated cortisol secretion in the evening. Moreover, in female adolescents this flattened cortisol profile mediated the link between prenatal maternal anxiety and depressive symptoms. Prenatal maternal anxiety during week 12–22 of pregnancy was also associated with attention-deficit/hyperactivity disorder (ADHD)-related symptoms, lower intelligence scores, and impairments in endogenous cognitive control (i.e., the ability from within one self to control actions, strategies, and thoughts) as measured with neuropsychological tasks in 15–17-year-old offspring. Importantly, results of event-related potentials (ERPs) at age 17 and functional magnetic resonance imaging (fMRI) at age 20 confirmed a less optimal endogenous cognitive control function and indicated aberrant brain functioning in adolescents of mothers reporting high levels of prenatal maternal anxiety.

Results from both prospective cohorts indicate that ELI (e.g., prenatal maternal anxiety and fatty acid status) enhance neurobiological vulnerability and influence offspring's cognitive, emotional, and behavioral functioning well into adolescence. A possible mechanism might be modulation of programming of the offspring's (neuro)physiology and brain structure–function relationships.

15.1 Atypical Early Influences During Fetal Life are Associated with Less Favorable Neurodevelopmental Outcomes in Later Life

The fetal programming hypothesis (Barker and Osmond 1986), Developmental Origins of Health and Disease (DOHaD; Gluckman and Hanson 2004; Gluckman et al. 2008), and Developmental Origins of Behavior, Health and Disease (DOBHaD; Van den Bergh 2011a) propose that human health and development have their origin in early life, in the womb. The fetus responds to its uterine environment and to changes and disturbances in this environment, e.g., those elicited by

maternal stress, micronutrient deficiencies, or placental dysfunction. The induced alterations in fetal physiology and metabolic responses may modulate the trajectory of developmental processes, i.e., "modulate the programming" of the developmental pattern within key tissues and organ systems (Gluckman et al. 2008). We deliberately choose to term these processes developmental modulation of developmental programming, because we presume that developmental modulation of developmental programming by means of early environmental cues in order to shape an organism's development is a fundamental part of the trajectory in typical development across species (Van den Bergh 2007, Van den Bergh 2011a).

Animal research starting around 1950 demonstrated that experimentally manipulated exposure to adverse environmental factors in early life (e.g., (induced) stress, stress hormones administered to the pregnant animal or fetus, cytokines, alcohol, hypoxia, cocaine) are causally related to several short- and long-term effects on offspring behavior, affects developing brain areas (i.e., hippocampus, amygdala, and frontal lobes), and is associated with changes in neuronal circuits that are involved in cognitive and emotional processing and in modulating stress responses (Bock et al. 2005; de Kloet et al. 2005; Seckl and Meaney 2004; Weinstock 2008; Stanwood et al. 2001; Stanwood and Levitt 2004; Son et al. 2006; Baier et al. 2012). In humans, since 1990, an increasing number of prospective studies shows that exposure to atypical ELI during pregnancy is associated with adverse birth outcomes and a range of less favorable child neurobehavioral outcomes. Most studies looked at the association between prenatal exposure to maternal stress, anxiety, or depression and emotional and behavioral problems (i.e., temperamental reactivity, externalizing behavior) measured with self-report questionnaires or behavioral observation scales. A small number of studies examined specific aspects of cognitive function; these studies revealed evidence for an association between prenatal exposure to atypical prenatal environmental factors and reduced attention, lowered IQ scores, and lowered linguistic competence. These findings from human studies are in accordance with results from animal studies, including inconsistent findings that probably result from genetic differences, differences in intensity/severity, duration/chronicity, controllability/coping, the developmental timing of ELI, and differences in postnatal environment (e.g., in adversity or in maternal care-giving style; for reviews, see Glover et al. 2010; O'Donnell et al. 2009; Van den Bergh et al. 2005b; Weinstock 2008; Räikkönen et al. 2011; Beijers et al. 2014; Graignic-Philippe et al. 2014).

