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The Impact of Prenatal Stress on the Mother-Infant Behavior at six Months after Birth: The Role of different Dimensions of Stress.

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LIST OF ABREVIATIONS

11ß-HSD2	11ß-hydroxysteroid dehydrogenase 2
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit hyperactivity disorder
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASQ	Anxiety Screening Questionnaire
AUCg	Area under the curve with respect to ground
BPD	Borderline Personality disorder
CRF	Corticotropin releasing factor
CRH	Corticotropin releasing hormone
C-section	Caesarian section
df	Degrees of freedom
DNA	Deoxyribonucleic acid
DV	Dependent variable
EDPS	Edinburgh Postnatal Depression Scale
e.g.	exampli gratia, for example
ELS	Early life stress
FFE	Face-to-face play episode/ first play episode
FI	Saliva collection immediately after awakening
FII	Saliva collection 30 minutes after getting up
FIII	Saliva collection 14 hours after awakening
GAS	General adaptation syndrome
HPA axis/ system	Hypothalamic-pituitary-adrenocortical axis/ system
IA	Interaction
i.e.	id est, that is
IQ	Intelligence quotient
ICEP	Infant and Caregiver Engagement Phases
IposMpos	Infant positive-mother positive dyad
IproMneg	Infant protesting-mother negative dyad
IproMpos	Infant protesting-mother positive dyad
IV	Independent variable
LES	Life Experiences Survey
M	Mean
MINI	Mini International Neuropsychiatric Interview
Part. Eta sq.	Partial Eta-squared

PAR	Predictive adaptive responses
PC1	First principal component
PCA	Principal component analysis
PDQ	Prenatal Distress Questionnaire
POSEIDON	Pre-, Peri- and POstnatal Stress: Epigenetic Impact on DepressiON
PS	Prenatal stress
PSS	Perceived Stress Scale
PTSD	Posttraumatic stress disorder
RE	Reunion episode
RM-ANCOVA	Repeated measures analysis of covariance
SAM	Sympathetic-adrenomedullary system
SD	Standard deviation
SE	Standard error
Soz-U	Social Support Questionnaire
STAIT/S	State-Trait Anxiety inventory

1 THEORETICAL BACKGROUND

1.1 Scope of the present dissertation

A broad range of early life stress (ELS) factors have been identified to have an impact on infant development, behavior and later vulnerability to cognitive and emotional problems, physical diseases and mental disorders (Glover, 2014; Glover, O'Connor, & O'Donnell, 2010). Besides the already established postnatal influencing factors, recent ELS research has also focused on the course of pregnancy and prenatal maternal conditions, which are discussed to have an impact on infant development (Graignic-Philippe, Dayan, Chokron, Jacquet, & Tordjman, 2014; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003). As pregnancy marks a special time in every woman's life, bringing with it adaptation processes of body, mind and environment, this time is also prone to upcoming worries and distress, potentially resulting, for example, in anxiety and depressive symptoms (Ehlert, Sieber, & Hebisch, 2003). As ELS has been defined as a potential risk factor, recent research has also focused on questions of quantity, quality, and the different forms of ELS, from daily hassles to catastrophes, and their short- and long-term impact on mothers and their unborn children (Babenko, Kovalchuk, & Metz, 2015; Murgatroyd & Spengler, 2011; O'Donnell, O'Connor, & Glover, 2009; Turecki & Meaney, 2016; Weinstock, 2008). Furthermore, with recent research also reporting positive effects of ELS on the infant, opposing theories of "stress sensitization" and "stress inoculation" have been proposed in the attempt to further the exploration of underlying processes (Bock, Rether, Groger, Xie, & Braun, 2014; Daskalakis, Bagot, Parker, Vinkers, & de Kloet, 2013).

The dissertation presented here aims to illuminate the possible negative or positive impact of prenatal stress on mother-infant dyadic behavior at six months after birth during the still-face situation. The theoretical background expands on a general definition of stress, the physiological stress, as well as the psychological components of the stress reaction. Furthermore, stress theories concerning beneficial as well as impairing impacts of ELS, especially prenatal stress and its impact on the infant, are introduced. Moreover, mother-infant behavior in the first years of the child's life is examined, with a focus on the still-face paradigm as an experimental method, along with the research questions derived from this.

1.2 Historical overview of the definition of "stress"

The term "stress" is used in various disciplines, and originates from the Latin word "stringere", which means "to draw tight" (Keil, 2004). Early investigations of "stress" and the subsequent research can be distinguished into two concepts: physiological and psychological stress

(Faraday, 2005). The physiological stress concept dates back to Hans Selye's and Walter Cannon's research in the early 20th century on physiological responses to different stressors. Their studies were rooted in the findings of Claude Bernard, who described an internal and external "milieu" of the body and assumed a constancy of the body's "internal milieu" (i.e., the internal environment) (Faraday, 2005; Goldstein & Kopin, 2007). Both Selye and Cannon shared the view of a common stress response, assuming that every stressor would lead to the same nonspecific stress reaction in the body (Thiel & Dretsch, 2011). Later on, psychological or biopsychological stress concepts were proposed, such as the "cognitive appraisal theory" by Lazarus and Folkman (1987), which tried to describe the origins of individual differences in the stress response, or the "allostatic load model" by McEwen (1998), which focuses on the consequences of reaction to a stressor. Both physiological and (bio-)psychological stress concepts, as well as recent definitions, are introduced in the following subchapters.

1.2.1 The general adaptation syndrome and homeostasis

Selye can be seen as the first researcher to coin the term "stress" in his reaction-related approach to the acute stress response (Goldstein, 1990; Krohne, 2017). First, he investigated a "general adaptation syndrome" (GAS) in rats when exposed to stressors, such as exposure to cold, surgical injury, production of spinal shock, excessive muscular exercise, and intoxications (Selye, 1936). The GAS was defined as a three-step phase comprising 1) the "alarm" phase, characterized as an anxiety reaction with acute symptoms, 2) the "resistance" phase, defined as the disappearing of symptoms due to successful adaptation of the body, and 3) the "exhaustion" phase, encompassing body damage when experiencing repeated stress exposure, and loss of resistance accompanied by relapse of symptoms (Filaretova, 2012; Fink, 2016). Focusing on the hypothalamic-pituitary-adrenal (HPA) axis, Seyle explained the stress reaction through an activation of the neuronal circuit, thus elevating the adrenocorticotropic hormone (ACTH) release and leading to an increase in the glucocorticoid release in the adrenal cortex (Goldstein & Kopin, 2007; Pinel & Pauli, 2012).

While Seyle largely ignored the functions of the sympathetic nervous system, Cannon focused on the "sympathoadrenal system" (i.e., adrenal medulla and sympathetic nervous system) and the function of catecholamines in the body (Pinel & Pauli, 2012). According to Cannon, the confrontation with an immediate stressor causes the activation of the "sympathoadrenal system" and the consequent release of epinephrine (e.g., adrenaline) into the bloodstream, causing an acceleration of the heart rate, blood pressure, and increased glucocorticoid release (Goldstein, 1990). Cannon also formulated the concept of "homeostasis", which describes the maintenance of blood glucose, oxygen tension, core temperature and other important physiological variables within a healthy range (Goldstein & Kopin, 2007). The maintaining mechanisms were described as sensors, which report changes within the organism and constantly detect whether the values lie within the healthy range of homeostasis, and also negative feedback systems consisting of effectors which initiate the reduction of discrepancies between the current state and the aimed-for setpoint (Goldstein & Kopin, 2007). For example, sensors which give feedback to the thermoregulatory systems initiate the body to sweat when the core temperature rises or to shiver when the core temperature falls (Goldstein & Kopin, 2007). Cannon also coined the term "fight or flight" to describe the possible behavioral outcome following the stress response, which corresponds to Selye's "general adaptation syndrome" (Fink, 2016).

Nowadays, further possible behavioral reactions have been identified as escape reactions, such as the "freezing" and "fright" reaction, especially when faced with fundamental threats to one's life (Bracha, 2004). This mechanism in humans dates back to the Middle-Paleolithic era and the survival advantages of Homo sapiens who showed freezing reactions when confronted with carnivores, which tend to be able to better identify their prey's movement compared to unmovable colors and shapes (Bracha, Ralston, Matsukawa, Williams, & Bracha, 2004). The emotion linked to flight, fight, freezing or fright reactions is fear (Maack, Buchanan, & Young, 2015). The "freezing" reaction was defined by Bracha and colleagues (Bracha et al., 2004) as "stop, look and listen" or a heightened alertness response, which should not to be confounded with tonic immobility as seen during traumatic events. The latter was described by Bracha et al. (2004) as "playing dead" when directly confronted with the predator or the "fright" reaction.

1.2.2 The allostatic load theory

In addition to the more reaction-related stress theories of Selye and Cannon, which understand the concept of stress as the organism's response when confronted with a threat, with the aim of restoring homeostasis, more hybrid biopsychologically oriented modern stress concepts emerged. These describe stress as consciously or unconsciously sensed threat to the organism and to homeostasis. According to McEwen (1998), for instance, the stress response is to a certain degree somewhat specific, depending among other things on the organism's perception of the stressor, it's appraisal of coping abilities, and the extent of impact on homeostasis (Goldstein & Kopin, 2007). The concept of "allostatic load" as presented by McEwen (1998) refers to Sterling and Eyer's concept of "allostasis", which is defined as a permanent adaptation process that constantly learns and expands its knowledge in order to provide a good prediction of required processes (Sterling, 2012). In line with the concept of "homeostasis" (Krohne, 2017), the organism tries to keep itself balanced and aims to adapt when confronted with stressors. If, however, the stressor is too strong to be handled, or is ongoing, the organism fails to return to its balanced condition and allostatic systems overreact. This overreaction or possible underreaction of the organism's stress response can result in pathophysiology, and was defined as "allostatic load" (McEwen & Seeman, 1999). Therefore, the "allostatic load" model refers to the consequences of chronic stress. Sterling explained the difficult process of keeping the organism's balance through the brain's ability to predict difficulties and threats and anticipate needs before initiating the adequate stress responses (Sterling, 2012).

The nature of stressors might have an external (e.g., threat) or an internal origin (e.g., negative thoughts, loss of control) (Sapolsky, 2015). In his review of possible mediators of the stress response, McEwen states that besides genetic components, two factors contribute to the individual stress experience, independently of its nature (i.e., chronic stress or acute stress): the individual perception of a situation and the general state of physical health, which is shaped by lifestyle choices such as diet and physical activity (McEwen 1998). The adjustment and habituation to stressors depends largely on the person's perception, which comprises thoughts and emotions elicited by the stressor, and can be supported by training behavioral and theoretical coping skills (McEwen 1998). Therefore, the stress reaction has not only a physiological but also a psychological dimension and results in individually different stress experiences.

1.2.3 The cognitive appraisal theory

In their "cognitive appraisal theory", Lazarus and Folkman focused on the psychological impact of coping abilities on the stress response. They defined "stress" as a transactional process dependent on differences in the cognitive appraisal and individual ability to cope with stress (Lazarus, 2000; Lazarus & Folkman, 1987). Thus, stressors are evaluated individually, depending on their appraised impact on the person's well-being (i.e., primary appraisal) and the available coping strategies (i.e., secondary appraisal) (Folkman, Lazarus, Gruen, & DeLongis, 1986). Two major coping strategies were identified: "emotion-focused coping" and "problem-focused coping" (Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen, 1986). The former tries to ameliorate the negative emotional reaction to a stressor, while the latter attempts to change the person-environment situation in order to alleviate the stressful circumstances (Yali & Lobel, 1999). Accordingly, coping processes were identified as possible mediators between a stressor and the subsequent stress response. The "cognitive appraisal theory" focused not only on the stress response but also on emotional states (Lazarus & Folkman, 1987). According to the authors, the stress response is subordinated under the term of emotions, being an essential requirement for both positive and negative emotional states (Lazarus & Folkman, 1987). Emotional states were themselves linked to physiological arousal states with the "two-factor theory" of Schachter and Singer, who suggested that the individual will link a felt arousal to a specific emotional label, or at least try to describe the felt arousal state using available thoughts in order to categorize it.

1.2.4 Recent stress definitions: Positive and negative impact of stress

Today, many "stress" definitions exist, but a more general view defines stress as the body's adaptation processes when confronted with a stressor, regardless of whether the stressor is internal or external or of a physical or psychological nature (Esch, 2002; Fink, 2016). This view comprises both negative and positive stressors, although the common perception tends to associate the term stress with a negative state (Filaretova, 2012; Fink, 2016). Nevertheless, events which are generally seen as highly positive, such as a wedding or a pregnancy, also have been identified as major stressors and listed, amongst others, in the "social readjustment rating scale" by Holmes and Rahe (1967) due to the required processes of adaptation. In common parlance, no distinction is generally made between the elicitor (i.e., stressor) and the consequential stress reaction (Nater, Ditzen, & Ehlert, 2011) when referring to "stress". Mostly, the term is used to describe an emotion (i.e., "feeling stressed"), but the term "stress" itself is not defined as an emotional state (Keil, 2004). What every stress theory has in common is the assumption that a normal, current stress reaction aims to protect the organism from harm, to adapt to the new circumstances and to subside once the stressor is gone. For example, positive consequences of stress were proposed by the Yerkes-Dodson law, which describes the association of stress and outcome as an inverted U-shaped curve, with the best outcome under moderate stress conditions (Chaby, Sheriff, Hirrlinger, & Braithwaite, 2015; Sapolsky, 2015). Memory recall of threat-related information, for instance, has been reported to be better under threat conditions than under non-threat conditions (Zhu, Zhao, Ybarra, Stephan, & Yang, 2015). Furthermore, emotionality and arousal were reported to enhance memory (Laney, Campbell, Heuer, & Reisberg, 2004).

Although stress is an important and healthy reaction, a prolonged stress experience, especially in early life, can lead to detrimental changes in physiology and psychology. This is discussed in terms of "fetal programming" in chapter 1.6.1.

1.3 Stress physiology and psychology

As Selye and Cannon already identified, two major systems play a role in the regulation and accomplishment of an acute stressful situation: the hypothalamus-pituitary-adrenal (HPA) axis for the long-term stress response, and the sympathetic-adrenal-medullary (SAM) system for the short-term stress response (Egliston, McMahon, & Austin, 2007).

The HPA axis on the one hand plays a key role in regulating and releasing steroids, leading to a neuroendocrine cascade, starting with the activation of cells in the hypothalamus, and triggering the release of the corticotropin-releasing factor (CRF). The CRF acts on the pituitary gland, which activates the secretion of the adrenocorticotropic hormone (ACTH) in the blood; see Figure 1 (Hyman, 2009). ACTH, in turn, stimulates the receptors on the cortex of the adrenal gland, triggering the synthesis and release of other hormones, including the most prominent cortisol (Egliston et al., 2007; Fink, 2016). Moreover, the cortisol plasma concentration inhibits ACTH and CRF release, working as a negative humoral feedback loop (Lang, 2011). The adrenal gland is subject to the circadian rhythm, which is reflected in the changing cortisol levels: With a stable circadian rhythm, cortisol levels reach the highest values during the night and early morning hours, and decline over the course of the day (Gudermann & Engel, 2014). Corticotropin-releasing hormone (CRH) and CRF receptors can be found in other brain regions besides the hypothalamic regions, such as the limbic system, the central sympathetic system of the brain stem, or the medulla (Kleine & Rossmanith, 2014a).

The sympathetic-adrenal-medullary (SAM) system, on the other hand, mainly regulates with the help of catecholamines, and therefore guarantees short-term stress reactions which need a heightened glucose decomposition in the muscle tissues, such as “freeze-flight-fight-fright” responses (Löffler, 2008). With the stimulation of preganglionic neurons and their acetylcholine release, the adrenal gland becomes activated to release epinephrine and norepinephrine directly into the blood. This causes an immediate stress response, resulting in a decreased activation of the parasympathetic nervous system and an increased activation of the sympathetic nervous system, as well as increased blood pressure, pulse, glucose levels and sweating (Ehrhart-Bornstein & Bornstein, 2008; Krohne, 2017; Souvatzoglou, 2005). The activation of the parasympathetic system leads to a return to the normal status, thus acting as a regulating antagonist to the sympathetic nervous system. The HPA and SAM systems share interconnections, such as the prefrontal cortex, the hippocampus, the limbic system, as well as the amygdala and the locus coeruleus in the pons and the paraventricular hypothalamic nucleus (Kleine & Rossmanith, 2014b; Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010).

Therefore, psychological factors, such as thinking styles, memories, and emotion regulation capacities, interfere with the resulting stress response (Esler et al., 2008). Although the SAM system’s main purpose is to initiate fast fight-or-flight stress responses (Krohne, 2017), previous studies reported that emotional arousal and cognitive activity influence the

SAM system activity (Thayer & Lane, 2009), and especially that cognitive appraisals contribute to HPA axis regulation (Krohne, 2017). Besides cognitive appraisals, cognitive restructuring and emotion regulation techniques are a powerful means by which to regulate stress reactions. With regard to anticipatory sensitization to expected stressful events and subsequent HPA axis activation, recent research has reported a stress-reducing influence of attention and emotion regulation techniques (Turan et al., 2015).

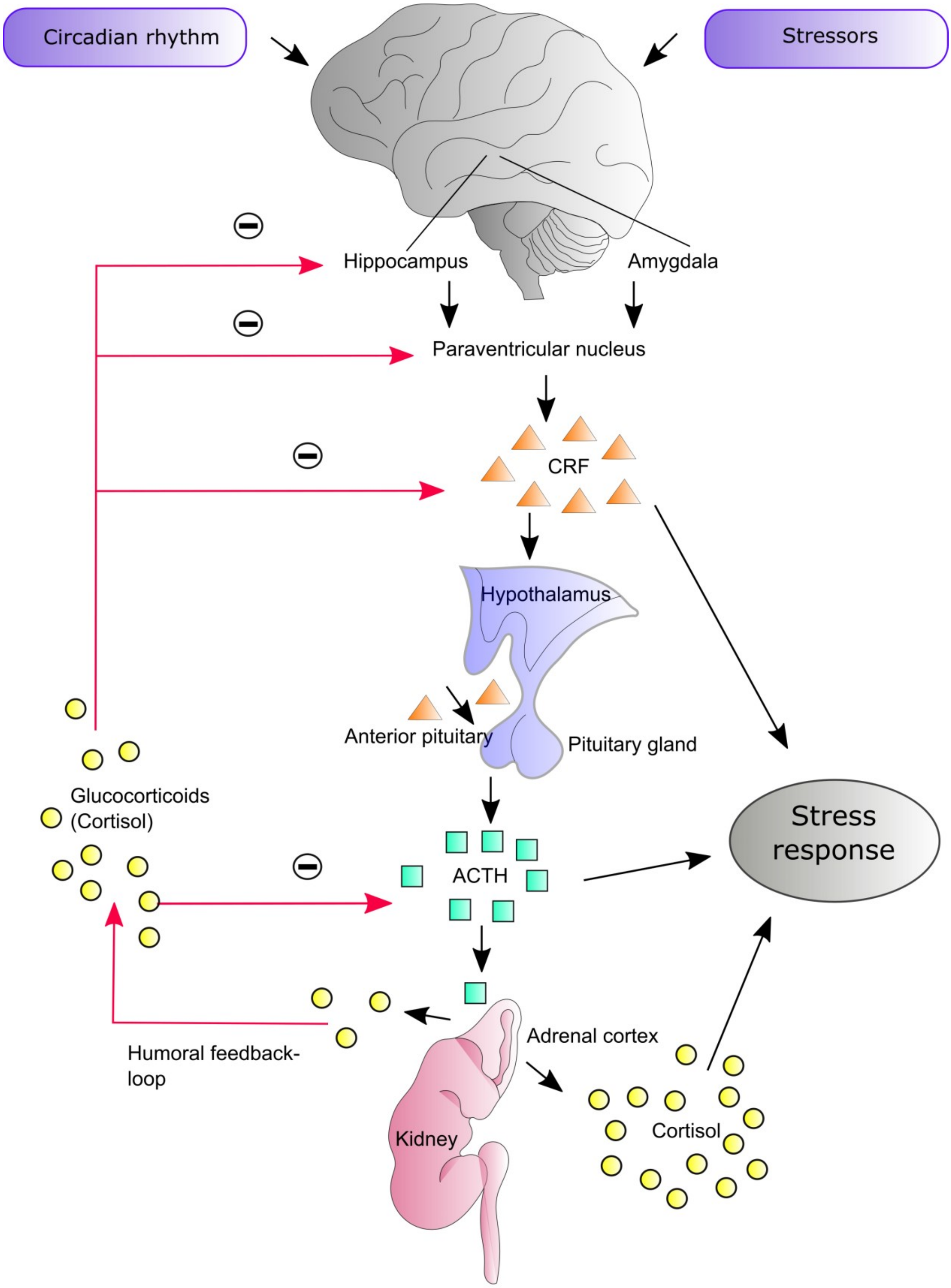
1.3.1 Stress physiology in pregnancy

During pregnancy, mothers-to-be are confronted not only with physical changes such as weight gain, hormonal changes, worries about the well-being of the unborn child, and sleep difficulties, but also with the challenging task of handling their new life, including changes to their family situation, work and social environment (Kivlighan, DiPietro, Costigan, & Laudenslager, 2008; Yali & Lobel, 1999). All of this is accompanied by changes in maternal stress parameters. During the normal course of pregnancy, the baseline of stress hormones rises, with a peak in the last trimester shortly before delivery (Allolio et al., 1990). In this respect, as the pregnancy proceeds, mothers-to-be become physiologically less responsive to stress (Glynn, Wadhwa, Dunkel-Schetter, Chicz-Demet, & Sandman, 2001). Elevated stress hormone levels in the last trimester of pregnancy have a dampening effect on the corticotropic system and thus on the response to ACTH, allowing the maternal organism to react only to a significantly higher dose of stress (Glynn et al., 2001; Schulte, Weisner, & Allolio, 1990). In this respect, the decrease in vulnerability to stress as pregnancy proceeds can be seen as a protection of the maternal organism from upcoming stressors including the childbirth (Glynn et al., 2001). The normal course of pregnancy and fetal development, such as organ maturation, are dependent on a sufficient increase in cortisol, which acts as a developmental promoter (Davis, Head, Buss, & Sandman, 2017).