Our studies were aimed at a better understanding of developmental modulation of programming of cognition, behavior, and emotion in humans: from birth to age 20. In the following paragraphs, we will present results from two prospective, longitudinal birth cohort studies. The first cohort: The Amsterdam-Born Children and their Development Study (ABCD study) started in 2003 and aims to examine a broad range of factors during pregnancy and in early life that are potentially related to the child's health and development at birth and in later life (van Eijsden et al. 2011). To date, mothers and children have been assessed until children were 5–6 years old. The second cohort of pregnant women which was started in 1986 in Leuven, Belgium, was followed up from 12–22 weeks of gestation until their offspring was 20 years old (Mennes 2008).

15.2 Results from the Amsterdam-Born Children and their Developmental Study

In the following paragraphs, we will briefly describe the study design and procedures of the ABCD study. Thereafter, we will present results with regard to the association between three ELI that are highly prevalent in pregnant women (i.e., experience of negative emotions, caffeine intake, and a suboptimal fatty acid status) and children's cognitive functioning and behavior.

15.2.1 ABCD-Study Design and Procedures

Pregnant women ($n = 8266$) filled out a questionnaire covering sociodemographic, obstetric, lifestyle, and psychosocial conditions on average at 16 weeks gestation and an extra blood sample was taken during routine blood collection for prenatal screening purposes ($n = 4389$). Pregnancy outcomes were obtained through Youth Health Care of the Public Health Service Amsterdam, and from the Dutch Perinatal Registry. Three months after delivery, mothers received a questionnaire concerning the course of pregnancy and delivery, the health and development of their baby, and questions about their own lifestyle ($n = 5131$ returned). When the children were 5 years old, mothers received three questionnaires ($n = 6161$ sent). The first questionnaire covered the child's health, medical conditions, family sociodemographics, and children's problem behavior ($n = 4488$ returned). The second was a food frequency questionnaire ($n = 2851$ returned). The third, which was addressed to the child's teacher, concerned school performance and problem behavior ($n = 3588$ returned). Furthermore, children were invited for a health check at school ($n = 3321$) where they took part in cognitive testing.

15.2.2 Maternal Anxiety during Pregnancy and Children's Neurocognitive Functioning and Behavior at the Age of 5–6

Analyses in a group of 922 mothers with a large range of anxiety scores (mean state-anxiety score = 36) and children revealed that there indeed is an association between maternal anxiety during the first and second trimester (mean 16th week) and alterations in children's neurocognitive functioning at the age of 5–6. Children of anxious pregnant mothers were more variable in their performance during a simple reaction time test than children of less anxious women, but no associations were found between antenatal anxiety and the children's mean reaction time during both a simple and a choice reaction time task. Examination of nonlinear associations revealed a significant nonlinear association between antenatal anxiety and the children's variability in reaction time in the incompatible part (i.e., incompatible

stimulus-response mode) of the choice reaction time task. Visual inspection of the data showed that higher levels of maternal anxiety were related to a stronger than linear increase in children's variability in reaction time. This finding suggested that the modulation of programming effects of antenatal anxiety become stronger when reported anxiety levels rise. Subsequent analyses in a highly anxious subsample (state-anxiety score > 90th percentile, mean state anxiety = 54.7, $n = 100$) showed that higher levels of antenatal anxiety were more strongly associated with longer reaction times and more intraindividual variability in reaction time in the incompatible part of the choice reaction time task. The child's sex moderated the relation between antenatal anxiety and intraindividual variability in the simple reaction time task in the highly anxious subsample. Boys performed more variables on the simple reaction time task, but no significant associations were found in girls (Loomans et al. 2012b).

In addition, children of mothers who reported higher levels of state anxiety (mean state−anxiety score = 36.7) during the first and second trimester (mean 16th week) showed more overall problem behavior, hyperactivity/inattention problems, emotional symptoms, peer relationship problems, and conduct problems and showed less pro-social behavior when mothers had rated their child's behavior ($n = 3446$). When child behavior was rated by their primary school teacher ($n = 3520$), maternal anxiety during pregnancy was related to more overall problem behavior and less pro-social behavior. The child's sex moderated the relation between antenatal anxiety with overall problem behavior and hyperactivity/inattention problems in children when reported by their mother. Higher levels of antenatal anxiety were more strongly related to overall problem behavior in boys than in girls. Furthermore, antenatal anxiety was significantly associated with hyperactivity/inattention problems in boys, while this was not the case in girls (Loomans et al. 2011).

15.2.3 Maternal Caffeine Intake During Pregnancy is not Associated with Problem Behavior in 5–6-Year-Old Children

Analyses in 3439 mothers and children indicated that maternal dietary caffeine intake (self-reported coffee, tea, and soft drink consumption) during the first and second trimester (mean 16th week) pregnancy was not associated with a higher risk for hyperactivity/inattention problems, emotional symptoms, conduct problems, peer relationship problems, suboptimal pro-social behavior, and overall problem behavior in their 5–6-year-old children. In addition, no evidence was found for moderation by the child's sex or for mediation by fetal growth restriction and gestational age. Given the fact that a relatively large group of women consumed considerable quantities of caffeine ($n = 862 > 4$ cups per day), we were able to fully explore the effect of high doses of caffeine intake; nevertheless, our findings did not provide evidence for a dose-response effect of intrauterine caffeine exposure. Because nausea, a common symptom in the first trimester of healthy pregnancies ($n = 1.586$

women reported nausea), did reduce caffeine intake significantly in our sample, we repeated analyses in a subsample of only nonnauseous women that revealed no associations between caffeine consumption and children's problem behavior (Loomans et al. 2012a).

15.2.4 Maternal Omega-3 and Omega-6 Fatty Acid Status During Pregnancy is Related to Children's Risk of Problem Behavior at Age 5–6

We found evidence for long-term developmental modulation of programming influences of maternal long-chain polyunsaturated fatty acid (LCPUFA) status during the first and second trimester of pregnancy (gestational week at blood sampling, mean = 13) on offspring's problem behavior at age 5–6 years when rated by mothers ($n = 2502$). Higher concentrations of omega-3 fatty acid DHA in maternal plasma phospholipids decreased the risk for offspring's overall problem behavior. Higher concentrations of omega-3 fatty acid EPA decreased the risk for overall problem behavior and emotional symptoms. In contrast, higher concentrations of omega-6 fatty acid AA increased the risk for peer relationship problems and a higher omega-6 to omega-3 ratio increased the risk for overall problem behavior, hyperactivity/inattention problems, and peer relationship problems. No associations were found when teachers rated children's behavior. No evidence was found for mediation by preterm birth and being born small for gestational age. The child's sex did not modify the association between maternal LCPUFA status and children's behavioral outcome (Loomans et al. 2014).

15.3 Results from the 1986 Leuven Cohort

Next, we describe the results of a second longitudinal study on the neurobehavioral effects of prenatal exposure to maternal anxiety and stress (PEMAS) on human offspring. Initiated in 1986, the Leuven Cohort investigated effects of PEMAS on fetal, infant, and childhood development, continuing into adolescence with follow-up investigations in 14–17- and 20-year-old adolescents. To uncover biological mechanisms underlying effects of PEMAS on depressed mood, we examined the offspring's pituitary HPA axis activity. In addition to HPA axis functioning, we examined cognitive processing and associated neural activity using ERPs and fMRI (Van den Bergh 2011a).

Maternal state anxiety, measured with the State Trait Anxiety Inventory (STAI), was assessed during weeks *12–22, 23–31,* and *32–40* of pregnancy in 86 pregnant women who completed the STAI as part of a larger battery of standardized psychological questionnaires probing anxiety and stress. It is important to note that we had access to the full range of anxiety scores in our sample. The mother also completed

the same battery of questionnaires at all postnatal research phases, allowing to control for a possible influence of postnatal maternal anxiety. Importantly, although postnatal maternal anxiety was associated with many outcome measures, it did not explain effects related to PEMAS. In addition, we were able to show that most of our findings were (statistically) independent of confounding factors including smoking and alcohol use during pregnancy or birth weight.