Prior research reported that CRH can be found in the fetus' hypothalamus, and ACTH can be found in the fetal plasma, around the 12th week of gestation. Fetal HPA activity can be found beginning at mid-gestation, but most of the fetal cortisol levels are of maternal origin (Mastorakos & Ilias, 2003). Nevertheless, the maternal and fetal HPA activity are two discrete systems and can react independently of each other (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001). The normal amount of cortisol which is metabolized through placental barriers lies between 80-90% of the maternal cortisol in the normal course of pregnancy, leaving 10-20% of the maternal cortisol able to influence the fetal organism (Gitau, Cameron, Fisk, & Glover, 1998). Research into prenatal stress responses of the fetus suggested heightened fetal HPA axis activity due to maternal cortisol crossing the placenta barrier, and due to an independent reaction of the fetal HPA axis (Gitau et al., 1998; Gitau et al., 2001).

However, owing to the much lower fetal cortisol levels, 10-20% of maternal cortisol could double the fetal cortisol concentrations (Gitau et al., 1998). The protecting placental enzyme 11ß-hydroxysteroid dehydrogenase 2 (11ß-HSD2), which converts cortisol to the inactive form of cortisone (Jensen Pena, Monk, & Champagne, 2012), was found to be downregulated by maternal stress during pregnancy (Mairesse et al., 2007). With studies showing a direct impact of a maternal stress reaction (i.e. maternal cortisol release) on the fetus and subsequently elevated fetal cortisol concentration, a further direct impact of maternal stress on the fetal development was suggested (Gitau et al., 2001). Furthermore, several studies reported associations between prenatal stress and prematurity as well as low birth weight (Bolten et al., 2011; Field et al., 2006; Harville, Giarratano, Savage, Barcelona de Mendoza, & Zotkiewicz, 2015). For example, Kivlighan et al. (2008) examined the relationship between the maternal psychological well-being during the last trimester of pregnancy, the maternal cortisol response during that time, and the infants' birth weight. They found that higher morning cortisol and steeper morning cortisol declines were associated with smaller, lighter neonates, and a flat maternal diurnal cortisol rhythm and blunted morning cortisol decline were associated with heavier neonates (Kivlighan et al., 2008).

These findings lent physiological support to theories on long-term influences of prenatal stress, such as the "fetal programming theory", as explained in chapter 1.6.1. (Yong Ping et al., 2015). The following chapters will expand on further research on the impact of stress in the pre-, peri- and postnatal period (see chapters 1.4 – 1.5).



CRF: Corticotropin releasing factor; ACTH: Adrenocorticotropic hormone

Figure 1: The HPA system sensu Hyman (2009) and Egliston (2007)

1.4 Prenatal and perinatal stress and its impact on the infant

Nowadays, the decision to start a family and become pregnant is a highly individual one, as reflected in the declining birth rates in Europe. Therefore, the decision to have a child is mostly well-deliberated and accompanied by joyous expectations (Ehlert, 2004). At the same time, expectations of having an uncomplicated pregnancy and birth, anxiety about the fetal well-being, and expectations regarding the quality of one’s own maternal behavior, as well as about the infant itself, are rising (Ehlert et al., 2003). All of this renders pregnancy and birth a major event in a woman’s life (Ehlert et al., 2003; Van den Bergh et al., 2017). A pregnancy brings with it changes and challenges in the partner relationship, the social environment, and in physiological and psychological terms, leading to the need for the mother and her environment to adapt to the new situation (La Marca-Ghaemmaghami & Ehlert, 2015). Consequently, prenatal stress is common, with one study finding that 64% of participants from a vast sample of 74.380 mothers reported at least one stressful life event during their pregnancy (Whitehead, Brogan, Blackmore-Prince, & Hill, 2003). Nevertheless, prenatal stressors have been identified as being associated not only with the course of pregnancy and birth outcomes, but also with later problems regarding the infant’s physiology and mental health (Ehlert, 2004; Weinstock, 2001).

The term “early life stress” describes possible influencing factors that have the power to impact on the infant’s development, and encompasses the prenatal period of pregnancy until late childhood (Pechtel & Pizzagalli, 2011). Research on severe early life stressors, such as natural or man-made catastrophes or the influence of wartimes, revealed a clear impact on the infant (Laplante et al., 2004; Yong Ping et al., 2015). However, daily hassles, minor life events and maternal mood also seem to provide fertile ground for prenatal stress and have been examined in previous research (Nast, Bolten, Meinlschmidt, & Hellhammer, 2013; Van den Bergh, Mulder, Mennes, & Glover, 2005), with findings supporting theories of “fetal programming” (see Chapter 1.6.1). Therefore, in the last decade, a vast amount of studies have focused on the impact of prenatal stress on the course of pregnancy, as well as on the infant’s development and later course of life (Charil, Laplante, Vaillancourt, & King, 2010; Glover, O'Connor, & O'Donnell, 2010; La Marca-Ghaemmaghami & Ehlert, 2015; Provenzi, Guida, & Montirosso, 2018). These research findings from studies in humans and animals will be presented in the following chapters 1.4.1 and 1.4.2. The term “prenatal” is defined as the time span until birth (Nast et al., 2013), in contrast to the term “perinatal”, which marks the time around birth, from the 22nd week of gestation until 7 days after birth (see DIMDI (Deutsches Institut für Medizinische Dokumentation und Information, im Auftrag des Bundesministeriums für Gesundheit unter Beteiligung der Arbeitsgruppe ICD des Kuratoriums für Fragen der Klassifikation im Gesundheitswesen, & (Hrsg.), 2018) . Researchers have deemed the term “perinatal” to be more appropriate due to the high probability of ongoing prenatal stressors in the mother around the time of birth and thereafter (Darnaudery & Maccari, 2008). The term “postnatal” or “postpartum” refers to the time after birth, focusing on the environment, experiences and developmental time windows the infant is undergoes up until one year after birth (O'Hara, 2009).

1.4.1 Research on the impact of prenatal stress in humans

Over the last decade, disaster-related studies have attempted to investigate the impact of severe stressors on pregnant mothers and their children. Some of the first evidence came from the investigations of data from mother-child dyads who survived the Dutch “Hongerwinter” in 1944/1945 during the Second World War: Studies found that birth outcomes, and the later risk of severe physical diseases and mental disorders were associated with the prenatal stress exposure of severe under-nutrition and war circumstances (de Rooij, Veenendaal, Raikkonen, & Roseboom, 2012; Roseboom et al., 2001). Possible outcomes identified in the offspring included cardiometabolic diseases (Painter, Roseboom, & Bleker, 2005; Roseboom, de Rooij, & Painter, 2006) and breast cancer (Painter et al., 2006), as well as schizophrenia (Susser et al., 1996), depression (Brown, van Os, Driessens, Hoek, & Susser, 2000) and addictive disorders (Franzek, Sprangers, Janssens, Van Duijn, & Van De Wetering, 2008). Likewise, research on the Chinese Famine of 1959-1961 showed a heightened risk of later schizophrenia in the infants of mothers who suffered from starvation during their pregnancy (Wang & Zhang, 2017). Furthermore, “Project Ice Storm” investigated infants who were prenatally exposed to stress during the Canadian ice storm in 1998 and found associations between prenatal maternal stress and birth outcomes (Dancause et al., 2011), difficult child temperament at 6 months postpartum (Laplante, Brunet, & King, 2016), as well as lower full IQs and lower verbal IQs in infants (Laplante, Brunet, Schmitz, Ciampi, & King, 2008). Elevated stress reactivity was linked to prenatal stress in another disaster-related study, which investigated the “Iowa Flood” of 2008. Infants of mothers who were pregnant during the flood showed a heightened cortisol stress response to a mother-toddler separation paradigm at the age of 2 ½ years (Yong Ping et al., 2015). Furthermore, mothers who were pregnant during the World Trade Center attacks and developed posttraumatic stress disorder (PTSD) rated their 9-month-old infants as significantly more distressed in response to novelty compared to infants whose mothers did not show PTSD symptoms (Brand, Engel, Canfield, & Yehuda, 2006). Overall, the findings suggest a distinctive form of severe prenatal stress and long-term consequences of ELS for physical and mental health. Regarding the aforementioned changes in HPA axis activity, prior studies most commonly reported raised cortisol levels in prenatally stressed mothers-to-be. For instance, positive relations between maternal depressive symptoms, maternal anxiety, panic symptoms during pregnancy and elevated cortisol levels in the newborn were reported (Van den Bergh et al., 2005). Furthermore, maternal mood in late gestation was identified as being directly linked to fetal behavior, as surveyed via ultrasound (Van den Bergh et al., 2005). However, besides findings of increased HPA axis activity in the newborn due to prenatal stress exposure, decreased cortisol levels were also found.

A disaster-related study including mothers with PTSD symptoms reported decreased cortisol levels in prenatally stressed infants (Yehuda et al., 2005). In general, a long-term impact on the offspring's HPA axis seems to be a common but not consistent finding for every kind of prenatal stressor (Glover, O'Connor, et al., 2010). Past research on disaster-related stress exposure also highlighted the importance of timing, identifying so-called "sensitive periods" (O'Connor, 2003). Studies on the "Dutch Hongerwinter" cohort showed associations between different adult diseases later in life, such as cardiometabolic diseases or diabetes, and the different timing of maternal famine during pregnancy (Roseboom et al., 2001). Interestingly, the risk of developing a major affective disorder was only elevated when stress exposure (i.e., famine) occurred in the second and third trimester of pregnancy (Brown et al., 2000). Moreover, severe stress was found to be associated with greater cortisol increase in toddlers (Yong Ping et al., 2015). However, previous studies linked severe disaster-related stress in the early stages of pregnancy to lower general IQ and language abilities in infants (Laplante et al., 2004). Along with these findings, in their review, Sandman and colleagues (2011) mentioned the detrimental influence of severe maternal stress in early pregnancy, resulting in delayed fetal maturation and impaired cognitive performance in infancy. Moreover, Glynn and colleagues found the impact of stress exposure early in gestation to be more pronounced and detrimental than later in pregnancy, as the stress appraisal in pregnant women experiencing an earthquake was highest in the first trimester of pregnancy and in the postpartum period (Glynn et al., 2001).

O'Connor and colleagues argued in their review that the early stages of gestation might be more vulnerable because the majority of organ formation occurs in this period (O'Connor, 2003). Interestingly, Davis and Sandman (2010) reported both impairing and at first glance seemingly beneficial consequences of prenatal stress exposure depending on its timing during gestation. Infants who were exposed to elevated maternal cortisol levels during early gestation showed a slower rate of development during the first year of life, whereas those exposed to elevated cortisol levels in late pregnancy showed an accelerated development over the first year

(Davis & Sandman, 2010; Sandman et al., 2011). Moreover, DiPietro and colleagues (2006) reported that maternal prenatal anxiety, general distress, and depressive symptoms were associated with accelerated infant motor development at the age of two years. The authors assumed that mild stress had an enhancing impact on fetal maturation. Similar results were reported by Karam et al. (2016), who revealed that prenatal stress in a sample of depressed pregnant women was associated with improved motor skills in their one-year-old infants. It appears that there is no general rule of impairing or beneficial influences of prenatal stress. This is illustrated by Laplante and colleagues, who found associations of mild prenatal stress and enhanced general intelligence in infants, as well as impairing associations of high prenatal stress with lower general intelligence outcomes in infants (Laplante et al., 2008).

1.4.2 Research on prenatal stress in animals

When studies in humans are not possible for ethical reasons, animal studies can provide insights into prenatal changes due to stress exposure. A further benefit of animal studies is the ability to provide a better controlled setting, while it is hardly possible to control for several variables in human studies, such as interfering physiological, psychological and social circumstances (Boersma & Tamashiro, 2015). For instance, Schneider and colleagues (2002) examined prenatal psychosocial stress in rhesus monkeys. Pregnant rhesus monkeys were stressed through repeated presentation of noise or a hormone stressor alone or combined with moderate-level alcohol exposure during different stages of gestation. Prenatal stress exposure was found to be associated with lower birth weight and more neurobehavioral problems (i.e. shorter attention span, reduced neuromotor capabilities) in monkey offspring and later on with behavioral abnormalities (i.e., stereotypies, decreased exploration, locomotion, social and play behavior) during monkeys' adolescence (Clarke & Schneider, 1997; Schneider, 1992; Schneider et al., 2002).

The authors discussed that prenatal stress and alcohol exposure are themselves contributing factors, which should be seen as a dynamic system, implicating each other rather than being the singular causal factor (Schneider et al., 2002). Further research in rhesus monkeys found prenatal stress to be related to diminished size of the monkeys' corpora callosum (Coe, Lulbach, & Schneider, 2002), reduced volume of the hippocampus and diminished neurogenesis in the dentate gyrus (Coe et al., 2003) and impaired concentration and learning behavior (Coe, Lubach, Crispen, Shirtcliff, & Schneider, 2010), as well as to less play behavior, linking ELS to changes in social behavior (Clarke & Schneider, 1993). Luoni and colleagues (2016) tested their hypotheses regarding the long-lasting impact of prenatal stress in a cross-species genome-wide approach in rats, non-human primates and humans. They found a protein (i.e., Ankyrin-3; Ank-3) which is strongly involved in genetic origins of psychiatric disorders to be affected by prenatal stress, with changes in genetic methylation patterns found in rats and alterations in working memory found in humans (Luoni et al., 2016). This provided evidence for the impact of prenatal stress on long-term alterations and vulnerability across different species.

Studies in rats revealed, among other things, consistent associations of prenatal stress with changes in brain development, deficits in motor development as well as learning behavior and memory abilities (Weinstock, 2001), dampened sexual behavior in male rats (Darnaudéry, Perez-Martin, Bélizaire, Maccari, & Garcia-Segura, 2006), anxiety-like behavior (Patin, Lordi, Vincent, & Caston, 2005), hyperactivity (Weller, Glaubman, Yehuda, Caspy, & Ben-Uria, 1988), drug addiction (Deminiere et al., 1992), depression-like behavior (Maccari, Darnaudery, & Van Reeth, 2001), and impaired fear extinction and stereotypical behaviors (Wilson, Vazdarjanova, & Terry, 2013). In contrast, research on mildly stressed rat dams and their prenatally stressed offspring showed positive associations between mild prenatal stress and facilitated learning performance of the offspring, but a negative association with emotionality (Fujioka et al., 2001).

The interaction of the timing of stress exposure and the current stage of gestation has also been investigated in animals with studies revealing differences in the influences of prenatal stress depending on its timing, as in the case in human studies. It should be kept in mind, however, that depending on the observed species, some sensitive time windows might differ from those identified for humans, and it is also known, for instance, that brain maturation in rats occurs in postnatal stages (Matthews, 2002; Weinstock, 2008). Nevertheless, animal models showed prenatal stress in early gestation to be associated with heightened vulnerability to reduced neuromotor functioning (Schneider et al., 2002). Studies examining mid to late gestational stress reported associations of prenatal stress and alcohol exposure with behavioral abnormalities (Schneider et al., 2002), as well as anxiety-like behavior in rats, although the latter only for around a four-day time-frame beginning in mid-gestation (Patin et al., 2005), revealing the detrimental effects of a time-stressor interaction. To sum up the present state of the art in ELS research, a vast amount of studies across different species has indicated an influence of prenatal stress on the offspring, mostly of an impairing nature. In contrast to these findings, however, it should be mentioned that some studies also found positive associations between mild prenatal stress and beneficial outcomes in the offspring (Fujioka et al., 2001).

1.5 Postnatal stress

Besides prenatal stressors, several postnatal stressors seem to have the power to influence development as well. Given, that prenatal stressors often still exist after birth and throughout childhood, perinatal stress and postnatal stress can be similar and can also be experienced by the offspring (Weinstock, 2001). Prenatal stress might cause early problems in the infant, such as regulation problems like crying and sleep or feeding problems, leading to maternal distress and a lack of faith in one's maternal caretaking skills (Sidor, Thiel-Bonney, Kunz, Eickhorst, & Cierpka, 2012). This might cause a vicious cycle, with maternal distress leading to postnatal depressive symptoms, which in turn have an impairing impact on the infant, probably leading to increasing regulatory problems in the infant and disturbances in the mother-infant relationship (Papousek, 2011; Papousek & Papousek, 1990).

Regulatory problems, such as sleep problems, colic, feeding problems or excessive crying, can be seen as outcome variables of prenatal stress, as well as stressors themselves (Miller-Loncar, Bigsby, High, Wallach, & Lester, 2004; Sadeh, Tikotzky, & Scher, 2010; Streit, Nantke, & Jansen, 2014; Zijlmans, Korpela, Riksen-Walraven, de Vos, & de Weerth, 2015). In particular, Sadeh and colleagues (2010) mentioned the bidirectional dynamics of pathways of infants' sleep problems and parents' behavior and psychopathology. Moreover, Streit and colleagues (2014) concluded that regulatory problems likely lead to disturbed body and eye contact between parents and infants, which supports the aforementioned vicious cycle theory.

Furthermore, it is important to consider critical sensitive developmental periods which are prone to be influenced by postnatal stressors, as well as mediating influences. For example, previous research has suggested that prenatal stress could be associated with infants' cognitive development, whereas postnatal stress seems to be associated with infants' temperament, thus hinting at sensitive time frames (Lin et al., 2017). Furthermore, the development of social skills seems to be dependent on a critical postnatal developmental time window (Kandel, 1999). Rudolph and Flynn (Rudolph & Flynn, 2007) also argued that depending on the onset of childhood adversities and context-specific factors, as well as gender and stage of development, the impact on the infant may vary.

This hypothesis is supported by animal models: Mice which were postnatally stressed by maternal separation showed impaired emotional long-term potentiation reinforcement during adolescence only when they were stressed during the stress-hyporesponsive period of the HPA axis (i.e. at postnatal day 9), but not when stressed before or after (Gruss, Braun, Frey, & Korz, 2008).

Considering that prenatal stress also has an impact on the mother and thus postnatally on maternal behavior and on the infant, symptoms of postpartum depression and adaptation problems directly come to mind. The previously reported three-month period prevalence of a postpartum depression (minor and major depressive episode) lay at 19.2% (Gavin et al., 2005). Research has revealed negative associations between postpartum depression and infant outcomes. For instance, Murray and colleagues reported that maternal postnatal depressive symptoms associated with poorer infant cognitive outcome at the age of 18 months (Murray, Fiori-Cowley, Hooper, & Cooper, 1996). The impact of postpartum depressive symptoms on the mother-child interaction has been reported in several studies and will be discussed further in Chapter 1.8. Interestingly, Murgatroyd and colleagues (2015) confirmed a general impact of maternal depression on the infant, but also found that a beneficial impact of maternal stroking was only effective for infants with low prenatal stress and high postnatal stress, as seen in mothers with postpartum depressive symptoms. In a study comparing the impact of persistent anxiety and depression, maternal depression was found to have a more robust impact on infants' behavior and emotionality (Prenoveau et al., 2017).

Concerning prenatal stress and maternal caretaking, previous studies have revealed conflicting findings in prenatally stressed rat pups and their mothers. For instance, one study found changes in the maternal behavior, with diminished nursing and reduced sniffing (Patin et al., 2002), whereas in another study, stressed mouse dams raising stressed pubs exhibited comparable nursing qualities to those of non-stressed pubs, but not when cross-fostering a non-stressed pup (Meek, Dittel, Sheehan, Chan, & Kjolhaug, 2001). Further research in rodents found that maternal care (i.e. licking, grooming, arched-back nursing) was associated with differences in epigenetic DNA methylation (Weaver et al., 2004). Another study reported that the offspring of rats showing high maternal care in the first postnatal days were less fearful later in life and showed a more modest HPA system response to stressors (Liu & Diorio, 1997).