15.3.1 PEMAS is Associated with Altered Fetal, Infant, and Child Neurobehavioral Development

The full cohort participated in fetal ultrasound measurements (120 min) that focused on body movements, eye movements, and heart rhythm, resulting in the identification of behavioral states (i.e., sleep–wake cycles). State-dependent motor activity was significantly higher and the percentage of time spent in quiet (or deep) sleep significantly lower in fetuses from pregnant women reporting high levels of anxiety compared to fetuses from pregnant women reporting low levels of anxiety. A mother's anxiety during pregnancy explained between 10 and 25% of the differences in irritability, excessive crying, irregularities in biological functions, and (difficult) temperament in the offspring during the first 7 months after birth. In contrast, we observed no significant relationship with PEMAS for (clinical) observations about the neurological condition, general cognitive and motor development, and feeding behavior (Van den Bergh et al. 1989, Van den Bergh 1990).

In a second research phase of the Leuven Cohort, we examined neurobehavioral development in the 8–9-year-old children ($n = 72$; 38 boys). Children from mothers reporting high PEMAS showed significantly more behavioral self-regulation problems compared to children from mothers reporting lower levels of PEMAS (explained variance between 17 and 22%). Importantly, problem behavior was reported at home (reported by the mother), in class (reported by the child's teacher), and during experimental test settings (reported by an observer). Reported problem behavior reflected impaired regulation of emotion and cognition, ADHD symptoms, increased externalizing behavior, and augmented self-reported feelings of anxiety (Van den Bergh and Marcoen 2004).

15.3.2 HPA Mediates the Link Between PEMAS and Adolescent Depressed Mood

In a third follow-up of the cohort, when children were 14–15 years old, we were able to examine whether offspring HPA axis mediated the link between PEMAS and reported emotional problems in the offspring. Such link was hypothesized based on the implication of HPA axis functioning in depressive symptomatology (Claes 2004; Swaab et al. 2005; Heim et al. 2000) and evidence from animal studies that early life stress can alter HPA axis functioning (Maccari et al. 2003; Macrì et al.

2007). Using cortisol measurements in the 15-year-old offspring ($n = 58$; 29 boys), we showed that in both, boys and girls, PEMAS during week 12–22 of pregnancy was associated with a high, flattened diurnal cortisol profile showing elevated cortisol secretion in the evening. However, only in girls we were able to partly explain the effect of PEMAS on depressed mood by the effect of the flattened cortisol profile on depressed mood (Van den Bergh et al. 2008). These results suggested that PEMAS can prenatally modulate the programming HPA axis functioning and induce a vulnerable phenotype in the offspring. A plausible, albeit untested, underlying mechanism might operate through a "resetting" of HPA axis set points by antenatal exposure to maternal anxiety during critical periods resulting in a hyperactive HPA axis (de Kloet et al. 2005; Seckl and Meaney 2004). However, PEMAS-related modulation of programming is likely not limited to the HPA axis. For instance, evidence from animal studies suggests PEMAS-related sequelae in neural circuits involved in emotional and cognitive processing.

The fundamental brain architecture of the fetus is established during the first two trimesters of pregnancy, and its sensory organs gain functionality during the third trimester. From the first month of gestation, brain development proceeds as a continuous dialogue between the fetus's genome and its environment. Accordingly, environmental factors (such as PEMAS) that disturb the expression of genes involved in cellular proliferation, migration, and differentiation may impact early brain development, thereby constraining sensory and cognitive/emotional development even in the absence of structural brain alterations (Meaney 2010; Van den Bergh et al. 2005b).

15.3.3 Neuropsychological, ERP, and fMRI Measures Reveal Evidence for Impaired Endogenous Cognitive Control Associated with PEMAS

In addition to assessing associations between PEMAS and emotional functioning, we included measures that enabled us to assess associations between PEMAS and neural functioning related to cognitive processes (e.g., inhibition, planning, memory). The field of cognitive neuroscience has produced several robust (now mostly computerized) tasks that target specific aspects of cognitive functioning. Classic examples are Go/NoGo paradigms assessing inhibition or N-back memory tasks that index memory capacity. By administering these tasks during ERP measurements and fMRI scans, neuroimagers have been able to assess the timing and speed of cognitive functions as well as make inferences about the involvement of specific brain regions or larger functional networks (e.g., Whelan et al. 2012). Just as the occipital cortex is essential to visual processing, the prefrontal cortex is given a central role in cognitive processing (Miller and Cohen 2001), including attentional control, error monitoring, and executive functions. In the context of our earlier findings suggesting altered attention-related, externalizing behaviors following high levels of

PEMAS, we expanded our research to investigate the association between PEMAS and prefrontal cortical functioning.

In follow-up phases of the Leuven cohort at ages 15 ($n=64$; 33 boys) and 17 ($n=49$; 29 boys), we investigated cognitive functioning with IQ tests and computerized neuropsychological tasks assessing working memory, sustained attention, and response control. These neuropsychological domains were specifically targeted based on the type of problem behavior shown to be associated with PEMAS in infancy and childhood. Specifically, at age 15 we included three tasks that assess functions closely tied to aspects of self-regulation and that have a well-established relationship with prefrontal cortex: (1) visual attention control and working memory (Encoding), (2) response control (Stop Task paradigm) and (3) sustained attention (Continuous Performance Task). For the follow-up at age 17 we extended our behavioral task battery to five tasks, taxing five prefrontal functions: (1) the ability to orient attention (Cued Attention), (2) working memory (N-back), (3) external response inhibition (Go/NoGo), (4) the ability to perform two tasks simultaneously (Dual Tasks), and (5) the ability to switch between response sets (Response Shifting).

By evaluating the cognitive functions needed to successfully perform in each of these tasks, we observed a specific pattern of cognitive deficits in adolescents of mothers reporting high levels of anxiety during weeks 12–22 of their pregnancy. Children of mothers reporting high levels of PEMAS were impaired in the Continuous Performance Task and Response Shifting tasks. Both tasks require the ability to endogenously (i.e., autonomously, from within oneself and without external sources) inhibit reactions to interfering and distracting stimuli or inhibit a learned response. In contrast, adolescents of mothers reporting high levels of PEMAS performed adequately in tasks that triggered response inhibition in an exogenous, external manner (e.g., through presentation of a sound in the Stop Signal Task). Next, to a deficit in endogenous cognitive control, adolescents of mothers reporting high levels of PEMAS during weeks 12–22 of their pregnancy exhibited lowered scores on Vocabulary and Block Design, two subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R) at age 15, and decreased performance when the cognitive load of the task was increased (e.g., in Dual Tasks) at age 17. Finally, we observed no association between PEMAS and performance on working memory tasks (Van den Bergh et al. 2005a; Van den Bergh et al. 2006; Mennes et al. 2006).

To further investigate the relationship between PEMAS and neuronal functioning associated with these cognitive functions, we measured ERPs during some tasks administered at age 17. ERPs are small changes in the electrical activity of the brain caused by an internal or external event, and they are interpreted as reflections of brain activity related to the processing of that event. Using small electrodes placed on the scalp of a participant, we can measure this electrical activity. Accordingly, when ERPs are measured during cognitive tasks, we can make inferences about the cognitive processes underlying the changes seen in the electrical currents and functional significance can be ascribed to the observed waveforms. We recorded ERPs with 19 scalp electrodes during 4 tasks. These included a Go/NoGo, N-back, and switching paradigm similar to those used in the behavioral assessments, as well

as a gambling paradigm specifically requiring high levels of endogenous cognitive control. In accordance with the behavioral results, we observed no relationship between PEMAS and ERPs measured during the Go/NoGo paradigm. This result confirmed that offspring of mothers reporting high levels of PEMAS have likely no behavioral or neuronal impairments in exogenous cognitive control. In contrast, we observed an association between PEMAS and decision making during the gambling task. This association was evident in both a less optimal behavioral performance and aberrant brain activity in adolescents of mothers reporting high levels of PEMAS during weeks 12–22 of their pregnancy. Particularly the early frontal P2a ERP component measured during endogenous cognitive trials was related to the level of PEMAS. As the P2a is thought to be related to the task relevance of a stimulus (Potts 2004), we speculated that adolescents of mothers reporting high levels of PEMAS based their decisions during the gambling tasks on different features of the gambling stimulus compared to adolescents of mothers reporting lower levels of PEMAS, thereby focusing on the most obvious features of the stimulus (e.g., color), while missing the intricacies of the stimulus present in less evident stimulus features (e.g., the numbers indicating a possible amount of gain/loss). As such, these results showed a link between brain activity of the offspring and the level of anxiety experienced by their mother during pregnancy, specifically targeting endogenous cognitive control processes (Mennes et al. 2009).