It should be kept in mind that there are certainly differences between the maternal caretaking of humans and rodents, with humans being more flexible in their caretaking (Stern, 1997), although the ample research in rodents does provide important insights into possible parallel pathways. While all maternal caretaking also requires signals from the offspring, thereby eliciting parental sensitivity and responsiveness (Braungart-Rieker et al., 2014; Stern, 1997), infants' reactions might also be influenced by prenatal factors, leading to a chicken-and-egg question.

Nevertheless, these findings underline the importance of a longitudinal view on the possible factors influencing child development, as well as the need to investigate the early life environment from the prenatal stage and continuing after birth, in order to identify possible influencing factors impacting the child.

1.6 Early life stress and its impact on infant behavior and psychopathology

In previous studies, prenatal stress was found to be associated with difficult infant temperament, both in humans (Laplante et al., 2016) and in nonhuman primates (Meyer et al., 2015; Rendina, Lubach, & Coe, 2016). Furthermore, heightened maternal anxiety and depressive symptoms in the third trimester of pregnancy were reported to be associated with greater negative behavioral reactivity to novelty in infants (Davis et al., 2004). Contrary to Davis and Sandman’s (2010) findings of a beneficial effect of high cortisol levels in late pregnancy, de Weerth and colleagues (2003) reported a heightened display of negative infant behavior (i.e., crying, fussing, display of negative facial expressions) at the age of five months in a group of mother-infant dyads with high cortisol levels in late pregnancy. The latter data were collected during normal everyday routine mother-infant interactions, such as a bathing situation, and trough maternal questionnaires, and revealed a high congruence between the mothers’ evaluation and the videotaped infant behavioral data.

In addition to the impact on temperamental or emotional indices in infants, extensive research in humans showed associations between prenatal stress experiences and later psychopathology. For example, general associations between prenatal maternal stress and children’s health were found (Zijlmans, Beijers, Riksen-Walraven, & de Weerth, 2017), as well as other positive associations between prenatal stress and, for instance, infant autism (Angelidou et al., 2012; Gardener, Spiegelman, & Buka, 2009; Kinney, Munir, Crowley, & Miller, 2008), schizophrenia (Fineberg et al.; Malaspina et al., 2008; O'Donnell, Glover, Barker, & O'Connor, 2014), attention-deficit/hyperactivity disorder (ADHD) (Linnet et al., 2003; O'Connor, Heron, Golding, Beveridge, & Glover, 2002), deficits in learning (Laplante et al., 2008), conduct disorders (MacKinnon, Kingsbury, Mahedy, Evans, & Colman, 2017), anxiety disorders (Davis & Sandman, 2012), depressive disorders (Post, 1992; Rudolph & Flynn, 2007) and bipolar disorders (Dienes, Hammen, Henry, Cohen, & Daley, 2006). Recent research focusing on gender differences reported that female infants were more vulnerable to affective disorders (Davis & Pfaff, 2014).

A further study on gender effects confirmed this greater vulnerability in female infants (Wainstock, Shoham-Vardi, Glasser, Anteby, & Lerner-Geva, 2015). Considering that these effects may manifest decades after birth, Weinstock (2001) argues that a specific recollection of important prenatal, perinatal and postnatal data might be biased by different factors (i.e., incomplete medical records, inaccurate memory recall). Furthermore, the "male culling hypothesis" highlights the possibility that female fetuses are better at adapting to problematic prenatal environments, reacting with adverse birth outcomes such as diminished size and weight, whereas male fetuses are probably prone to stillbirths or pregnancy loss (Clifton, 2010; Torche & Kleinhaus, 2012). This might mean that the more resilient male fetuses react less when confronted with prenatal stress compared to the generally more adaptive female fetuses (Wainstock et al., 2015). Altogether, these findings emphasize the need for a longitudinal investigation of ELS by considering prenatal maternal and infant factors.

Animal research on the impact of early life stress showed altered fetal HPA axis activity in rodents and their offspring, accompanied by later behavioral abnormalities (Weinstock, 2017). For example, in their review, Darnaudéry and Maccari (2008) reported associations between prenatal restraint stress in rats and later sleep disturbances and anxiety-related behavior due to novelty. The authors assumed that HPA system activation is dependent on the kind and intensity of the stressor and the rat's gender, underlining the importance of considering further influencing factors. Increased HPA axis activation was associated with anxiety-like behavior in male rats but not in female rats. Gender effects were also seen in ELS-experienced adult rats, with female rats showing improved memory in comparison to the male adults.

Moreover, research in monkeys revealed diminished social behavior (i.e., mutual clinging, abnormal behavioral stereotypies) when prenatally stressed (Clarke & Schneider, 1993). Another study investigating monkeys found the offspring's corpus callosum to be altered in size and shape when the mothers were prenatally stressed, suggesting neuropathological factors interfering with the information exchange between the brain hemispheres (Coe et al., 2002).

Summing up the presented findings, the prenatal period is prone to influence from maternal stress, thus heightening the infant's risk of emotional and behavioral problems as well as psychopathology (Charil et al., 2010). Depending on the timing of stress exposure, different effects have been observed, lending support to the "fetal programming theory", which will be presented in the following subchapter (Davis & Sandman, 2010).

1.6.1 Fetal programming and epigenetic methylation

The "fetal programming theory" aims to illuminate the underlying mechanisms of the impact of ELS on the infant, and was first introduced by Barker and colleagues (2002; 1986). Their pioneering research described changes in developmental processes, which are initiated through changes in the immediate fetal environment (Glover, O'Connor, et al., 2010). The authors discovered an association between ischemic heart disease in infants and their birth weight, and deduced that the prenatal nutrition status was responsible for the elevated occurrence of disease (D. J. P. Barker, Winter, Osmond, Margetts, & Simmonds, 1989). They assumed an association between an adverse prenatal environment, the subsequent birth outcome, and disease diagnosed later in life. Further research revealed associations between birth weight and increased risk of cardiovascular diseases, diabetes and metabolic disorders later in life (D. J. P. Barker, 1995, 2004). Mairesse and colleagues (2007) described the programming mechanism as the maternal stress signaling the fetus' organism to adjust developmental processes and thus shaping the subsequent adult phenotype. In contrast to theories describing mechanisms of altering the phenotype based on an early prediction of the later environment (see Chapter 1.6.1), fetal programming describes early environmental conditions that are sufficiently powerful to alter the course of fetal development, leading to enduring structural and functional modifications in the infant's organism (A. J. Lewis, Galbally, Gannon, & Symeonides, 2014).

Different forms of stress transmission paths have been suggested in the literature, drawing on investigations in both human and animal models. These pathways were found to be related to the maternal physical status and possible hormonal changes, as well as changes in the maternal immune system, leading in turn to changes in the placental permeability and thus influencing the fetus (Cottrell & Seckl, 2009; Wadhwa, 2005). For example, research in animals revealed associations between decreased 11ß-HSD2 enzyme activity and fetal development, such as restricted fetal growth (Mairesse et al., 2007). Besides Barker's initial findings, animal research also reported a relationship between fetal growth restriction and cardiovascular diseases or metabolic disorders later in life (Levitt, Lindsay, Holmes, & Seckl, 1996). Further research in humans reported the same relationship (Mäkikallio et al., 2016). The physiological mechanism underlying these findings is the down-regulation of the protecting placental enzyme 11ß-HSD2 as a consequence of prenatal stress and life adversities, which is responsible for the augmentation of plasma glucocorticoid levels in the fetus, and is able to cause epigenetic alterations (Charil et al., 2010; Jensen Pena et al., 2012). Whereas in a normal course of pregnancy, the amount of maternal cortisol passing to the fetus is about 10-20% of the maternal HPA system activity (Benediktsson, Calder, Edwards, & Seckl, 1997), the 11ß-HSD2 downregulation can cause elevated cortisol levels to reach the fetus. Previous research reported that a rise of 10-20% in maternal cortisol levels can double the fetal glucocorticoid concentrations (Gitau et al., 1998; Gitau et al., 2001), suggesting tremendous effects of higher maternal cortisol passing the placental barrier due to 11ß-HSD2 downregulation (see Figure 2). This can lead to long-lasting effects on gene expression, such as DNA methylation, subsequently impacting on, for example, insulin resistance or brain development (Welberg &

Seckl, 2001). The DNA methylation, one of the most prevalent epigenetic alterations, regulates the gene activity by the addition/ binding of a methyl group on specific 5'-cytosine-guanine-3' dinucleotides (i.e., CpG sites) of the DNA sequence (Provenzi, Guida, & Montirosso, 2017; Stonawski et al., 2017). The methylation mechanism is able to change switches in the DNA activity ranging from gene activation to gene silencing (Bird, 2007; Haselbeck et al., 2013; McGowan & Szyf, 2010). It begins from the prenatal period and reaches over the lifespan, leading to long-lasting changes and constantly changing methylation patterns as well (Bird, 2007). During the prenatal period, as well as later in life, DNA methylation seems to depend among other things on the HPA axis activity and is therefore individual, based on individual experiences and their appraisal (Fraga et al., 2005; Haselbeck et al., 2013). A previous study exploring methylation patterns in monozygotic twins found that while the methylation of younger twin pairs was epigenetically indistinguishable, older twin pairs (over 50 years) showed remarkable differences, with 2.5 times as many DNA methylation differences and four times as many differentially expressed genes compared to their younger counterparts (Fraga et al., 2005). The authors explained the differences through possible internal and external factors known to be related to long-term epigenetic modifications, such as lifestyle, diet, smoking, or physical activity, as well as the "epigenetic drift", namely small defects during epigenetic information transmission, which accumulate to yield different epigenetic patterns (Fraga et al., 2005). Nevertheless, early DNA methylation can start in prenatal periods and can have a profound impact on the offspring, concerning all aspects of development, from physical to neurodevelopmental (Glover, O'Connor, et al., 2010; Talge, Neal, & Glover, 2007), as well as later psychopathology (E. D. Barker, Walton, & Cecil, 2018). The vast body of research reporting impairing influences of prenatal stress stands in contrast to the few findings documenting possible beneficial effects of prenatal stress, lending support to different theories which will be discussed in the next chapter (1.7).

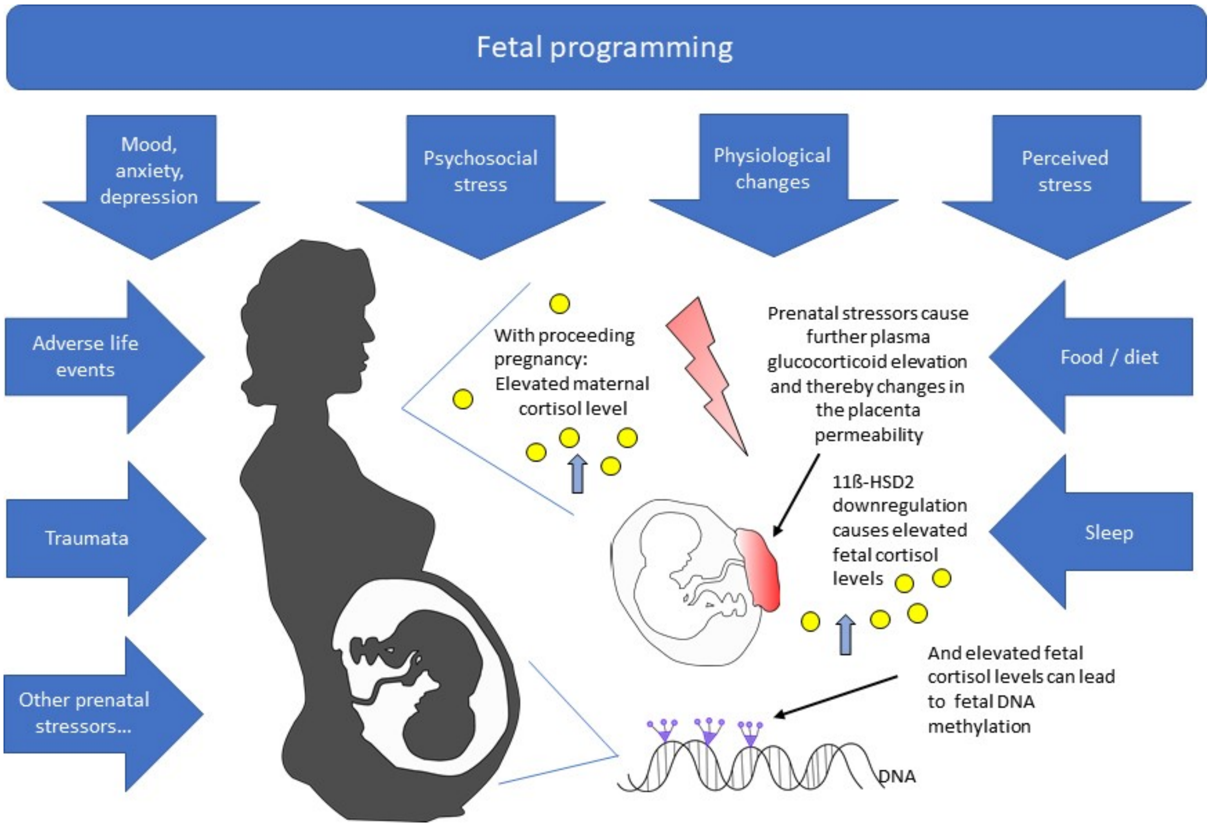


Figure 2: Prenatal stressors and fetal programming

1.7 Theories on the impact of early life stress experiences

In the last few years, different theories have emerged, which attempt to explain or reconcile study findings of both a possible positive and negative impact of ELS on the infant. These include the "stress sensitization" and "stress inoculation" models. Hybrid models have also been proposed, which suggest an explanation of possible simultaneously impairing and beneficial impacts on ELS, such as the "match-/mismatch theory" and the "predictive adaptive responses" model. These models on the impact of ELS form the background for the present study and will be presented in the following subchapters.

1.7.1 Stress sensitization

The "stress sensitization" model was first introduced by Post (1992), who proposed that adaptation processes of the human neuroendocrinological system follow a stress exposure. Post assumed that the stress reaction and its adaptation processes would leave "neurobiological scars", powerful enough to sensitize the organism to future stressors like those already experienced, and thus increasing the vulnerability to future disorders. Subsequent animal research demonstrated the impairing influence of prenatal stress in rats (Henry et al., 1995):

When pregnant rats were exposed to restraint stress in pregnancy, the rat offspring showed different functional alterations in their mesolimbic dopaminergic system depending on elevated D2 and decreased D3 receptor densities, as well as an enhanced amphetamine-induced motor sensitization, supporting the development of sensitization to psychostimulants (Henry et al., 1995). Further research in rodents found an impairing impact of prenatal stress in rats irrespective of its physiological or psychological nature, resulting in heightened HPA axis activity response and higher anxiety in male offspring (Brunton & Russell, 2010). Subsequent research emphasized alterations in epigenetic programming depending on the variety of stress types, quantity and time span, repetition, as well as critical developmental time windows (Charil et al., 2010; Murgatroyd, Wu, Bockmuhl, & Spengler, 2010), suggesting a long-term impact on the infants' development and later health outcome (Brunton & Russell, 2010). As already presented in chapters 1.4 and 1.6, prenatal stress impacts on different offspring parameters. However, stressors tend to show different degrees of influence, and not every stressor may lead to additive effects when combined with other stressors, resulting in different changes in offspring outcomes, such as anxiety in rat pups (Badache et al., 2017). Currently, the concept of stress sensitization is seen as the state of hyperresponsiveness (to a certain stressor or a different set of stimuli) after stress exposure (Belda, Fuentes, Daviu, Nadal, & Armario, 2015). Altogether, the unclear pathways and different outcomes of stressor impact have led to further theories on the influences of different types of stress, presented in the following subchapters.

1.7.2 Stress inoculation

More recent research revealed a potential beneficial impact of stress, which was encompassed in the "stress inoculation" model. First reports from Levine (1957) showed positive influences of early life stress in rats which were "handled". The "handling" was defined as the repeated procedure of taking the rat pups out of their cages, away from their mothers, into another compartment before replacing them in their nest. The procedure took place once a day for the first 20 days of the pup's life. The "handled" rats showed higher body weight and lower adrenal gland weights than the "non-handled" rat control group, suggesting that experiencing stress in early life (i.e., handling) has a positive impact on the rats' adaptation ability (Levine, 1957). Subsequent studies on "handling" also reported beneficial effects of handling, with handled rats showing reduced stress reactivity and enhanced novelty seeking (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Kudryashova, Markel, Sharova, & Yakobson, 2004). Meaney (2001) found changes in brain regions of handled rats that are associated with the regulation of stress reactivity, suggesting a long-term influence of PS. Other research reported reversal effects of neonatal handling on behavioral abnormalities in rats caused by PS exposure (Wakshlak &

Marta, 1990). For controls, neonatal handling was not associated with a beneficial or impairing impact on the rat pups.

In a review of handling, Levine (2005) stated that there is evidence for both a beneficial and an impairing impact of ELS on rat pups. Further support for both possible outcomes was reported by recent research on rats, which revealed positive influences of handling (i.e., decreased anxiety- and depression-like behavior, increased exploratory behavior), as well as negative influences (increased anxiety- and depression-like behavior) depending on the rat species and their genetic differences (Rana, Pugh, Jackson, Clinton, & Kerman, 2015).

Current views on "stress inoculation" suggested that the quantity and quality of stress are the decisive factors, with the best beneficial outcomes when experiencing mild stressors and the least beneficial or impairing impact when experiencing insufficient stressors or too powerful stressors, comparable to a U-shaped function (Brockhurst, Cheleuitte-Nieves, Buckmaster, Schatzberg, & Lyons, 2015; DiPietro, 2004). This model contributes to research on resilience factors as well. Support for the model was found, among others, by DiPietro and colleagues (2006), who revealed that a small amount of prenatal stress (i.e., maternal anxiety, nonspecific experienced stress and depressive symptoms) had an improving influence on motor and cognitive development.

1.7.3 The match-/mismatch theory of stress

As proposed by Nederhof (2012), the match-/mismatch theory tries to reconcile the opposing findings on the impact of early life stress by explaining these individual differences with a predictive pathway. In animal models, this kind of developmental plasticity is seen when the phenotype develops after an early prediction in order to provide the best fit for survival of the animal in the anticipated environment, but leads to diseases when the environment does not fit (Cartier, Zeng, & Drake, 2016; Nederhof, 2012).

In humans, this pathway begins with the experiences in the earliest environment of the organism, in the womb during pregnancy, as well as during early childhood. According to the match-/mismatch theory, the individual benefits from early experiences if they are similar to the experiences later in life, meaning that the early and the later environment match one another. If, however, the early life experiences differ from those later in life, the individual will not be attuned/adjusted to these circumstances and will be more likely to be vulnerable to react to the different types of stress with proneness to diseases or psychiatric disorders (Santarelli et al., 2014). Whether the effect has a positive or negative connotation depends on the environment in which the child lives. For example, a heightened sensitivity to cues might protect from danger in an unsafe environment, but is maladaptive and leads to vulnerability to psychiatric disorders in an safe environment, such as anxiety disorders (van Bodegom, Homberg, & Henckens, 2017).

The match-/mismatch theory is supported by other comprehensive theories such as the "three-hit concept" (Daskalakis et al., 2013) or the "predictive adaptive responses" (PAR) model (Gluckman, Hanson, & Spencer, 2005). With their "three-hit" theory, Daskalakis and colleagues explained the relationship between vulnerability and resilience to mental disorders through three "hits" in gene-environment interactions. The interaction of the genetic predisposition (hit 1) with the early-life environment (hit 2) leads to certain patterns of gene expression, as well as fetal programming. The resultant phenotype is programmed in a certain way by these two hits. When exposed to the anticipated environment later in life (hit 3), the phenotype, should react with more resilience. Exposure to environments which exceed the coping abilities of the phenotype should lead to a higher vulnerability, such as psychiatric symptoms (Daskalakis et al., 2013). The "predictive adaptive responses" (PAR) model also established a relationship between the predicted environment later in life and the vulnerability or resilience of the individual. With phenotypic plasticity, a single genotype can result in different phenotypes, most of the time triggered by environmental cues. These "predictive adaptive responses" should ensure the best fit of the phenotype to the expected later environment. Therefore, the "PAR model" also shares the assumption of enhanced resilience or vulnerability depending on a match or mismatch of the predicted responses and later environmental circumstances (Gluckman et al., 2005). Sandman and colleagues (2012) also found advantages in the congruence of prenatal and postnatal environments for the fit with the later-life environment, even when this environment was unfavorable. Accordingly, they reported advanced motor and mental development in infants' first year of life when their mothers had the same severity of depressive symptoms before and after birth. This underlines the need for longitudinal studies which take into account different types of stressors in order to illuminate the different pathways of possible beneficial or impairing impacts of stressors on the offspring.

1.8 Mother-infant dyadic behavior

The interaction capacities of an infant assume a pivotal role in the first months of life, as they are essential for the later emotion regulation capacities (Blehar, Lieberman, & Ainsworth, 1977; Conradt & Ablow, 2010; Gekoski, Rovee-Collier, & Carulli-Rabinowitz, 1983; Reck et al., 2011). Children's everyday training in the dyadic communication with their caregiver (typically their mother) serves to gain information from the environment and thereby train emotion regulation abilities over time (Tronick, 2006). It is characterized as a bidirectional communicative system, consisting of the infant and the mother acting as interchanging signal and receptor (Tronick, 2006). The higher risk of dissipation as the infant gains more complex abilities is regulated by the external organizational system of maternal dyadic communication, leading to a constant interplay of internal and external organization (Tronick, 2006). Development itself brings with it stress and disorganization and is characterized by the overcoming in a transition in more organized system (Tronick, 2006).

This requires an intact and functioning dyadic system. Although it was reported, that mother-infant interaction depends to a large degree on the infant's contribution and responsiveness, the availability of maternal responsiveness in the mother-infant dyad has also been considered as essential for providing a basis for training in emotion regulation (Van Egeren, Barratt, & Roach, 2001). For example, Haley and Stansbury (2003) found that infants were better at handling the still-face episode (e.g. showed a greater regulation of heart rate and negative affect) when their parents showed greater responsiveness. At the same time, if the dyadic system does not fit optimally into its coordinated interplay, is unbalanced or troubled, the resulting stress is even greater due to its dyadic nature, and has also been suggested to influence other systems, such as the motor development (Tronick, 2006).

Furthermore, Sethna and colleagues (2017) found mother-infant interaction to be associated with variations in the infants' brain development. Other theoretical models investigated different aspects of dyadic behavior, such as "matching states", or "synchrony". Tronick and Cohn (1989) described mother-infant matching as the time during which the mother and their infant share the same behavior simultaneously, and the mother-infant synchrony as the time during which the dyad behaves consistently regardless of the behavioral content. Both "matching states" and "synchrony" are time-bound conceptualizations (Cohn & Tronick, 1989; Feldman, 2007b). In their review, Leclère and colleagues mentioned the possibility to assess "synchrony" via frequencies, mean duration, latencies of specific behavior relations, proportions, percentage of time of mother-infant gazes at each other, or by measuring correlations between the mother's and the infant's behaviors (Leclère et al., 2014). However, despite these different operationalizations of "synchrony", the growing body of research investigating dyadic mother-infant behavior, besides exploring maternal and infant behavior separately, is attempting to further the understanding by focusing on mutual behavior and developmental factors.

Despite methodological differences, the investigation of mother-infant behavior could provide insight into associations found between behavioral deviations and psychological disorders. Disturbed mother-infant interaction was repeatedly reported by studies exploring the consequences of postpartum depression. For example, previous research found disturbed maternal affect to be associated with reduced positivity and sensitivity and increased intrusive, negative, hostile, and withdrawn behavior (Cohn, Campbell, Matias, & Hopkins, 1990; Murray et al., 1996). Further results indicated that infants of depressed mothers already showed depressive affect (i.e. more sadness and anger expressions) as early as three months after birth (Pickens & Field, 1993). Furthermore, Field and colleagues reported that infants' reactions of depressive affect generalized to their interactions with non-depressed adults (Field et al., 1988). The authors' speculations about the origins of the children's depressive affect comprised prenatal factors, as well as genetic inheritance or temperamental factors and postnatal factors, such as mimicking the mothers' interactive style (Field et al., 1988).

Furthermore, maternal anxiety was reported to have an impact on mother-infant interaction, with prenatal maternal anxiety being associated with lower mother-infant synchrony in mother-infant behavior at six months postpartum (Moore, Quigley, Voegtline, & DiPietro, 2016). Interestingly, high positivity in mothers was associated with lower mother-infant synchrony as well, suggesting that too much infant arousal caused by negative or positive maternal factors may both lead to problems in infants' emotional regulation (Moore et al., 2016). Concerning the prediction of long-term consequences, Allely and colleagues found specific elements of mother-infant mutual behavior (i.e., low maternal vocalization and joint attention) to be associated with infant psychopathology at age 7 years (Allely, Johnson, et al., 2013; Allely, Purves, et al., 2013). Therefore, the mother-infant behavior can be viewed as an outcome of impairing influences (such as ELS), as well as an stressor itself, when disturbed or of an impairing nature (Oitzl, Champagne, van der Veen, & de Kloet, 2010).

1.8.1 The still-face paradigm

The still-face paradigm was introduced in the 1970s by Tronick and colleagues (1978), with the aim of showing that young infants engage actively in their interaction with caregivers. The paradigm was rated as a powerful method for the investigation of mother-infant interaction and the effects of current distress (i.e. still-face episode) on both mother and infant (Müller, Zietlow, Tronick, & Reck, 2015). With the examination of the behavior before and after a stressful interaction episode, behavior patterns, emotional states and repairing behaviors were identified and reviewed by Mesman and colleagues (2009). The classic still-face experiment consists of a three-step caregiver-infant interaction:

1) a normal face-to-face play situation with the caregiver and the infant for about three minutes,

2) the characteristic non-responsive still-face episode with the caregiver sitting silently in front of the infant with an expressionless face, not looking at, touching or reacting to the infant for about two minutes, and
3) the reunion episode, with the caregiver resuming the normal play as in the first episode for about three minutes (Adamson & Frick, 2003; Tronick et al., 1978).

Mostly, the still-face paradigm has been used in investigations of infants aged between 1 and 12 months, with a mean of 5.2 months (Adamson & Frick, 2003). The well-known "still-face effect" was found to be robust (Mesman et al., 2009), and is characterized by the change in infant behavior during the still-face episode with increased gazing away, decreased smiling and an increased arousal (Toda & Fogel, 1993).

A "carry-over effect" of the still-face episode's perturbation into the third part, the reunion episode, has been identified by many studies and is characterized by an only partial decrease of negative infant affect (Ekas, Haltigan, & Messinger, 2013; Mesman et al., 2009). Infants' emotional reactions to the still-face episode are wide-ranging, including anger and sadness amongst others, and there are differing extents of re-engagement in the reunion episode, with mixed patterns of positive and negative affect (Haley & Stansbury, 2003; M. Lewis & Ramsay, 2005; Weinberg & Tronick, 1996).

Concerning physiological reactions to the still-face paradigm, past research reported higher HPA axis activity in infants due to the still-face episode when they showed sadness but not when they showed anger (M. Lewis & Ramsay, 2005). Another study found an increase in infants' heart rate and cortisol response after the still-face episode (Haley & Stansbury, 2003). Moreover, the authors also found higher baseline HPA activity to be positively correlated with more infant negative behavior during the still-face episode (Haley & Stansbury, 2003). Previous research on age-dependent changes in infant behavior during the still-face experiment showed that the decrease in infant gaze from the first play episode to the reunion episode was stronger in younger infants (range 2 to 6 months, (Adamson & Frick, 2003)). Concerning gender differences, mother-son dyads were reported to show higher synchrony scores but also more difficulties in interaction repairing compared to mother-daughter dyads (Weinberg, Tronick, Cohn, & Olson, 1999). Furthermore, studies with male infants found a larger decrease in positive behavior from the first play to the reunion play episode (Mesman et al., 2009). Differences in infants' temperament were also found, with children with negative temperament showing more difficulties in self-regulation (Braungart-Rieker, Garwood, Powers, & Notaro, 1998). However, due to the scarcity of findings, further studies on temperament as a potential mediator of infant behavior are warranted (Mesman et al., 2009).

In sum, the still-face paradigm is a powerful tool for investigating maternal and infant behavior in a model which creates an interruption of the dyadic communication, which is close to normal interaction, e.g. comparable to mothers driving a car or making a phone call (Tronick, 2006). As the infant-caretaker interaction is a major milestone in infant development over the first months of life, and has also been considered as a learning process (Gekoski et al., 1983) as well as a sign of early development (Blehar et al., 1977), the still-face paradigm provides the opportunity to investigate the infant's emotion regulation capacity in response to a moderate stressor, which has also been considered as one major developmental objective (Conradt & Ablow, 2010; Mesman et al., 2009).

1.8.2 Behavior coding with ICEP

Tronick designed the "Infant and Caregiver Engagement Phases" (ICEP) to measure the infant-caregiver interaction during the still-face paradigm. It allows an examination of the mother and infant behavior, as well as matching behavior states, which are considered as an indicator of healthy interaction (Reck et al., 2011; Tronick & Cohn, 1989). The ICEP system comprises a set of mutually exclusive infant and caregiver behavior categories, which are coded microanalytically videoframe by videoframe (Reck et al., 2011; Tronick et al., 2005). The ICEP behavior categories consist of facial expression and emotional information, the gaze direction, head position, body movements and vocalizations of infants and their caregivers (Reck et al., 2011; Tronick, Als, & Brazelton, 1977). The six maternal and infant behavior codes within the ICEP system are depicted in Figure 3 (Montirosso, Borgatti, Trojan, Zanini, & Tronick, 2010; Reck et al., 2011; Tronick et al., 2005). Besides the mentioned behavior codes, additional infant self-regulation codes have been defined, for example when clasping hands, hiccupping, touching the mouth, turning away or creating distance (Tronick et al., 2005). Furthermore, dyadic gazing and shared attention, for example when looking at the same toy, can also be coded within the ICEP system (Riva Crugnola, Ierardi, Gazzotti, & Albizzati, 2014; Tronick et al., 2005).

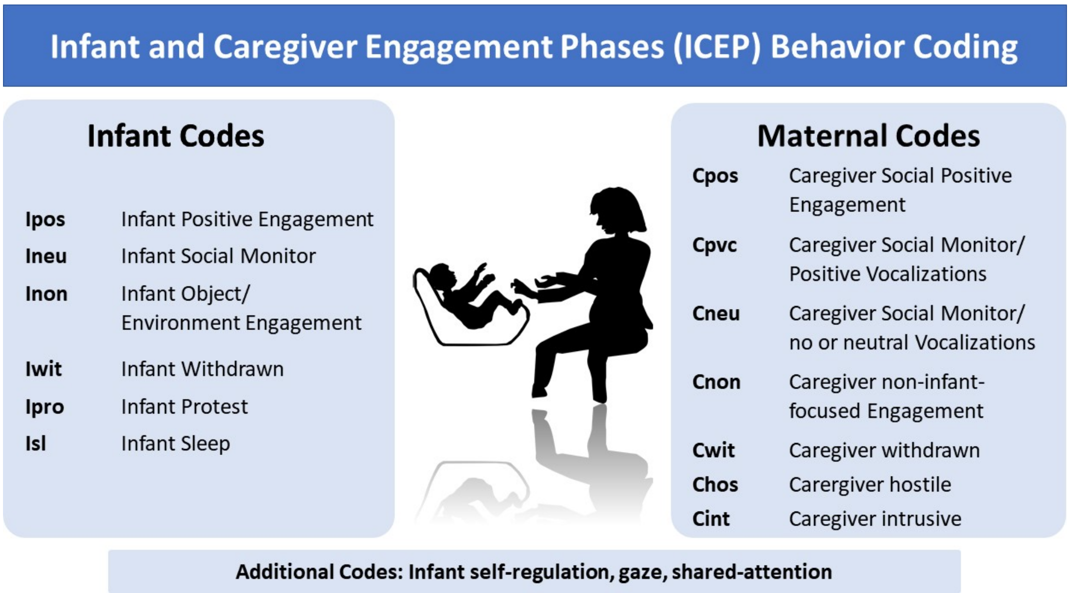


Figure 3: ICEP behavior codes

1.9 Research questions

From the vast background of findings of a possible impact of early life stressors, especially prenatal stress on the behavior of the infant and the mother, as well as previous findings supporting “stress sensitization” as well as “stress inoculation” theories, we formulated the following hypotheses on the impact of prenatal stress on mother-infant dyadic behavior at six months postpartum:

a) Prenatal stress (i.e., psychological and physiological PS) was predicted to have an impact on mother-infant dyadic behavior during a normal mother-infant play situation (i.e., first play episode in the still-face paradigm), either positive or negative.
b) The experienced stress of the still-face episode was predicted to produce a carry-over effect in the second play phase (i.e., reunion episode in the still-face paradigm), with a slower decline in protesting (i.e., negative) infant behavior.
c) Prenatal stress was predicted to have an impact on mother-infant dyadic behavior during a play situation after having experienced a current stressor (i.e., the still-face episode; comparison of first play episode with the reunion episode). The impact was hypothesized to be either negative or positive.
d) Maternal behavior was predicted to play a mediating role in the relationship between prenatal stress and infant behavior.

Hypothesis a) will be examined in Study I and hypotheses b) and c) will be investigated in Study II in the following two chapters. Hypothesis d) will be tested in both Study I and Study II.

2 STUDY I: IMPACT OF PRENATAL STRESS ON THE DYADIC BEHAVIOR OF MOTHERS AND THEIR SIX-MONTH-OLD INFANTS DURING A PLAYSITUATION: ROLE OF DIFFERENT DIMENSIONS OF STRESS

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2.1 Abstract

Prenatal stress (PS) is an established risk factor in the etiology of mental disorders. Although mother-child interaction is the infant's first important training in dealing with stress, little is yet known about the impact of PS on mother-infant dyadic behavior. The current study aimed to elucidate the prospective influence of psychological and physiological stress during pregnancy on mother-infant dyadic behavior. Mother-infant interactions were videotaped at six- months postpartum and coded into three dyadic patterns: 1) both positive, 2) infant protesting-mother positive and 3) infant protesting-mother negative, using the Infant and Caregiver Engagement Phases. Exposure to PS was assessed during pregnancy using psychological (i.e., psychopathological, perceived and psychosocial PS; n = 164) and physiological stress measures (i.e., maternal cortisol; n = 134). Group comparisons showed that psychosocial PS was predictive of mother-infant behavior at six- months postpartum, indicating that dyads of prenatally high-stressed mothers exhibited significantly more positive interaction patterns (i.e., infant positive-mother positive) as compared to the prenatally low-stressed group. Physiological PS was unrelated to mother-infant behavior. These results suggest that mild psychosocial PS may be advantageous for positive mother-infant dyadic behavior, which is in accordance with the stress- inoculation model that assumes a beneficial effect of PS.

Keywords: prenatal stress, cortisol, mother-infant behavior, pregnancy, stress inoculation

2.2 Background

A child's life is like a piece of paper on which every passerby leaves a mark. – Chinese Proverb.

2.2.1 Introduction

In recent years, research has accumulated evidence that early life stress (ELS) impacts children's development and behavior (de Weerth & Buitelaar, 2007; Glover, 2014; Graignic-Philippe et al., 2014; Murgatroyd et al., 2010; Turecki & Meaney, 2016). Associations of prenatal stress (PS), as partly reflected by cortisol levels of pregnant women or prenatal maternal mood and anxiety, with the infant's postnatal cortisol levels have been repeatedly reported (Brennan et al., 2008; Davis, Glynn, Waffarn, & Sandman, 2011; Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011). Maternal cortisol that "escapes" placental inactivation by 11ß-hydroxysteroid dehydrogenase 2 (11ß-HSD2) may affect the child's neuroendocrinological system of 'fetal programming' (Glover, O'Connor, et al., 2010; O'Donnell et al., 2013; O'Donnell et al., 2009). Fetal programming is defined as the alteration of the fetus' development by changes of the in utero environment (D. J. P. Barker et al., 1989). Its impact on the hypothalamic-pituitary-adrenal (HPA) axis is long- term and based on gene-environment interactions during critical phases of brain development (Murgatroyd et al., 2009). These gene-environment interactions include, among others, epigenetic methylation of DNA (Bock, Murmu, Biala, Weinstock, & Braun, 2011; Bock et al., 2014; Schmidt et al., 2016). Early environmental stress experiences affect epigenetic states, which in turn influence gene expression and subsequently neural functions (Turecki & Meaney, 2016). Critical moderating factors of these processes include, amongst others (i.e., sensitive time frames) the quantity and quality of stressors (i.e., daily hassles versus severe traumata) (Glover, O'Connor, et al., 2010; Graignic-Philippe et al., 2014). As one example, maternal exposure to a natural catastrophe during pregnancy has been shown to adversely impact brain maturation and to yield higher prevalence of later mental disorders in the offspring (O'Donnell et al., 2009; Yong Ping et al., 2015). In contrast to the large amount of studies that claim an impairing influence of ELS (Baker et al., 2013; Buchmann et al., 2010; Buss et al., 2012; Ehlert, 2013; Lazinski, Shea, & Steiner, 2008; Weinstock, 2001), a number of recent studies have reported a contrary pattern of results following exposure to ELS, indicating positive effects of ELS on stress resilience in later life (Bock et al., 2014; Daskalakis et al., 2013; Ehlert, 2013). Such contradictory findings support the conflicting hypotheses postulated by the stress sensitization model (Post, 1992) and the stress inoculation model (Rudolph & Flynn, 2007).

2.2.2 Stress sensitization

According to the stress sensitization model (Post, 1992), ELS leads to an adaptation of the child's neuroendocrine system as a result of the stress reaction, and to epigenetic alterations depending on stressor severity and the child's developmental time frame (Charil et al., 2010; Murgatroyd et al., 2009; Murgatroyd & Spengler, 2011; Murgatroyd et al., 2010). Later in life, this sensitization can result in a reduced threshold for a psychopathological response to current stressors (Rudolph & Flynn, 2007). With such a heightened individual vulnerability following exposure to ELS, even a small number of low-intensity stressors suffice to trigger symptoms of a later mental disorder such as depression (Rudolph & Flynn, 2007). Numerous studies have focused on the relationship between ELS and behavioral problems (Fareri & Tottenham, 2016; Nugent, Tyrka, Carpenter, & Price, 2011; Weinstock, 2008), indicating that fear and anxiety in the offspring are one of the primary consequences of PS (Davis & Sandman, 2012). Similarly, prenatally perceived stress of mothers was found to be associated with both difficult affective temperament in their three-month-old children and the mothers' perception thereof (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002; Pesonen, Räikkönen, Strandberg, & Järvenpää, 2005). Ample research in animals has supported these findings highlighting the translational approach. For example, Weinstock (2001) reported the long-term impact of prenatal stress on the offspring in rodents by identifying behavioral and developmental abnormalities in prenatally stressed rats. Further studies confirmed the association of PS with increased stress vulnerability and anxiety later in life (Green et al., 2011), suggesting that dysfunctional stress reactions later in life were related to both genetic predisposition and prenatal / early childhood stressors which lead to altered functioning of the HPA axis (Murgatroyd & Spengler, 2011).

2.2.3 Stress inoculation

In contrast to the stress sensitization model, recent research has focused on the ambiguous role of stress by highlighting its positive impact. ELS can lead to favorable effects in relation to specific interactions of the individual with its environment, i.e. increased resilience (Bock et al., 2014; Daskalakis et al., 2013; Nugent et al., 2011). The first indication of a possible positive influence of ELS was reported in the late 1950s by Levine (1956) who found less stress reactivity in "handled" rats. Handling is a mild stressor and was defined as picking up the rat pups, separating them from the mother and the nest, placing them in a compartment (Levine, 1957). In adulthood, the handled rats showed increased exploration and learning when stimulated as well as less emotional reactivity and diminished HPA axis activation compared to non-handled rats (Levine, 1956, 1957; Levine, Haltmeyer, Karas, & Denenberg, 1967). Subsequent studies also found reduced stress reactivity and decreased severity of hypertension in handled rats (Kudryashova et al., 2004) and a reversal of unwanted effects of PS through handling, such as dendritic atrophy in hippocampal subregions (Bock et al., 2011). In his review, Meaney (2001) argued that the inoculation effect of handling is mediated by maternal behavior. The more recently evolved “match-/mismatch hypothesis” combines the two aspects of stress sensitization and stress inoculation: When early (prenatal) and later adult (postnatal) environments are similar, the offspring can benefit, resulting in a better adaptation to the later environment – the circumstances match. If, however, the early and the later adult environments differ from each other, i.e., mismatch, the offspring is likely to suffer from diseases later in life (Nederhof, 2012; Nederhof & Schmidt, 2012).

In their “biological sensitivity to context theory”, Ellis and Boyce (2008) postulated an association between children’s individual susceptibility to stress and their environmental conditions, suggesting that higher reactive infants were more susceptible both to positive and negative early environments, leading to increased harm as well as benefit (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). Significant positive associations of prenatal maternal stress with infant motor and mental development were found for mild stressors in humans (DiPietro et al., 2006), with mild stressors being positively related to more optimal child development. The associated mechanisms are still unknown, but the authors assumed that changing maternal cardiovascular and gastrointestinal sounds due to maternal anxiousness may provide a more stimulating environment for the fetus (DiPietro et al., 2006). Recent research has demonstrated that the two models of the long-term consequences of ELS are not mutually exclusive by indicating that adolescents who experienced early childhood adversities developed either an early onset of depression or a later good adaptation to high-stress circumstances together with a higher risk of depressive episodes in current low-stress environments (Oldehinkel, Ormel, Verhulst, & Nederhof, 2014). These results are in line with both the stress inoculation and the stress sensitization model.