ERPs are measured with millisecond accuracy and have an excellent temporal resolution regarding the ongoing cognitive processes. However, ERPs lack spatial specificity, preventing tying specific cognitive processes to specific brain regions. Therefore, to complement the ERP results with spatial information about which areas in prefrontal cortex show differences in functionality related to PEMAS, we assessed endogenous cognitive control using fMRI in the follow-up phase of the Leuven Cohort at age 20. During fMRI scans, the blood oxygenation level dependent (BOLD) response is measured while performing a (cognitive) task. Based on the ratio of deoxy- and oxygenated hemoglobin in the blood, the BOLD response is thought to be coupled with oxygen consumption in the context of neuronal processes. As such, fMRI is said to provide an indirect measurement of neuronal activity (Menon 2012). By relating variations in the BOLD response over time to the timing of events in an experimental paradigm, neuroimagers can relate cognitive processes to specific areas of the brain. For the follow-up phase at age 20, we invited all ten boys of the high anxious group present in the Leuven Cohort as well as ten boys, matched on IQ, of the low-average anxious group (final $n = 18$). All participants performed four cognitive tasks during fMRI scanning, again similar to the tasks included in the follow-up phases at ages 15 and 17: response switching, N-back, Go/NoGo, and gambling. Confirming the previous results, we observed that offspring of mothers reporting high levels of PEMAS during weeks 12–22 of pregnancy exhibited altered, endogenously controlled decision making. This behavioral difference was complemented by altered patterns of brain activation in regions involved in cognitive control including inferior frontal junction (e.g., Zysset et al. 2006) and areas in the middle frontal gyrus. Again, we observed no association between PEMAS and brain activity during the Go/NoGo task requiring exogenous cognitive control (Mennes 2008).

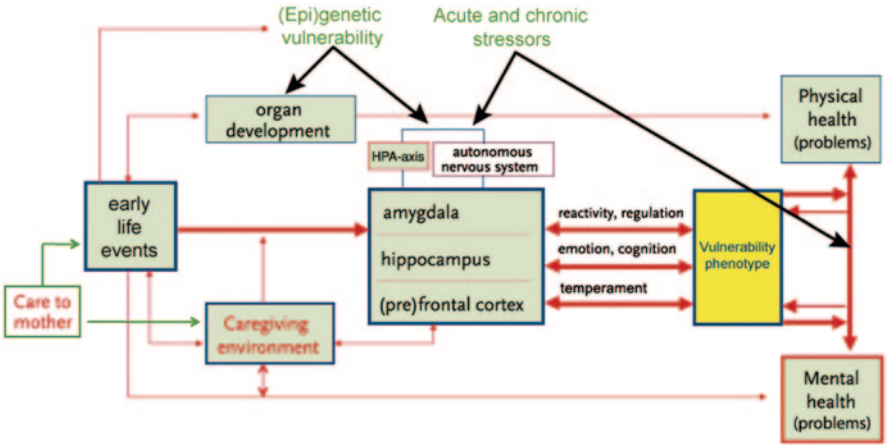

Fig. 15.1 Developmental programming of early brain and behavior development and mental health and physical health (problems). (Adapted from Van den Bergh 2011b)