2.2.4 Impact of cortisol

The influence of stress on the cortisol levels of mothers-to-be, and their impact on both the fetal stress response and cortisol levels in later childhood have been demonstrated in various studies (Davis et al., 2007; O'Donnell et al., 2013; Tollenaar et al., 2011). Gitau et al. (Gitau et al., 1998; Gitau et al., 2001) reported that 10-20 percent of maternal cortisol passes the placenta and influences the fetus’ cortisol levels. In conditions of maternal stress, high cortisol levels may exceed the ability of the placenta to metabolize cortisol, which may lead to much higher cortisol levels in the fetus, which have been associated with health and behavioral problems, poorer mental and behavioral development in the offspring during childhood (Zijlmans, Riksen-Walraven, & de Weerth, 2015), as well as a larger amygdala volume (Buss et al., 2012).

2.2.5 Stress and mother-infant behavior

The models described above provide a basis for the assumption that PS affects the behavior of mothers and their infants. In prior studies, infant behavior and interaction with the caregivers was defined as outcome of learning processes and development (Blehar et al., 1977; Gekoski et al., 1983). Furthermore, Conradt and Ablow (2010) rated the capacity to regulate emotion effectively in response to stress as an important developmental objective in the first year of life. Regarding the possible impact of PS, in their review, Van den Bergh and colleagues (Van den Bergh et al., 2005) reported a direct link between prenatal maternal mood and the infant's behavior and cognitive development. Glover et al. (2010) named attention deficit hyperactivity disorder (ADHD) and anxiety disorders as the most consistent adverse outcomes of PS. Considering interaction effects, caregiver-infant synchrony was defined as both the caregiver's following the child's lead in interaction or a "serve-and-return" with the infant serving and the caregiver returning the initiation of communication (Bernard, Meade, & Dozier, 2013; Blehar et al., 1977; Shonkoff & Bales, 2011) as well as the infant's reply to the caregiver's initiation (Bernard et al., 2013). Anyway, the synchronous interplay of caregiver and infant, called "contingent reciprocity" is seen to be a fundamental milestone in development, amongst others taking part in the wiring of the brain in the early years of infancy (Shonkoff & Bales, 2011). Further studies focused on "matching states", representing the total time mothers and infants shared joint states, such as smiling at each other (Field, Healy, Goldstein, & Guthertz, 1990; Ginger A. Moore & Susan D. Calkins, 2004; Tronick & Cohn, 1989). Moore and Calkins (2004) reported differences in infants' physiological regulation of social interaction in relation to their mother-infant dyadic behavior. Infants wo did not suppress vagal tone when stressed showed less synchrony in mother-infant play and less positive affect. Prior research on a play situation of mother-infant dyads with depressed mothers reported more matched negative states and less matched positive states in depressed compared to non-depressed dyads (Field et al., 1990).

To our knowledge, the present study is the first to investigate the effect of different PS dimensions (e.g. psychological, psychosocial and physiological prenatal stress) in pregnant women on dyadic behavior in a mother-infant play situation 6 months postpartum. Given the evidence for a beneficial as well as an adverse impact of PS on behavior later in life, we aimed to study both possible effects (Rudolph & Flynn, 2007). Considering the potential role of confounding factors, the analyses were first controlled for the covariates maternal age, parity, gender of the child, perinatal complications, and, in a second step, for current maternal depression, Apgar score five minutes after birth, breastfeeding, and maternal perceived stress six month after birth (Tearne et al., 2016; Weinstock, 2007). We focused on mother-infant dyadic behavior because of its important influence on children's brain development and self-regulation in the first year of life (Feldman, 2007b; Reck et al., 2011; Shonkoff & Bales, 2011).

2.3 Materials and methods

The following subchapters present the applied materials and methods.

2.3.1 Participants

Mothers-to-be were participating in the "Pre-, Peri- and POstnatal Stress: Epigenetic Impact on DepressiON" (POSEIDON) study and were recruited in their third trimester of pregnancy (N = 410, 4 - 8 weeks prior to term) in three obstetric clinics of the Rhine-Neckar region of Germany (see Dukal et al. (2015) for further information). The study protocol was approved by the Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg and the Ethics Committee of the Medical Association of Rhineland-Palatinate and conducted in accordance with the Declaration of Helsinki. All mothers provided written informed consent prior to enrolment in the study. Participation in the mother-infant play six months after birth was voluntary. Two-hundred videos were collected based on an a-priori participant selection procedure that relied on a composite stress measure (i.e., total adversity score) which enabled the identification of the 100 most stressed and 100 least stressed mothers (i.e. high-stress and low-stress groups; for details see Appendix SI A1 and Dukal et al. (2015)). Several video-sets had to be excluded due to technical problems of the filmed material (i.e., light and sound overexposure, missing sequences, early-ending; n = 8) and outliers in infant behavior assumed as disturbed due to interfering circumstances (i.e., sleepiness and >80% infant protest behavior; n = 28; c.f. baseline of 10% negative infant behavior reported by Moore and Calkins (2004)). Thus, 164 mother-infant dyads remained for statistical data analysis (see Figure 4). For the analysis of maternal diurnal cortisol, data of 134 mother-infant dyads were available, as 30 dyads were excluded due to missing data (i.e., too little saliva provided, no return of samples; n = 17), outliers (≥ / ≤ 2 SD; n = 10), or not plausible, impossible morning cortisol (FI and/or FII ≤ 7 nmol/l values; n = 3). We used a strict limit of ≥ / ≤ 2 SD to enable us to filter the lowest outliers in morning cortisol scores (c.f. (Hellgren, Akerud, Skalkidou, & Sundstrom-Poromaa, 2013). Statistical analyses testing the outliers for selection effects (e.g., gender, total adversity score, maternal age) were not significant (all p >.05). For detailed maternal and infant characteristics of the high-stress and low-stress groups, see Table 1.

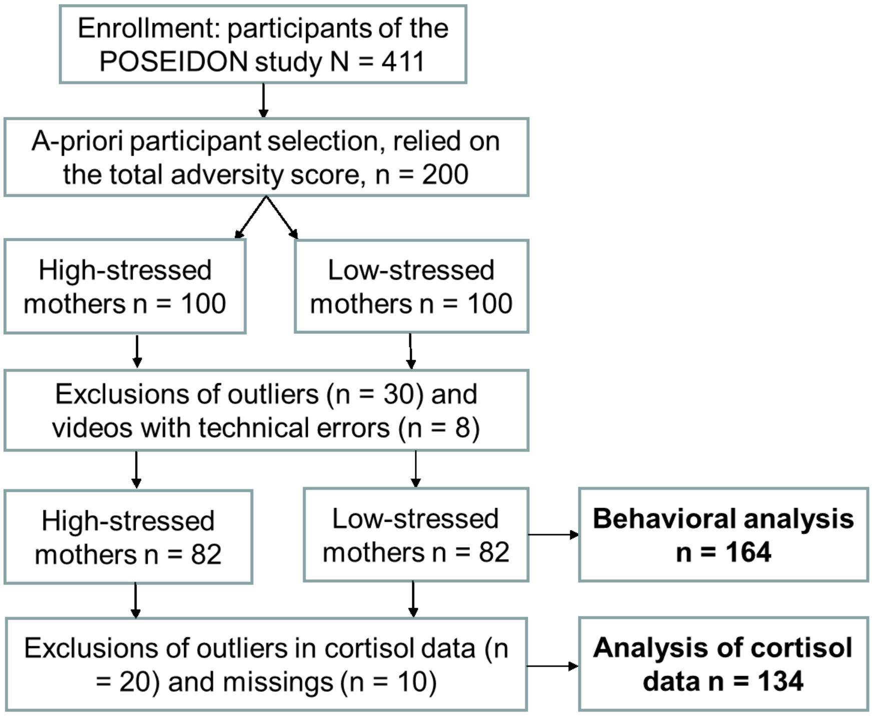

Figure 4: A-priori participant selection according to total prenatal adversity score

Table 1: Health characteristics of mothers and infants included in the study sample (all data: mean ± SD or percentage).

Variable	High-stressed; (N = 82)	Low-stressed; (N = 82)	p
Maternal sociodemographic and health characteristics			
Maternal Age (M, SD)	29.9; 5.4	32.3; 4.3	.002
Primiparous (N, %)	39; 47.6%	50; 61.0%	ns
Married (N, %)	82; 100.0 %	69; 84.2%	<.001
Education: College or higher education (N, %)	46; 56.1%	57; 69.6%	ns
Monthly net- income (N, %)			
151 to 2000€	30; 36.6%	2; 2.4%	
2001 to 5000€	44; 53.7%	53; 64.7%	
More than 5000€	8; 9.7%	27; 32.9%	<.001
Prenatal depression (N, %)	10;12.2%	0; 0%	.001
Perceived Stress Scale (PSS) 6 month postpartum (M, SD)	27.1 ± 7.6	16.8 ± 5.9	<.001
Videos filmed in mothers' homes	60; 36.6%	60; 36.6%	ns
Child characteristics			
Gender: Female (N, %)	51; 62.2%	51; 62.2%	ns
Breastfeeding (N, %)	61; 74.4 %	75; 91.5 %	.003
Apgar score after 5 minutes (M, SD)	9.7± 0.5	9.7± 0.7	ns
Perinatal complications (N, %)	44; 53.7%	51; 62.2%	ns
Maternal cortisol scores	**High-stressed; (N = 65)**	**Low-stressed; (N = 69)**	**p**
Cortisol slope (M, SD; nmol / L)	19.1; 8.1	20.7; 6.9	ns
	High-stressed; (N = 64)	**Low-stressed; (N = 67)**	**p**
Cortisol AuCg (M, SD; nmol / L)	15758.4; 3997.5	15610.4; 4518.4	ns

M= mean; SD = standard deviation; % percentage; ns = not significant; AuCg= Area under the curve with respect to ground.

2.3.2 Mother-infant interaction

Videos were filmed six months postpartum at the Central Institute of Mental Health, Mannheim or in the mothers' homes. Mother-infant dyads performed the well-established still-face paradigm (Tronick et al., 1978), in which the mothers were instructed to play for three minutes with the infant as they would normally do, then sit for two minutes in front of the infant, not looking at or reacting to the infant. After the two minutes of still-face, the mothers resumed the play for another three minutes. Toys, pacifiers or other items could not be used. Mother-infant dyads were left alone during the play. The start and end of the play was indicated by a sound signal. Here, we investigated the dyadic play behavior in the first three minutes of mother-infant play. Videos were filmed with two video cameras (Sony™ HDR-CX130), one focusing on the mother's face and the other focusing on the infant. The infants sat opposite to their mothers on the same level in a Maxi-Cosi™ or similar baby chair and were belted during the experiment.

For the coding procedure, both videos were synchronized and transformed into one split-half screen video using Corel™ Videostudio Pro X4 software. Behavioral coding of the videos was conducted using Interact™ software (Mangold International GmbH 2013, Ver. 9.7.8) by a trained and certified Infant and Caregiver Engagement Phases [ICEP; (Tronick et al., 2005; Weinberg et al., 1999)] coder, who was blind to the mothers' stress exposure (JS). The codings were computed into percentages related to the duration of the play. In line with the ICEP coding system, all caregiver and infant behaviors were coded. For data reduction, three mother-infant dyadic behavior categories were formed: 1) Infant positive-mother positive dyad (IposMpos) was coded when mothers showed social monitor/positive vocalization or social positive engagement and infants showed social positive engagement simultaneously; 2) Infant protesting-mother positive dyad (IproMpos) was coded when mothers showed social monitor/positive vocalization or social positive engagement and infants showed protesting behavior (i.e., crying, distress, being fussy); 3) Infant protesting-mother negative dyads (IproMneg) was coded when mothers showed intrusive, social monitor/neutral vocalization or non-infant-focused engagement, with the children showing protesting behavior. Calculation was performed using Interact™ software by accumulating the time during which both partners showed the respective dyadic behavior at the same time during play.

2.3.3 Subjective stress experience indices

Mothers were interviewed and given questionnaires in the last trimester of pregnancy (for further details see Dukal et al. (2015)). To provide different psychological stress measurements, we used three composite scores computed by principle component analysis, distinguishing between psychopathology, perceived stress, and psychosocial stress of the mother during pregnancy (for further information see Appendix SI A1).

2.3.4 Objective stress indices

Salivary cortisol measures were acquired as a reliable indicator of total free plasma cortisol (Kirschbaum & Hellhammer, 1994). Maternal diurnal cortisol data were obtained via saliva samples using Salivettes (Sarstedt™, Leicester, UK) which contained an untreated cotton swab. Saliva samples were collected in the late trimester of pregnancy during one “normal working day”. Mothers were instructed to chew on the saliva collectors immediately after awakening (FI), but while they were still in bed; 30 minutes after getting up (FII) and 14 hours after awakening (FIII). Instructions included precautionary information regarding meals, drinks, brushing teeth and smoking. Mothers indicated the date and times of sampling and sent the probes back to the study coordinators. All samples were stored at -25°C. After thawing, the samples were centrifuged for 5 minutes at 3,000 rev/min, resulting in a clear supernatant of low viscosity. Salivary cortisol was measured by means of a time-resolved immunoassay with fluorescence detection. The lower limit of detection was 0.43 nmol/l, with interassay and intraassay coefficients of variation of less than 10% across the expected range of cortisol levels. The mean week of gestation for the saliva collection was 36.77 (SD 1.89). The measure of diurnal cortisol slope was computed as the difference between the evening cortisol score and the highest morning score (FI or FII – FIII), as the cortisol morning peak is expected 0 – 0.5h after awakening (Ranjit, Young, Raghunathan, & Kaplan, 2005). We also computed the measure of cortisol area under the curve with respect to ground (AuCg) according to the formula by Pruessner and colleagues (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The AuCg indicates the total amount of cortisol concentration per day and is defined by a trapezoid formula, calculating the area under the diurnal cortisol decline.

2.3.5 Statistical analysis

All statistical analyses were performed using PASW Statistics 21 (SPSS Inc., Chicago, USA). To examine the relationships between the three dependent variables (i.e., dyadic behavior), we computed correlations using Pearson’s r. Stress variables were dichotomized via median splits to form six groups with a high and a low stress group per psychological stress index (i.e., maternal psychopathology, perceived stress, and psychosocial stress) and four groups with a high and a low physiological stress group per objective stress parameter (i.e., maternal cortisol slope and cortisol area under the curve with respect to ground); see Appendix Study I for details. To test whether the mothers with low stress differed from those with high stress during the play situation, we ran a series of one-way analyses of covariance (ANCOVA), with the between-subjects factor group and the covariates mother's age, infant's gender and parity. In a second step, to adjust for further confounders, the covariates current maternal depression during pregnancy, breastfeeding, Apgar score five minutes after birth, perinatal complications and perceived stress six months postpartum (assessed via the perceived stress scale, PSS (Cohen, Kamarck, & Mermelstein, 1983) were included (see Appendix SI A2)). Furthermore, we examined the possibility that the relationship between PS and infant behavior was mediated by maternal behavior. Therefore, we computed mediation analyses with z-standardized maternal positive behavior as a mediator between psychosocial PS and z-standardized infant positive behavior, including the covariates gender, maternal age and parity in a first step and the additional covariates current maternal depression during pregnancy, breastfeeding, Apgar score five minutes after birth, perinatal complications and perceived stress six months postpartum (assessed via the perceived stress scale) in a second step. Total, direct, and indirect effects of a predictor on the outcome through the mediator are assessed with regression analysis and bias corrected bootstrapping, using the PROCESS model tool (Hayes & Scharkow, 2013).

2.4 Results

Correlations between dyadic behavior patterns were significant. While IposMpos correlated negatively with IproMpos ($r = -0.260$, $p = .001$) and IproMneg ($r = -0.168$, $p = .032$), IproMpos correlated positively with IproMneg ($r = 0.482$, $p < .001$). Although psychological stress variables (e.g. psychopathological, perceived and socioeconomic and psychosocial stress) showed highly significant intercorrelations ($r = 0.582$ to 0.721; all $p < .001$; see Table 2), parameters were regarded separately to assess the effect of distinct stress dimensions with obvious power to influence each other. Although it is likely that mothers with socioeconomic adversities experience more perceived stress and vice versa, the two measures are not necessarily dependent on each other and can individually differ, for example in a negative association. In contrast, physiological stress and psychological stress measures showed a significant negative association of cortisol slope with psychopathological stress ($r = -0.203$; $p = .019$) and psychosocial stress ($r = -0.184$; $p = .033$), whereas perceived stress was unrelated to cortisol slope. Moreover, the cortisol AuCg was unrelated to the three psychological stress measures (all $p >= .360$; see Table 2). Furthermore, the prenatal stress dimensions correlated highly significantly with the Perceived Stress Scale (PSS), assessed postnatally six months after birth (all $p <.001$; see Table 2).

We also found PSS to be significantly correlated with the IposMpos dyad ($r = 0.190$, $p = .021$), but not with IproMpos or IproMneg ($p > .05$). The following subchapters presents the impact of psychological prenatal stress (i.e., psychopathological, perceived and psychosocial stress), as well as physiological prenatal stress (i.e. diurnal cortisol decline, AUCg) on mother-infant dyadic behavior.

Table 2: Pearson correlations between the prenatal psychosocial stress and psychophysiological stress indices, and the Perceived Stress Scale (PSS) six months after birth

	Perceived PS	Psychosocial PS	Cortisol Slope T1	Cortisol AuCg T1	PSS six months after birth
Psychopathological PS	.721; p < .001; N = 134	.629; p < .001; N = 134	- .203; p = .019; N = 127	- .061; p = .491; N = 131	.609; p < .001; N = 150
Perceived PS	1	.582; p < .001; N = 134	- .003; p = .974; N = 127	.081; p = .360; N = 131	.693; p < .001; N = 150
Psychosocial PS		1	- .184; p = .033; N = 127	- .013; p = .879; N = 131	.473; p < .001; N = 150
Cortisol slope T1			1	- .398; p < .001; N = 131	.032; p = .723; N = 124
Cortisol AuCg T1				1	- .053; .562; N = 122

Abbreviations: AuCg: Area under the curve with respect to the ground; PS: prenatal stress; PSS: Perceived Stress Scale

2.4.1 Psychopathological PS

No significant main effect of psychopathological PS on any mother-infant interaction pattern was obtained (all $p > .05$, see Table 3).

2.4.2 Perceived PS

There was a significant effect of perceived stress on the IposMpos dyad, with higher rates of positive dyadic behavior in the high-stress group as compared to the low-stress group ($F(1,157) = 5.984$, $p = .016$, partial $\eta^2 = .037$). In contrast, no significant effects of perceived stress were found on IproMpos and IproMneg (all $p > .05$, see Table 3).

2.4.3 Psychosocial PS

A significant effect of psychosocial stress ($F(1,157) = 11.578$, $p = .001$, partial $\eta^2 = .069$) on IposMpos dyadic behavior emerged, indicating higher levels of positive dyadic behavior in the high-stress group as compared to the low-stress group. Due to the positive correlation of PSS T3 with the IposMpos dyad, we decided to run another ANCOVA with the IposMpos dyad and 4 covariates (maternal age, gender, parity, PSS T3). The results still showed a significant effect of psychosocial PS ($F(1,148) = 7.263$, $p = .008$, partial $\eta^2 = .049$) on the IposMpos dyad, but no effects for the covariates. In a third step, taking all covariates into account, there was still a significant effect for psychosocial PS ($F(1,138) = 7.872$, $p = .006$, partial $\eta^2 = .054$), while no significant effects were found for psychosocial PS on IproMpos and IproMneg (all $p > .05$, see Table 3 and Appendix SI A2). The same occurred when adjusting for all covariates (all $p > .05$, see Table 4).

2.4.4 Diurnal cortisol decline

There were no significant effects of cortisol slope on any interaction patterns (all $p > .05$, see Table 3).

Table 3: Effect of PS on mother-infant dyadic behavior.

(Means, standard deviations and results of ANCOVAs adjusted for gender, maternal age and parity) in the high-stress (H) and low-stress (L) groups).

	IposMpos dyad				**IproMpos dyad**				**IproMneg dyad**			
	M	SD	F/ (dfs)	p	M	SD	F/ (dfs)	p	M	SD	F/ (dfs)	p
Psychopathological	H: 6.13	4.53	2.426	.121	H: 1.30	3.14	0.498	.481	H: 0.43	1.64	0.322	.571
PS	L: 4.76	4.67	(1,157)		L: 1.92	4.27	(1,157)		L: 0.39	1.33	(1,157)	
Perceived PS	H: 6.42	4.58	5.984	.016	H: 1.01	2.68	2.190	.141	H: 0.42	1.64	0.201	.654
	L: 4.46	4.51	(1,157)		L: 2.21	4.51	(1,157)		L: 0.40	1.33	(1,157)	
Psychosocial PS	H: 6.76	4.60	11.578	.001	H: 0.93	2.48	2.963	.087	H: 0.36	1.51	0.001	.980
	L: 4.12	4.30	(1,157)		L: 2.29	4.60	(1,157)		L: 0.47	1.47	(1,157)	
Physiological PS	M	SD	F/ (dfs)	p	M	SD	F/ (dfs)	p	M	SD	F/ (dfs)	p
Cortisol slope	H: 5.13	4.67	0.909	.342	H: 1.56	3.63	0.175	.909	H: 0.37	1.23	.341	.560
	L: 5.77	4.38	(1,127)		L: 1.54	3.82	(1,127)		L: 0.58	1.91	(1,127)	
Cortisol AuCg	H: 6.03	3.64	0.977	.325	H: 1.59	3.69	0.004	.949	H: 0.42	1.37	0.098	.755
	L: 5.02	5.28	(1,124)		L: 1.58	3.83	(1,124)		L: 0.55	1.89	(1,124)	

All means and standard deviations are percentages. Abbreviations: PS: prenatal stress; Infant positive-mother positive: IposMpos; Infant protesting-mother positive: IproMpos; Infant protesting-mother negative: IproMneg, Area under the curve with respect to ground: AuCg.

Table 4: Effect of PS on mother-infant dyadic behavior (ANCOVAS additionally adjusted).

(Means, standard deviations and results of ANCOVAs additionally adjusted for breastfeeding, maternal depression before birth (except for psychopathological ELS), Apgar score after 5', perinatal complications, current perceived stress) in the high-stressed (H) and low-stressed (L) groups).

	IposMpos dyad				**IproMpos dyad**				**IproMneg dyad**			
	M	SD	F/ (dfs)	p	M	SD	F/ (dfs)	p	M	SD	F/ (dfs)	p
Psychopathological PS	H: 5.72	4.10	0.002	.960	H: 1.46	3.30	1.051	.307	H: 0.49	1.73	1.069	.303
	L: 4.73	4.78	(1,139)		L: 1.79	4.29	(1,139)		L: 0.30	0.97	(1,139)	
Perceived PS	H: 6.19	4.40	2.240	.137	H: 1.10	2.79	0.012	.912	H: 0.46	1.71	0.774	.380
	L: 4.24	4.36	(1,138)		L: 2.15	4.60	(1,138)		L: 0.32	0.98	(1,138)	
Psychosocial PS	H: 6.58	4.51	7.827	.006	H: 0.96	2.55	0.337	.563	H: 0.41	1.61	0.032	.858
	L: 3.95	4.08	(1,138)		L: 2.24	4.65	(1,138)		L: 0.38	1.17	(1,138)	
Physiological PS	M	SD	F/ (dfs)	p	M	SD	F/ (dfs)	p	M	SD	F/ (dfs)	p
Cortisol slope	H: 5.04	4.70	0.015	.903	H: 1.51	3.62	0.090	.765	H: 0.26	0.79	1.971	.163
	L: 5.41	4.07	(1,112)		L: 1.59	3.93	(1,112)		L: 0.63	2.00	(1,112)	
Cortisol AuCg	H: 5.56	5.07	0.170	.681	H: 1.52	3.71	0.012	.914	H: 0.31	0.93	0.266	.607
	L: 5.05	3.69	(1,110)		L: 1.62	3.88	(1,110)		L: 0.57	1.91	(1,110)	

All means and standard deviations are percentages. Abbreviations: PS: prenatal stress; Infant positive-mother positive: IposMpos; Infant protesting-mother positive: IproMpos; Infant protesting-mother negative: IproMneg, Area under the curve with respect to ground: AuCg.

2.4.5 Cortisol area under the curve with respect to ground (AUCg)

Additionally, for the cortisol AuCg, no significant effects emerged on the three mother-infant dyadic behavior categories (all $p > .05$, see Table 3).

2.4.6 Mediating role of maternal behavior

Mediation analyses were run to investigate whether maternal behavior mediates the relationship between prenatal stress and child behavior. No significant direct, indirect or total effects were found, see Appendix SI A3.

2.5 Discussion

To our knowledge, the present prospective study is the first to provide evidence of the impact of different indices of prenatal stress (PS) (both psychological and physiological in nature) on mother-infant dyadic interaction behavior during a play situation. With the dyadic behavior categories “Infant positive-mother positive”, and “Infant protesting-mother positive”, we covered positive synchronous behavior and positive parenting. With the dyadic “Infant protesting-mother negative” behavior, we tried to investigate negative synchronous behavior. The results indicated that psychosocial PS had a significant effect on mother-infant interaction at six months postpartum, with mothers-to-be who were prenatally exposed to psychosocial adversities showing significantly more positive behavior than those in the low-stress group. The same applied for perceived maternal PS, but the effect disappeared when adjusting for all covariates, which we consider as restricted evidence. No other stress index reached significance in predicting dyadic behavior. Neither psychopathological nor psychophysiological stress of the mother during pregnancy was found to be related to dyadic interaction behavior. The present findings are in accordance with the stress inoculation model, but are in contrast to previous research reporting general associations of PS (Huizink, Mulder, & Buitelaar, 2004) and associations of socioeconomic and psychosocial PS with infant psychopathology (Entringer et al., 2009; Russell, Ford, Rosenberg, & Kelly, 2014).

One explanation for the present findings might be that our study sample did not consist of clinically stressed mothers-to-be, such as inpatients requiring treatment (Reck et al., 2011). Rather, we examined a general population sample of pregnant women with stress levels varying in the normal range. There were 12.2% of depressed mothers in the high-stressed group and none in the low-stressed group. Whereas studies concentrating on extreme PS (i.e., traumata, natural catastrophes) provided evidence for the stress sensitization model (Baibazarova et al., 2013), our findings are in line with previous research (Weinstock, 2008) showing that moderate

PS-induced HPA activation seems to be beneficial for children's neuronal development. Considering prior findings, reporting mother-infant behavior in time of no or little stress to be associated with the infants' ability to use their mother as an external regulator during stress (Conradt & Ablow, 2010), our results contribute to a deeper understanding of the development of mother-infant interaction as an early indicator for emotion regulation abilities. Furthermore, our results support previous research indicating a beneficial effect of moderate stress (Shapero et al., 2015). In contrast, the physiological stress measures of maternal cortisol decline and cortisol AUCg were found to be unrelated to dyadic behavior. The cortisol decline showed only a weak negative association with psychosocial stress (while AUCg was unrelated). In view of the fact that cortisol levels are elevated during pregnancy (Jung et al., 2011), and diurnal cortisol levels in "normal", uncomplicated late pregnancy (36th week – as in our sample) are approximately 1.5 times higher than mean values reported for non-pregnant controls, the cortisol data in our sample might be mainly determined by the pregnancy itself. Overall, there was no significant difference between the stress groups in terms of cortisol scores (see Table 1). A possible explanation for this finding might be that the cortisol levels of our non-clinical sample were less influenced by their normal daily stress range in comparison to studies focusing on clinical samples (Hellgren et al., 2013). Compared to other research examining maternal cortisol in pregnancy, our cortisol outcomes seemed to be located in the normal range of prenatal cortisol levels (de Weerth & Buitelaar, 2005) and slightly lower than reported results with respect to prenatal stress (Pluess et al., 2012). Furthermore, a recent study showed that low psychosocial status was associated with attenuated maternal cortisol (Bublitz, Vergara-Lopez, O'Reilly Treter, & Stroud, 2016). Taking into account that in contrast to the vast literature of elevated cortisol and stress, several studies indicated that a more blunted cortisol response was associated with stress (Harville, Savitz, Dole, Herring, & Thorp, 2009; Salacz, Csukly, Haller, & Valent, 2012), further research is needed on the activating and constraining mechanisms in HPA axis functioning and their impact on positive and negative outcomes, i.e., resilience and vulnerability.

Although we took into account the covariate current maternal depression, our sample size of depressed mothers in the cortisol sample (n = 7; 5.2%) was too small for further analyses. Concerning the mediation analyses, the hypothesis of a moderating effect of maternal behavior on the relationship between PS and infant behavior has to be rejected due to missing significant effects. We suggest a dynamic view on the impact of PS and the mutual impact of influencing factors, as seen in prior research (Tarabulsy et al., 2003). Despite the lacking significant effects of PS on infant behavior, we suggest a relation between PS and mother-infant dyadic behavior.

We did not compute further analysis because of missing further maternal behavior measurements. Due to the operationalization of the dyads, maternal behavior and the mother-infant dyadic behavior are deterministically dependent form each other. Furthermore, ICEP coding did not include a separate coding, e.g. for maternal sensitivity and infant responsivity, leaving the need for further coding strategies and research on mentioned temporal structure of synchronous behavior. Nevertheless, Leclère and colleagues (2014) reported in their review vast differences in the measurement of synchronous behavior, indicating on one hand that the assessment of synchrony with behavior frequencies is possible, on the other hand, that the current results are difficult to be compared with results of prior studies because of different measures.

The present prospective follow-up study distinguishes between different psychological and physiological stress dimensions as well as different mother-infant dyadic behavior. Nevertheless, some methodological limitations also have to be taken into account. One limitation of the cortisol data lies in the self-reporting of saliva collection by the mothers. For this reason, we decided to apply strict limitations of outliers. In addition to the impact of the study design, given the disclosure of the intended measurement (i.e., PS) and probable maternal attempts to compensate for the estimated stress- level by trying to show the best possible parenting skills during the play situation, it has to be considered that the prenatally assessed stress conditions are most likely followed by certain postnatal factors (e.g., current stressors) which may also impact the infant's environment and development.

2.6 Conclusions

Overall, our data support the stress inoculation hypothesis, with mild psychosocial PS being related to positive mother-infant dyadic behavior. Nevertheless, further research is needed to identify the mediating factors between positive and negative outcomes in prenatally stressed children. Furthermore, it will be of interest to investigate mother-infant interaction behavior in later stages of childhood and adolescence. Although PS seems to have a positive impact at six months postpartum, it might have adverse effects in later life, as reported for elevated anxiety in preadolescent children (Davis & Sandman, 2012). Equally, it might be possible that PS has further positive influences on child development, as previously reported (DiPietro et al., 2006; Shapero et al., 2015). To elucidate the conditions of beneficial and adverse effects of PS, the underlying mechanisms still need to be understood, emphasizing an urgent need for longitudinal studies.

2.7 Acknowledgements

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2.8 Appendix Study I

2.8.1 Appendix SI A1: Assessment of the stress indices

Mothers-to-be (N = 410) were assessed in the last trimester of pregnancy using a structured interview and a series of questionnaires in order to collect information concerning a broad range of environmental and sociodemographic risk factors, prenatal medical risk factors, general medical characteristics, and psychosocial risk factors. Eight main stressor variables derived from eight different questionnaires were selected to represent a variety of prenatal adversities, yielding three different dimensions of stress: a) maternal psychopathology (primarily depressive and anxiety symptoms); b) perceived stress; and c) socioeconomic and psychosocial stress. The composite score of psychopathology was derived from three questionnaires (Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, & Sagovsky, 1987); State-Trait Anxiety inventory (STAIT/S) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983); Anxiety Screening Questionnaire (ASQ) (Wittchen & Boyer, 1998), and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) indicating current depression or anxiety disorder. The composite score perceived stress was derived from the Perceived Stress Scale (PSS) (Cohen et al., 1983) and the Prenatal Distress Questionnaire (PDQ) (Yali & Lobel, 1999). The composite measure of socioeconomic and psychosocial stress was obtained from the Life Experiences Survey (LES) (Sarason, Johnson, & Siegel, 1978), which scores for negative life events, and the Social Support Questionnaire (Soz-U) (Fydrich, Sommer, & Brähler, 2007). Furthermore, the interview scores for the categories living without a partner, encouragement through partner, separation(s) in the last year, daily arguments, physical conflicts within the preceding 12 months, the composition of the household (e.g. rooms per person), no academic qualification, no professional education, monthly income per household less than 1,750 Euro and debt were included in the psychosocial stress axis (positively-impacting data were inverted; for detailed record see Dukal et al. (2015). In addition, an “adversity score” was calculated by summing up the number of dichotomous stressful prenatal adverse conditions and environmental circumstances. To obtain a homogeneous composite measure of prenatal stress, a principal component analysis (PCA) was performed. This involved the eight main stressor variables and the total adversity score as a ninth main variable. This analysis yielded a first principal component (PC1), which explained around 60% of the common variance.

2.8.2 Appendix SI A2: Supplementary analyses with extended covariates

Rationale: In order to adjust for a broader set of covariates (mother's age, infant gender, parity, breastfeeding, Apgar score after 5', perinatal complication, maternal depression before birth and current stress at six months postpartum), further analyses were conducted.

Psychopathological PS: Adjusting for the further covariates breastfeeding, Apgar score after 5', perinatal complication, maternal depression before birth and current stress at six months postpartum did not change the effect of maternal age on IproMpos ($F(1,139) = 4.114$, $p = .044$, partial $\eta 2 = .029$), while effects on IposMpos and IproMneg disappeared (all $p > .05$; see Table 4).

Perceived PS: After adjustment for the further covariates breastfeeding, Apgar score after 5', perinatal complication, maternal depression before birth and current stress at six months postpartum, there were no significant main effects of perceived stress as well as for the other covariates (all $p > .05$; see Table 4)

Psychosocial PS: Computed analyses with all covariates still showed a main effect in the IposMpos dyad ($F(1,138) = 7.827$, $p = .006$, partial $\eta 2 = .054$). No main effects occurred for IproMpos or IproMneg dyads when adjusting for all covariates (all $p > .05$).

Cortisol decline: After taking all covariates into account, maternal age still showed a significant effect in the IproMpos dyad ($F(1,112) = 4.650$, $p = .033$, partial $\eta 2 = .040$). Furthermore, the covariate Apgar score after 5' showed a significant effect on the IposMpos dyad ($F(1,112) = 5.354$, $p = .022$, partial $\eta 2 = .048$), indicating a negative association between Apgar scores and synchronous positive behavior in the mother-infant dyads. No further significant effects of cortisol decline were found in the IposMpos ($F(1,112) = .015$, $p = .903$, partial $\eta 2 < .001$), the IproMpos ($F(1,112) = .090$, $p = .765$, partial $\eta 2 = .001$) or the IproMneg dyads ($F(1,112) = 1.971$, $p = .163$, partial $\eta 2 = .017$).

Area under the curve with respect to ground: When taking all covariates into account, significant effects for the factor maternal age remained in the IproMpos dyad ($F(1,110) = 4.755$, $p = .031$, partial $\eta 2 = .041$). Furthermore, a significant main effect was found in the IposMpos dyad for the factor Apgar score after 5' ($F(1,110) = .098$, $p = .024$, partial $\eta 2 = .045$), showing a negative association between Apgar scores and IposMpos dyadic behavior.

2.8.3 Appendix SI A3: Results of the mediation analyses

The results of the mediation analysis respecting the covariates maternal age, gender, and parity indicated that psychosocial PS was no significant predictor of infant positive behavior ($b = .120$, $SE = .067$, $p = .078$), or of maternal positive behavior ($b = .088$; $SE = .060$, $p = .184$). Furthermore, maternal positive behavior did not significantly predict infant positive behavior, $b = -.151$, $SE = .100$, $p = .134$). Tests for direct and indirect effects were nonsignificant (all $p > .05$), as well as the test for the total effect ($b = .106$, $t = 1.623$, $p = .107$), suggesting that neither mediator effects nor predictor-outcome relationship can be assumed. Only the total effect model revealed significant results (R-squared = .046, $p = .047$) but neither predictor, mediator, nor covariates reached statistical significance. The same finding was obtained with regard to the mediator analysis respecting all eight covariates with no significant results of direct, indirect, or total effect (all $p > .05$), although maternal behavior was found as a significant predictor of infant behavior ($b = -.225$, $SE = .113$, $p = 048$).

3 STUDY II: IMPACT OF PRENATAL STRESS ON MOTHER-INFANT DYADIC BEHAVIOR DURING THE STILL-FACE PARADIGM

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3.1 Abstract

3.1.1 Background

Mother-infant interaction provides important training for the infant's ability to cope with stress and the development of resilience. Prenatal stress (PS) and its impact on the offspring's development have long been a focus of stress research, with studies highlighting both harmful and beneficial effects. The aim of the current study was to examine the possible influence of both psychological stress and hypothalamic-pituitary-adrenal (HPA) axis activity during pregnancy with mother-child dyadic behavior following stress exposure.

3.1.2 Methods

The behavior of 164 mother-infant dyads during the still-face situation was filmed at six months postpartum and coded into three dyadic patterns: 1) both positive, 2) infant protesting-mother positive, and 3) infant protesting-mother negative. PS exposure was assessed prenatally according to psychological measures (i.e., psychopathological, perceived and psychosocial PS; n = 164) and HPA axis activity measures (maternal salivary cortisol, i.e., cortisol decline and area under the curve with respect to ground (AUCg); n = 134).

3.1.3 Results

Mother-infant dyads in both the high- and low-stress groups showed decreasing positive and increasing negative dyadic behavior in the reunion episode, which is associated with the well-known "still-face" and "carry-over" effect. Furthermore, mother-infant dyads with higher psychosocial PS exhibited significantly more positive dyadic behavior than the low psychosocial PS group in the first play episode, but not in the reunion episode. Similarly, mother-infant dyads with high HPA axis activity (i.e. high AUCg), but steeper diurnal cortisol decline (i.e. cortisol decline) displayed significantly less negative behavior in the reunion

episode than dyads with low HPA axis activity. No significant results were found for psychopathological stress and perceived stress.

3.1.4 Conclusions

The results suggest a beneficial effect of higher psychosocial PS and higher prenatal maternal HPA axis activity in late gestation, which is in line with “stress inoculation” theories.

3.1.5 Keywords

prenatal stress, face-to-face still-face paradigm, resilience, psychosocial stress, cortisol

3.2 Background

Early mother-infant interaction plays a pivotal role in the infant’s development of emotion regulation, which is essential for the development of resilience (Beeghly & Tronick, 2011; DiCorcia & Tronick, 2011). In the mutual interaction with their caregivers, infants learn and train age-appropriate self-regulation strategies when confronted with everyday stressors. This allows for the creation and integration of new experiences, enabling infants to accomplish age-related developmental tasks (Tronick, 2006; Tronick & Beeghly, 2011). Previous studies have highlighted the role of mother-infant dyadic behavior not only in the children’s vocalization (Asada & Endo, 2015), but also in the brain development in the first year of life (Laucht, Esser, & Schmidt, 2002). Moreover, mother-infant attachment has been identified as a beneficial factor in the cognitive development of prenatally stressed infants (Bergman, Sarkar, Glover, & O'Connor, 2010). For example, Conway and McDonough (2006) reported an association between maternal sensitivity during infancy and the children’s resilience during preschool age. In their review, Leclère and colleagues (2014) emphasized the crucial role of synchrony in mother-infant behavior in terms of contributing to benefits or vulnerabilities in the infant. The majority of recent studies focusing on early life stress (ELS) and its role in the development of health and disease, as well as resilience (Bock et al., 2014; Glover, 2014; Juruena, 2014; Merlot, Couret, & Otten, 2008), suggest that ELS, and especially prenatal stress (PS), has an important impact on epigenetic alterations in the DNA and thus on changes in the hypothalamic-pituitary-adrenal (HPA) axis (Murgatroyd & Spengler, 2011). “Stress sensitization” and “stress inoculation” theories represent conflicting positions concerning the impact of PS on adolescent or adult life (Bock et al., 2011; Daskalakis et al., 2013; Murgatroyd et al., 2010; Rudolph & Flynn, 2007).

According to the “stress sensitization model”, exposure to PS can subsequently lead to negative consequences later in life, such as higher prevalence of psychiatric disorders, e.g.

anxiety disorders, depression, attention-deficit/hyperactivity disorder or autism spectrum disorders (Angelidou et al., 2012; Davis & Sandman, 2012; Gardener et al., 2009; Juruena, 2014). The underlying process is known as “fetal programming”, defined by Glover and colleagues (2010) as the alteration of infants’ early development due to changes in the direct environment (i.e. in utero). Studies have found that in normal pregnancy, 10 - 20% of maternal cortisol crosses the placental barrier (Gitau et al., 1998). Therefore, maternal cortisol can have a major effect on fetal cortisol concentrations and is able to double them. However, when the mother-to-be experiences more stress, a down-regulation of maternal 11ß-hydroxysteroid dehydrogenase 2 (11ß-HSD2) due to complications, maternal stress, and adversities might lead to a reduced protective enzymatic effect and a further elevation of the maternal glucocorticoids passing the placental barrier (Cottrell & Seckl, 2009; Jensen Pena et al., 2012; O'Donnell et al., 2013; O'Donnell et al., 2009). Accordingly, infants who are overexposed to glucocorticoids may suffer from long-term alterations, mainly referred to as epigenetic methylation of the DNA (Bock et al., 2014). The severity of these alterations is influenced by gene-environment interactions, which depend on several factors such as the timing (i.e., sensitive time frames), duration, and quantity of stressors (Glover, O'Connor, et al., 2010).