15.4 Discussion

Results from both our prospective longitudinal birth cohorts corroborate and extend results from preclinical studies as they provide evidence for adverse neurodevelopmental consequences of atypical ELI from early childhood until late adolescence, and are in accordance with the DOBHaD paradigm proposed by Van den Bergh (2011a). Especially high levels of maternal anxiety during the first and second trimester of pregnancy were associated with self-regulation problems, (externalizing) behavior problems, and enhanced self-reported feelings of anxiety in the offspring, taking important confounders (e.g., postnatal maternal anxiety) into account. Neuropsychological, ERP, and fMRI measures provided evidence for impaired cognitive functioning and altered brain activity patterns related to prenatal maternal anxiety. In addition, data from the ABCD study showed that maternal omega-3 and omega-6 fatty acid status during early pregnancy are related to children's problem behavior at ages 5–6, whereas maternal caffeine intake was not associated with offspring's behavior.

15.4.1 Modulation of Developmental Programming of Early Brain and Behavior Development and Mental Health

In Fig. 15.1, Van den Bergh (2011a, b) attempts to integrate results from preclinical, clinical, neurobehavioral, developmental, and epidemiological research that revealed direct or indirect evidence for the DOBHaD hypothesis. Importantly, early brain and behavior development are integrated and put in a central place in the figure. Research in animals has convincingly shown that developmental exposure

to excess glucocorticoids or stress may modulate the programming the peripheral and central nervous system (CNS) involved in the two coacting stress-regulating subsystems: (1) the hypothalamic–pituitary–adrenal axis (with the hormones corticotrophin-releasing hormone, vasopressin, adrenocorticotrophic hormone, mineralocorticoid, and glucocorticoid) and (2) the autonomous nervous system (with noradrenaline and adrenaline). Effective coping with stress is important throughout life (de Kloet et al. 2005) and is an important behavioral regulation factor. The perinatal period is seen as a unique period in ontogeny where the fine-tuning of the stress-regulating system and resilience can be permanently modulated which may lead to enhanced vulnerability to develop diseases in later life. Evidence for alterations in neuronal circuits was shown in preclinical research. For instance, in limbic brain structures (hippocampus, amygdala) and prefrontal cortex, both are involved in stress reactivity and regulation patterns, in emotional (e.g., anxiety, anger) and cognitive (e.g., learning, memory) processing, and in temperamental variation in behavior (e.g., novelty seeking, harm avoidance, reactive temperament) (Gluckman and Hanson 2004; Seckl and Holmes 2007; Barker 1998; Räikkönen et al. 2011; Oitzl et al. 2010; Lupien et al. 2009). These changes may influence how an individual "behaves" (i.e., perceives, interprets, and reacts) to its environment and to situations of acute and chronic stress. In concert with physiological activity (the hypothalamic–pituitary–adrenal axis and the autonomous nervous system), these processes may underlie behavioral problems and psychopathology, or more in general, mental health problems. In accordance, recent theories hold that individuals vary in their biological sensitivity (Boyce and Ellis 2005) or in their susceptibility (Belsky and Pluess 2009) to environmental influences. These theories predict that some individuals are more susceptible than others to both the adverse and beneficial effects of, respectively, unsupportive and supportive environments. The nature of the environment and this difference in sensitivity or susceptibility will influence how mental health or mental health problems are shaped; these processes covary with physical health and health problems (Van den Bergh 2011, p. 21–22).

15.4.2 Potential Underlying Mechanisms

While the mediating and moderating factors and the long-lasting effect of ELI on offspring are quite well established in animal studies (for reviews, see other chapters in this book), in humans they are only beginning to be understood (Schlotz and Phillips 2009; Van den Bergh 2011). In studies focusing on offspring biological systems possibly altered by ELI, some studies examined HPA axis function. While animal research showed that exposure to excess glucocorticoids during specific sensitive periods in utero might alter the homeostasis of the fetal HPA axis (see Weinstock 2008), this hypothesis is not tested in a direct way in humans. However, altered basal or stress-related cortisol secretion were seen in infants and adolescent offspring subjects of anxious (e.g., O'Connor et al. 2005; O'Donnell et al. 2009) or highly stressed women developing posttraumatic stress disorder (Yehuda et al.

2005). Accordingly, results from the Leuven cohort showed that the offspring HPA axis mediates the link between prenatal maternal anxiety and offspring's emotional problems.