In contrast, according to the “stress inoculation model”, increased prenatal stress can be beneficial in terms of increasing hardiness and resilience (Ellis et al., 2011; Meaney, 2001; Nederhof, Ormel, & Oldehinkel, 2014). This theory posits that infants exposed to ELS experience a so-called “steeling effect” (Rutter, 2006), resulting in less reactivity to similar future stressors (Rudolph & Flynn, 2007). In their “match-/mismatch hypothesis”, Nederhof and Schmidt (Nederhof & Schmidt, 2012) combined stress sensitization and stress inoculation theories. They assumed that a match of the early (prenatal) environment with the later adult (postnatal) environment would lead to a better adaptation and thus to a benefit in the offspring, while a mismatch would lead to an elevated disease vulnerability later in life (Nederhof, 2012).

Regarding the interaction with caregivers in the first years of life, Tronick and Beeghly (2011) suggested in their “mutual regulation model” that the development of the infant’s emotion regulation relied on the constant training of matching dyadic mother-infant behavior and the reparation of mismatching dyadic behavior states. The still-face paradigm is a well-known experimental method to examine the infant’s management of an acute stressor. It explores the infant’s capacity to cope with induced stress during a mother-infant play situation (Tronick & Cohn, 1989; Tronick et al., 2005). Infants’ reactions to the still-face paradigm have been shown to be stable over short time intervals (Provenzi, Olson, Montirosso, & Tronick, 2016), with numerous studies reporting a typical “still-face effect”, characterized by a decrease in infant positive behavior and an increase in infant protesting behavior, as well as an increase in self-regulating behavior (i.e.; touching the mouth, thumb-sucking, hand-to-mouth movements) following the stressful still-face episode (Ekas et al., 2013; Mesman et al., 2009; Tronick et al., 1978).

Conway and McDonough (2006) employed the still-face paradigm during mother-infant interaction, and found that maternal sensitivity, but not infants' negative affect, predicted resilience in preschool children. Further, Müller and colleagues (2015) reported an association between the latency of mismatching states in the mother-infant dyad during the still-face paradigm and the infants' salivary cortisol responses. Along with further studies on mother-infant synchrony, research findings on the impairing influence of disturbed mother-infant dyads on child development (Feldman, 2007a; Field et al., 1990; Ginger A. Moore & Susan D. Calkins, 2004) underlined the important role of "contingent reciprocity" in mother-child interaction (Shonkoff & Bales, 2011). For example, mother-infant dyads with depressive mothers, demonstrated less maternal positivity and increased negative affect, and infants showed increased negative, depressive-like affect compared to controls (Cohn et al., 1990; Field et al., 1988; Pickens & Field, 1993). Interestingly, a study in mothers with borderline personality disorder (BPD) found that their three-month-old infants had generally less positive vocalization and showed less non-autonomic self-regulation during the still-face paradigm compared to controls (Apter et al., 2016). Moreover, the infants seemed especially troubled by the still-face episode resulting in decreased infant gazing behavior. The mothers with BPD seemed to be more challenged during the reunion episode after the stressor when resuming the play, and showed less smiling and more intrusive behavior (Apter et al., 2016).

Concerning maternal HPA axis activity, prenatal maternal morning cortisol was found to be associated with children's HPA axis reactions to the first day in school after the summer break (Gutteling, de Weerth, & Buitelaar, 2005). Previous research also revealed prenatal maternal cortisol to be positively associated with early negative infant affect and behavior, resulting in more infant crying and fussing at age five months (de Weerth et al., 2003). On the other hand, it may be not only that maternal HPA axis activity relates to future infant behavior, but also that maternal behavior is associated with future HPA axis activity in the offspring. Schmid et al. (2013) demonstrated that less maternal stimulation during early mother-infant interaction predicted later diminished plasma adrenocorticotropic hormone (ACTH) and cortisol increase in 19-year-old male offspring experiencing acute psychosocial stress. In view of the essential role of the HPA axis in coping with stress, early PS experiences and related alterations in HPA axis function have been discussed to lead to prolonged reactions to stressors, which could be related to infant behavior and temperament as well as later disease propensity (e.g., depression; (Guerry & Hastings, 2011)).

Taken together, these mixed results generated a background for further research on the impact of PS on mothers and infants. To our knowledge, the present study is the first to examine the potential influence of HPA axis and psychological stress in pregnancy with mother-infant dyadic behavior in the still-face paradigm, while reacting to an acute induced stressor (i.e.; still-face procedure). Given that previous studies provided evidence for both a beneficial and an adverse impact of prenatal stress on mother-infant dyadic behavior (Boyce & Ellis, 2005; Rudolph & Flynn, 2007), we tested for both potential outcomes. Furthermore, we expected less positive infant behavior in the still-face episode and more negative infant affect provoked by the "still-face effect". Based on previous research using the still-face paradigm, we expected an overall increase in negative infant behavior after the still-face episode, seen as a "carry-over effect" of the "still-face effect" (see Figure 5 and (Mesman et al., 2009)).

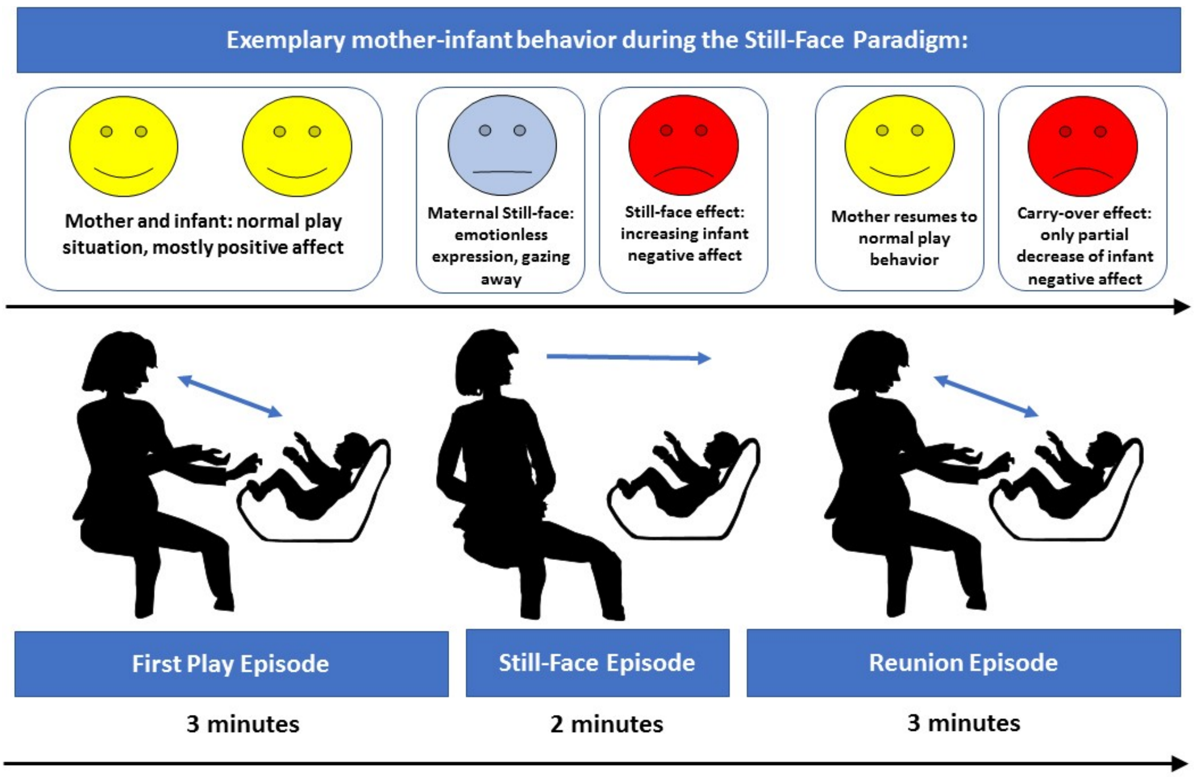


Figure 5: Exemplary Still-Face Paradigm procedure with 3'-2'-3' time intervals revealing the still-face and carry-over effect.

3.3 Materials and Methods

3.3.1 Participants

Expectant mothers were participating in the "Pre-, Peri- and POstnatal Stress: Epigenetic Impact on DepressiON" (POSEIDON) study and were recruited in their third trimester of pregnancy (N = 410, 4 - 8 weeks prior to term) in three obstetric clinics in the Rhine-Neckar-region of Germany (see Dukal et al. (2015) for further information). The study protocol was approved by the Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg and the Ethics Committee of the Medical Association of Rhineland-Palatinate and was conducted in accordance with the Declaration of Helsinki. All mothers provided written informed consent prior to enrolment in the study. Participation in the still-face paradigm six months after birth was voluntary. Inclusion criteria for the mothers-to-be were: German-speaking; main caregiver; and age 16-45 years. Exclusion criteria were: hepatitis B or C, human immunodeficiency virus (HIV) infection; any current psychiatric disorder requiring inpatient treatment; any history of current diagnosis of schizophrenia/psychotic disorder; or any substance dependency other than nicotine during pregnancy. The exclusion criteria for infants were birth weight < 1500 grams; gestational age < 32 weeks; or the presence of any congenital diseases, malformations, deformations, and/or chromosomal abnormalities. For further information, see Appendix SII A1.

3.3.2 Mother-infant behavior

Two-hundred mother-infant videos were collected based on an a-priori participant selection procedure that relied on a composite stress measure (i.e., total adversity score), which enabled the identification of the 100 most stressed and the 100 least stressed mothers (for details see Dukal et al. (2015)). Several video-sets had to be excluded due to technical problems of the filmed material; for detailed information, see Appendix SII A1. For the analysis of maternal diurnal cortisol, data of 134 mother-infant dyads were available, as 30 dyads were excluded due to missing data (i.e., too little saliva provided, no return of samples; n = 17), outliers (≥ / ≤ 2 SD; n = 10), or implausible, impossible morning cortisol (FI and/or FII ≤ 7 nmol/l values; n = 3) (for details, see Wolf et al. (2017)). We used a strict limit of ≥ / ≤ 2 SD to be able to filter the lowest outliers in morning cortisol scores (c.f. (Hellgren et al., 2013)). Statistical analyses examining the outliers for selection effects (e.g., gender, total adversity score, maternal age) were insignificant (all p's >.05). For detailed maternal and infant characteristics, see Table 1 and Table 5, as well as (Wolf et al., 2017).

Table 5: Means and standard deviations of behavior dyads (psychological stress groups and HPA axis activity groups).

	IposMpos dyad		IproMpos dyad		IproMneg dyad	
Psychological PS (n = 164)	**FFE**	**RE**	**FFE**	**RE**	**FFE**	**RE**
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Psychopathological PS	H: 6.13 (4.53)	H: 3.85 (3.76)	H: 1.30 (3.14)	H: 6.54 (10.16)	H: 0.43 (1.64)	H: 2.30 (4.78)
	L: 4.13 (4.68)	L: 3.82 (4.30)	L: 1.92 (4.27)	L: 5.97 (8.86)	L: 0.39 (1.32)	L: 1.74 (3.44)
Perceived PS	H: 6.42 (4.58)	H: 4.10 (3.64)	H: 1.01 (2.68)	H: 6.03 (9.10)	H: 0.42 (1.64)	H: 2.40 (4.81)
	L: 4.50 (4.57)	L: 3.58 (4.38)	L: 2.21 (4.51)	L: 6.49 (9.99)	L: 0.40 (1.36)	L: 1.64 (3.40)
Psychosocial PS	H: 6.76 (4.60)	H: 3.96 (3.81)	H: 0.93 (2.47)	H: 6.08 (10.16)	H: 0.36 (1.51)	H: 2.44 (5.05)
	L: 4.15 (4.32)	L: 3.72 (4.25)	L: 2.29 (4.60)	L: 6.43 (8.87)	L: 0.47 (1.47)	L: 1.60 (3.01)
HPA axis activity (n=134)						
Cortisol decline	F: 5.77 (4.38)	F: 3.76 (3.89)	F: 1.54 (3.82)	F: 6.59 (9.23)	F: 0.58 (1.91)	F: 2.54 (3.99)
	S: 5.13 (4.67)	S: 3.90 (4.19)	S: 1.56 (3.63)	S: 5.49 (8.86)	S: 0.37 (1.30)	S:1.29 (3.18)
AUCg	H: 6.03 (5.28)	H: 4.31 (4.31)	H: 1.59 (3.69)	H: 5.62 (9.32)	H: 0.42 (1.37)	H: 1.37 (2.99)
	L: 5.02 (3.64)	L: 3.54 (3.93)	L: 1.58 (3.83)	L: 6.24 (8.59)	L: 0.55 (1.89)	L: 2.51 (4.21)

Abbreviations: IposMpos: Infant positive-mother positive; IproMpos: Infant protesting-mother positive; IproMneg: Infant protesting-mother negative, FFE: face-to-face/ play episode; RE: Reunion episode; M: mean, SD: standard deviation, F: flat decline, S: steep decline, AUCg: area under the curve with respect to ground.

Videos were filmed at six months postpartum at the Central Institute of Mental Health, Mannheim or in the mothers' homes. Mother-infant dyads performed the well-established still-face paradigm (Tronick et al., 1978). The paradigm consists of three episodes: 1) the first play episode (three minutes), in which the mother interacts normally with the child, 2) the still-face episode (two minutes), in which the mother stops the play and, remains silently sitting with an expressionless face in front of the child, without reacting to or looking at the child, and 3) the reunion episode (three minutes), in which the mother resumes the normal play (see Figure 5). Mother-infant dyads were left alone during the episodes; toys and pacifiers could not be used. The start and the end of the episodes were indicated by a sound signal. Videos were filmed with two video cameras (Sony™ HDR-CX130), one focusing on the mother's face and, the other focusing on the infant. The infants sat opposite to their mothers at the same level in a Maxi-Cosi™ or similar baby chair and were belted during the experiment.

For the coding procedure, the two videos were synchronized and transformed into one split-half screen video using Corel™ Videostudio Pro X4 software. Behavioral coding of the videos was conducted using Interact™ software (Mangold International GmbH 2013, Ver. 9.7.8) by a trained and certified Infant and Caregiver Engagement Phases (ICEP; (Tronick et al., 2005; Weinberg et al., 1999)) coder, who was blind to the mothers' stress exposure. According to the ICEP coding system, all caregiver and infant behaviors were coded (for further details, see Table 6). For data reduction, three dyadic mother-infant behavior categories were formed: 1) Infant positive-mother positive dyad (IposMpos) was coded when mothers showed social monitor/positive vocalization or social positive engagement and infants showed social positive engagement simultaneously; 2) Infant protesting-mother positive dyad (IproMpos) was coded when mothers showed social monitor/positive vocalization or social positive engagement and infants showed negative/protesting behavior (i.e., crying, distress, being fussy); 3) Infant protesting-mother negative dyad (IproMneg) was coded when mothers showed intrusive, social monitor/neutral vocalization or non-infant-focused engagement, with the infant showing protesting behavior. Calculations were performed using Interact™ software by summing up the time for which both partners showed the respective dyadic behavior at the same time during play. The codings were computed separately for each episode into percentages referring to the duration of the play episode.

Table 6: Means, standard deviations and range of the ICEP behavior codes.

	Play episode		Reunion Episode	
ICEP Behavior Codes (n = 164)	**M (SD)**	**Range**	**M (SD)**	**Range**
Infant positive (Ipos)	18.54 (15.53)	Min: 0 Max: 60.81	15.15 (14.54)	Min: 0 Max: 63.95
Infant protest (Ipro)	5.47 (12.17)	Min: 0 Max: 49.78	23.17 (31.59)	Min: 0 Max: 100
Mother positive (Cpos and Cpvc)	77.25 (18.04)	Min: 7.07 Max: 100	70.79 (20.21)	Min: 5.91 Max: 100
Mother negative (Cint, Cneu, Cnon)	21.75 (17.29)	Min: 0 Max: 92.91	27.32 (19.43)	Min: 0 Max: 94.09
intrusive behavior (Cint)	13.23 (15.09)	Min: 0 Max: 89.93	15.14 (17.44)	Min: 0 Max: 85.48
social monitor/neutral vocalization (Cneu)	8.35 (9.99)	Min: 0 Max: 51.58	11.62 (11.82)	Min: 0 Max: 52.39
non-infant-focused engagement (Cnon)	.17 (.53)	Min: 0 Max: 3.42	.56 (.431)	Min: 0 Max: 52.39

All means and standard deviations are percentages. Abbreviations: ICEP: Infant and Caregiver Engagement Phases

3.3.3 Assessment of stress: subjective stress experience indices

Mothers were interviewed and given questionnaires during the final trimester of pregnancy (for further details, see Dukal et al. (2015)). To provide different psychological stress measurements, we used three composite scores computed by principle component analysis distinguishing psychopathological, perceived, and psychosocial stress of the mother during pregnancy (for further information, see Appendix SII A2).

3.3.4 HPA axis activity

Salivary cortisol measures were acquired as a reliable indicator of total free plasma cortisol (Kirschbaum & Hellhammer, 1994). Maternal diurnal cortisol data were obtained via saliva samples using Salivettes (Sarstedt™, Leicester, UK), which contained an untreated cotton swab. Saliva samples were collected in the late third trimester of pregnancy during one "normal working day". We chose a threefold determination based on the protocol of Lederbogen and colleagues (Lederbogen et al., 2011). Mothers were instructed to chew on the cotton swab immediately after awakening (FI), but while still in bed; 30 minutes after getting up (FII); and 14 hours after awakening (FIII). Instructions included precaution information regarding meals, drinks, brushing one's teeth and smoking. Mothers indicated the date and times of saliva collection and sent the probes back to the study coordinators. All samples were stored at - 25°C. After thawing, the samples were centrifuged for five minutes at 3000 rev/min, resulting in a clear supernatant of low viscosity. Salivary cortisol was measured by means of a time resolved immunoassay with fluorescence detection. The lower limit of detection was 0.43 nmol/l, with interassay and intraassay coefficients of variation of less than 10% across the expected range of cortisol levels. The mean week of gestation for the saliva collection was 36.77 (SD 1.89). The measure diurnal cortisol decline was computed as the difference between the evening cortisol score and the highest morning score (FI or FII – FIII), as the cortisol morning peak is expected 0 – 0.5h after awakening (Ranjit et al., 2005). The cortisol measure area under the curve with respect to ground (AUCg) was computed according to the formula by Pruessner and colleagues (Pruessner et al., 2003). The AUCg indicates the total amount of cortisol concentration per day and is defined by a trapezoid formula, calculating the area under the diurnal cortisol decline.

3.3.5 Statistical analysis

All statistical analyses were performed using PASW Statistics 21 (SPSS Inc., Chicago, USA). To examine the relationships between the three dependent variables (i.e., types of dyadic behavior), Pearson's r correlations between the mother-infant dyadic behavior categories, as well as between the psychological and HPA axis activity stress groups were computed. Furthermore, paired *t*-tests for the ICEP infant behavior codes "infant social positive engagement" and "infant negative/protesting behavior" were calculated in order to compare each play phase with one another. For each psychological stress index (i.e., maternal psychopathology, perceived stress, and psychosocial stress) and for each HPA axis parameter (i.e., prenatal maternal cortisol decline, and cortisol area under the curve with respect to ground (AUCg)), the corresponding stress variable was dichotomized via median splits to form two groups with high and low stress levels (see Appendix SII A2 for more details). To examine whether the stress groups (i.e., mothers with low and high stress) differed from each other in the still-face paradigm, we ran a series of repeated-measures analyses of covariance (ANCOVA), with group as the between-subjects factor, the still-face episodes (e.g.; play episode and reunion episode) as within-subjects factor and the covariates maternal age, infant gender, parity, and video setting (home vs. lab). As a second additional validation, we adjusted for further confounders and included the covariates breastfeeding, current maternal depression during pregnancy, Apgar score after five minutes, perinatal complications, and perceived stress six months postpartum (assessed via the Perceived Stress Scale, PSS (Cohen et al., 1983)) were included. Significant interaction effects were followed up by post- hoc contrasts comparing the two stress groups separately for each episode. Furthermore, mediation analyses were computed to test for the possibility of maternal behavior mediating the relationship between prenatal stress and infant behavior, using regression analysis and bias-corrected bootstrapping with the PROCESS model tool (Hayes & Scharkow, 2013). We ran mediation analyses with z-standardized maternal behavior (i.e., positive and negative behavior) as a mediator between PS (i.e., psychosocial PS, cortisol decline) and z-standardized infant behavior (i.e., infant positive and protesting behavior) in the reunion episode, including the covariates gender, maternal age, parity, and video setting (home vs. lab) in a first step and the additional covariates current maternal depression during pregnancy, breastfeeding, Apgar score five minutes after birth, perinatal complications, and perceived stress six months postpartum (assessed via the PSS) in a second step.