While in humans the role of the maternal and fetal HPA axis in mediating the transmission of stress from mother to fetus are still not clear, current data indicate that key targets for programming may include not only cortisol secretion itself but also glucocorticoid receptor (GR) and 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) gene expression in a range of tissues (Bertram and Hanson 2002; McGowan et al. 2009; Oberlander et al. 2008; Hompes et al. 2013). For instance, preclinical research has shown that early life experiences may induce epigenetic modifications in the expression of the GR gene (*NR3C1*) and in other key players in the biological stress response (Weaver et al. 2004; Zhang et al. 2010, Meaney and Ferguson-Smith 2010; Meaney et al. 2007). In humans, McGowan et al. (2009) showed that childhood abuse leads to increased promoter methylation and decreased expression at the *NR3C1* gene in hippocampal brain tissue. Oberlander et al. (2008) observed a link between prenatal emotional stress and methylation of the *NR3C1* gene 1_F promoter in DNA from human cord blood. Furthermore, an altered stress response reactivity at 3 months of age correlated with a higher methylation status of the *NR3C1* gene. Hompes et al. (2013) investigated the association between prenatal stress, in combination with HPA axis functioning, and the methylation pattern of the *NR3C1* 1_B, 1_D, and 1_F promoter regions in cord blood mononuclear cells. Their results indicate that prenatal maternal emotional state, particularly pregnancy related anxiety, is associated with the methylation state of the *NR3C1* gene in the infant.

The few studies that focused on CNS structures or on the structure-functioning relationship found associations between ELI and altered brainstem auditory evoked potential (DiPietro et al. 2010), auditory ERPs (Harvison et al. 2009), and gray matter volume reductions in several parts of the brain, such as the prefrontal and premotor cortex, the medial temporal lobe, and cerebellum (Buss et al. 2010). As indicated above, the results of the Leuven cohort indicated that altered patterns of brain activation in regions involved in cognitive control such as inferior frontal junction and areas in the middle frontal gyrus were involved. However, it is clear that more studies confirming these results are needed before firm conclusions can be reached.

It is known that a wide spectrum of micronutrients during pregnancy may have long-lasting effects on offspring's physical health (Godfrey and Barker 2001), as well as cognitive functioning and behavior (Monk et al. 2013). Findings from the ABCD cohort suggest that maternal LCPUFA concentrations during pregnancy might modulate the programming offspring's neurodevelopmental outcomes. Despite the fact that long-chain polyunsaturated fatty acids are essential components in brain development, it is possible that the alterations in cognitive functioning and increased risk for problem behavior could be attributed to deficiencies in other nutrients relevant to brain development, such as iron, zinc, selenium, iodine, folate, and vitamin A (Georgieff 2007; Monk et al. 2013). In addition, fetal exposure to maternal bacterial or viral infections during pregnancy, as a result of stress-induced immune dysregulation (Coussons-Read et al. 2007; Meyer and Feldon 2009; Meyer et al. 2009; Bilbo 2013), could be an alternative explanation for the increased prevalence in problem behavior and altered cognitive functioning in our studies.

15.5 Conclusion

The DOBHaD hypothesis has led to convergence of knowledge from different fields and has stimulated interdisciplinary research. There is clear evidence that prenatal and early postnatal adversity may affect lifelong behavior and both mental and physical health. Our chapter may further stimulate research examining the influence of ELI that are highly prevalent in women in the childbearing age (e.g., negative emotions, micronutrient deficiencies, environmental toxins) on offspring's neurodevelopmental outcomes, with the use of objective, sensitive assessment techniques.

Both the prenatal and early postnatal periods are targets for innovative, preventative, and intervention strategies. Because maternal lifestyle and stress are modifiable, expected potential, societal, and economic returns on investment, e.g., by improving behavior and health of the next generation, are substantial (Shonkoff 2010). The pregnancy and the early postnatal period are times of both great opportunity and considerable risk, and their influence can extend over a lifetime.

Conflict of Interest The authors declare no conflicts of interest.

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