3.4 Results

Correlations between mother-infant dyadic behavior categories across the play episodes were significant (all p's between $< .001$ and $p = .014$), with the exception of IposMpos in the first play episode and IproMneg in the reunion episode ($r = - 0.003$; $p = .968$; for details see Table 7). Given the highly significant intercorrelations between the psychological stress variables (see Table 8; $r = 0.604$ to 0.739; all p's $< .001$), we decided to assess the impact of the distinct stress dimensions separately in order to examine specific effects, similar to previous findings from our group by Dukal et al. (2015) and Nieratschker et al. (2014). HPA axis activity and psychological stress measures showed a significant negative association of cortisol decline with psychopathological stress ($r = -0.203$; $p = .019$) and psychosocial stress ($r = -0.184$; $p = .033$), whereas perceived stress was unrelated to cortisol decline ($r = -0.003$; $p = .974$). Moreover, the cortisol AUCg was unrelated to the three psychological stress measures (r between - 0.061 and 0.081; all p's $> .360$; see Table 9).

Table 7: Pearson correlations between the mother-infant dyadic behavior categories across the still-face episodes (N = 164).

		IposMpos	**IproMpos**		**IproMneg**	
		RE	**FFE**	**RE**	**FFE**	**RE**
IposMpos	**FFE**	0.430; p < .001	- 0.260; p = .001	- 0.211; p = .007	- 0.168; p = .032	- 0.003; p = .968
	RE		- 0.297; p < 001	- 0.357; p < .001	- 0.220; p = .005	- 0.268; p = .001
IproMpos	**FFE**				0.482; p < .001	- 0.320; p < .001
	RE				0.282; p < .001	0.427; p < .001

Abbreviations: FFE: first play / Face-to-face play episode; RE: Reunion episode; IposMpos: Infant positive-mother positive, IproMpos: Infant protesting-mother positive; IproMneg: Infant protesting–mother negative.

Table 8: Pearson correlations between the prenatal psychological stress indices and the postnatal Perceived Stress Scale (N = 164).

	Psychopathological stress	**Perceived stress**	**Psychosocial stress**
Perceived stress	.739; p < .001	1	
Psychosocial stress	.614; p < .001	.604; p < .001	1
PSS	.609; p < .001	.693; p < .001	.473; p < .001

Abbreviations: PSS: Perceived Stress Scale, surveyed six months after birth.

Table 9: Pearson correlations between the psychosocial stress and psychophysiological stress indices (N = 134).

	Perceived stress	**Psychosocial stress**	**Cortisol Decline**	**Cortisol AUCg**
Psychopathological stress	.721; p < .001; N = 134	.629; p < .001; N = 134	- .203; p = .019; N = 127	- .061; p = .491; N = 131
Perceived stress	1 N = 134	.582; p < .001; N = 134	- .003; p = .974; N = 127	.081; p = .360; N = 131
Psychosocial stress		1 N = 134	- .184; p = .033; N = 127	- .013; p = .879; N = 131
Cortisol Decline			1 N = 127	.467; p < .001; N = 126

Abbreviations: AUCg: area under the curve with respect to ground

Cortisol AUCg and cortisol decline were significantly positively correlated (r = 0.398; p < .001). Moreover, as expected, paired *t*-tests for the infant behavior showed significant episode effects between the first play and the still-face episode (*t* (163) = 14.64; p < .001), indicating a decrease in positive behavior, both for the still-face episode and the reunion for infant positive behavior (*t* (162) = -12.51; p < .001) and an increase in positive behavior. Furthermore, the paired *t*-test for infant positive behavior showed a significant decrease in positive behavior between the first play and reunion episode (*t* (162) = 3.04; p = .003). The results additionally revealed a significant episode effect on infant protesting behavior between the first play episode and the still-face episode (*t* (163) = -6.64; p < .001), with an increase in protesting behavior, but not for the still-face episode and the reunion episode (*t* (162) = -1.83; p = .070). However, a paired *t*-test for infant protesting behavior between the first play episode and the reunion episode showed a significant increase in negative behavior (*t* (162) = -8.28; p < .001).

3.4.1 Impact of subjective psychological PS on mother-infant dyadic behavior during the still-face paradigm: Psychosocial PS

The psychosocial PS x episode interaction showed a significant effect with regard to positive dyadic behavior ($F(1,156) = 9.647$, $p = .002$, partial $\eta^2 = .058$), indicating that the effect of stress group differed depending on the play episode (for details, see Table 10). Post-hoc contrasts revealed that, in the first play episode, the low-psychosocial PS group showed more positive dyadic behavior ($p = .001$) than the high-psychosocial PS group, while this was not the case in the reunion episode ($p = .793$; see Figure 6).

Table 10: Effect of psychosocial PS on mother-infant positive dyadic behavior
Results of ANCOVA adjusted for gender, maternal age, parity and video setting.

Effect	**IposMpos dyad**		
	F/ (df)	p	Part. Eta Sq.
Psychosocial PS	4.721 (156)	.031	.029
Episode	0.140 (156)	.709	.001
Psychosocial PS x episode IA	9.647 (156)	.002	.058

Abbreviations: PS: prenatal stress; Part. Eta Sq.: partial Eta-squared; df: degrees of freedom; IA: interaction; IposMpos: Infant positive-mother positive; Ipro-Mpos: Infant protesting-mother positive; IproMneg: Infant protesting-mother negative.

When adjusting for additional covariates, the interaction effect of psychosocial PS x episode relating to the IposMpos dyad remained significant ($F(1,136) = 4.784$, $p = .030$, partial $\eta^2 = .034$). There were no significant effects of the psychosocial PS group on IproMpos and IproMneg (all p's > .05). When adjusted for additional covariates, the results remained unchanged (see Table 11).

Table 11: Effect of psychosocial PS on mother-infant dyadic positive behavior.
Results of ANCOVA additionally adjusted for breastfeeding, maternal depression before birth (except for psychopathological ELS), Apgar score after 5', perinatal complications, and current perceived stress in high-stress and low-stress groups.

Effect	IposMpos dyad		
	F/ (df)	P	Part. Eta Sq.
Psychosocial PS	3.714 (136)	.056	.027
Episode	0.187 (136)	.666	.001
Psychosocial PS x episode IA	4.784 (136)	.030	.034

Abbreviations: PS: prenatal stress; Part. Eta Sq.: partial Eta-squared; IA: interaction; Infant positive-mother positive: IposMpos; Infant protesting-mother positive: IproMpos; Infant protesting-mother negative: IproMneg; FFE: Face-to-face episode / first play episode; RE. Reunion episode.

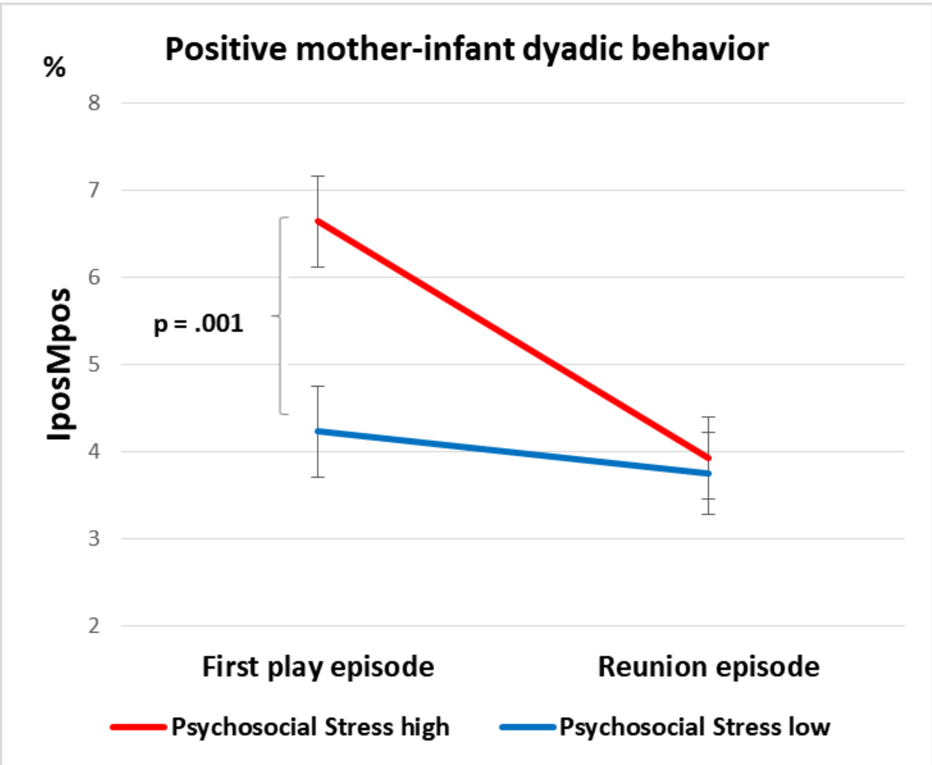


Figure 6. Positive mother-infant dyadic behavior depending on psychosocial PS groups during the play and reunion episode (Means and standard errors adjusted for covariates and significant contrasts).

3.4.2 Psychopathological PS and Perceived PS

No significant main effects were found for either of these stress dimensions (all p's > .05).

3.4.3 Impact of HPA axis activity on mother-infant dyadic behavior during the still-face paradigm: Cortisol decline

The cortisol decline x episode interaction effect on IproMneg dyadic behavior just reached significance ($F(1,126) = 3.949$, $p = .049$, partial $\eta 2 = .030$), see Table 12. Moreover, after adjusting for additional covariates, the cortisol decline x episode interaction relating to IproMneg dyadic behavior remained significant ($F(1,111) = 4.982$, $p = .028$, partial $\eta 2 = .043$). Post-hoc contrasts showed a significant difference between the cortisol decline groups following the still-face manipulation in the reunion episode ($p = .011$) but not in the first play episode ($p = .163$, see Figure 7). While both mother-infant dyad groups showed an increase in negative dyadic behavior in the reunion episode, the mother-infant dyads whose mothers-to-be had a prenatally flatter decline in cortisol levels exhibited more IproMneg dyadic behavior ($M = 2.54$; standard error = 4.44) compared to the dyads with a steeper prenatal maternal cortisol decline ($M = 1.27$; standard error = 0.44). No further significant effects were obtained when adjusting for additional covariates (see Table 13; all p's > .05).

Table 12: Effect of prenatal HPA axis activity on Infant protesting-mother negative dyadic behavior. Results of ANCOVAs adjusted for gender, maternal age, parity and video setting.

Effect	**IproMneg dyad**		
	F/ (df)	p	Part. Eta Sq.
Cortisol decline	3.192 (126)	.076	.025
Episode	0.775 (126)	.380	.006
Cortisol decline x episode IA	3.949 (126)	.049	.029
Cortisol AUCg	3.433 (123)	.066	.027
Episode	0.540 (123)	.464	.004
Cortisol AUCg x episode IA	4.736 (123)	.031	.037

Abbreviations: Part. Eta Sq.: partial Eta-squared; df: degrees of freedom; IA: interaction; IposMpos: Infant positive-mother positive; IproMpos: Infant protesting-mother positive; IproMneg: Infant protesting-mother negative; AUCg: area under the curve with respect to ground.

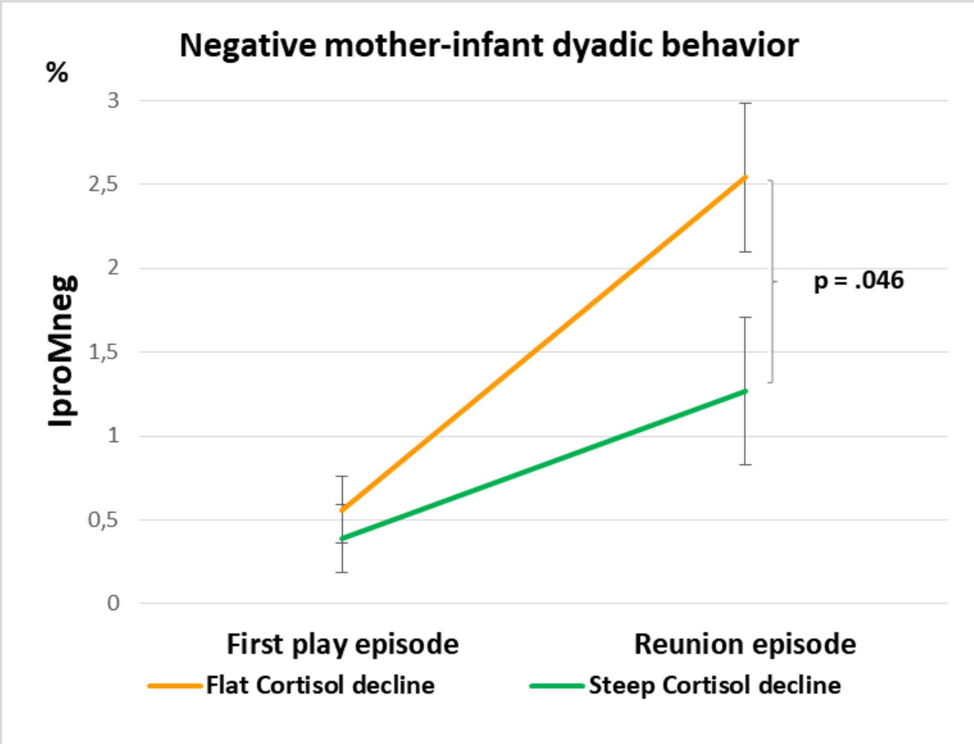


Figure 7: Negative mother-infant dyadic behavior depending on cortisol decline groups in the play and reunion episode (Means and standard errors adjusted for covariates and significant contrasts).

Table 13: Effect of maternal HPA axis activity on infant protesting-mother negative dyadic behavior (ANCOVAs additionally adjusted).

Results of ANCOVAs additionally adjusted for breastfeeding, maternal depression before birth, Apgar score after 5', perinatal complications, and current perceived stress in high HPA axis activity and low HPA axis activity groups.

Effect	**IproMneg dyad**		
	F/ (df)	P	Part. Eta Sq.
Cortisol decline	7.157 (111)	.009	.061
Episode	1.364 (111)	.245	.012
Cortisol decline x episode IA	4.982 (111)	.028	.043
Cortisol AUCg	5.285(109)	.023	.046
Episode	.565 (109)	.454	.005
Cortisol AUCg x episode IA	5.242 (109)	.024	.046

Abbreviations: Part. Eta Sq.: partial Eta-squared; IA: interaction; IposMpos: Infant positive-mother positive; IproMpos: Infant protesting-mother positive; IproMneg: Infant protesting-mother negative; FFE: Face-to-face episode / first play episode; RE. Reunion episode; AUCg: area under the curve with respect to ground.

3.4.4 Cortisol area under the curve with respect to ground (AUCg)

An interaction effect of the AUCg x episode relating to the IproMneg dyad emerged ($F(1,123) = 4.736$, $p = .031$, partial $\eta^2 = .037$); see Figure 8 and Table 12. When controlling for additional covariates, this effect remained significant ($F(1,109) = 5.242$, $p = .024$, partial $\eta^2 = .046$). Post-hoc tests showed that there were significant associations between higher diurnal cortisol AUCg levels and the mother-infant dyads in the reunion episode ($p = .039$), but not in the first play episode ($p = .607$). Mother-child dyads with higher maternal diurnal cortisol AUCg levels showed only half as much ($M = 1.23$; standard error = 0.45) negative dyadic behavior as the less stressed mother-child dyads during the reunion episode ($M = 2.64$; standard error = 0.45), see Figure 8. No interaction effects were found of AUCg x episode relating to the IposMpos dyads or the IproMpos dyads (all p's > .05). Finally, when adjusted for all covariates, there were no significant main effects of AUCg on either mother-infant dyad group (all p's > .05).

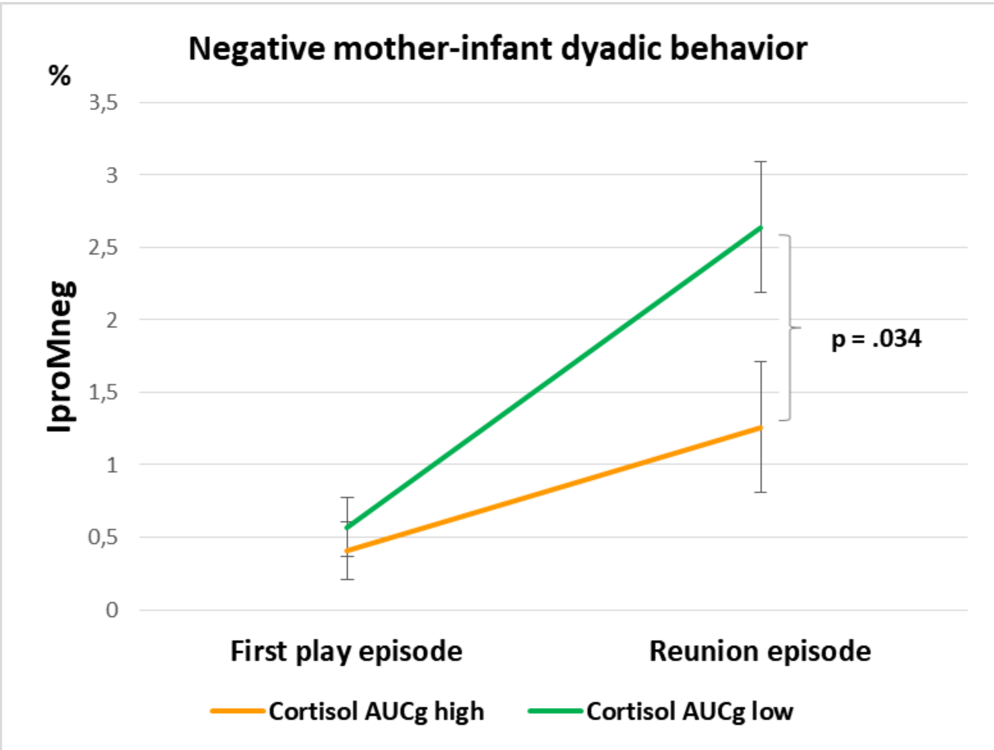


Figure 8: Negative mother-infant dyadic behavior depending on AUCg groups in the play and reunion episode (Means and standard errors adjusted for covariates and significant contrasts).

3.4.5 Mediation analyses

Mediation analyses (adjusted for the covariates gender, parity, maternal age and video setting) were computed to examine whether maternal negative behavior mediates the relationship between maternal cortisol decline and negative infant behavior during the reunion episode. The results indicated that cortisol decline was a significant predictor of infant negative behavior during the reunion episode (b = -.023, SE = .011, p = .038), but not of maternal negative behavior (b = -.023, SE = .014, p = .095). In contrast, maternal negative behavior did not significantly predict infant negative behavior during the reunion episode (b = -.151, SE = .078, p = .053). The total effect and the indirect effect were also nonsignificant (p > .05). When adjusting for further covariates, cortisol decline remained a significant predictor of infant negative behavior during the reunion episode (b = - .032, SE = .014, p = .018), with results showing a significant total effect (b = -.028, t = -2.049, p = .042) and thus indicating no mediating factors. Analyses computed to examine a potential mediation effect of maternal positive behavior on the relationship between psychosocial stress and infant positive behavior in the reunion episode did not show any significant direct, indirect or total effects (see Appendix SII A3). Moreover, mediation analyses testing maternal negative behavior as a possible mediator between maternal AUCg and infant negative behavior during the reunion episode failed to show any significant results (see Appendix SII A3).

3.5 Discussion

The present study used the well-known still-face paradigm within mother-infant interaction to examine infants' emotion regulation abilities (Mesman et al., 2009). Evidence emerged for the well-known "still-face effect" and the "carry-over effect" (i.e., increase in negative infant behavior following still-face exposure and consequent decrease in positive dyadic behavior during reunion (Ekas et al., 2013; Mesman et al., 2009). Significant effects of the still-face paradigm were shown separately for infant positive and negative behavior, demonstrating the effectiveness of the still-face episode. Regarding mother-infant dyadic behavior, effects were found for both positive and negative interaction patterns and with respect to both psychological and physiological prenatal stress. While mother-infant dyads with high psychosocial PS showed significantly more positive dyadic behavior (i.e. IposMpos) in the first play episode, they did not differ from the low-stress group in the reunion episode. In contrast, the effects of physiological prenatal stress were restricted to negative interaction patterns. Mother-infant dyads with a flatter cortisol decline displayed a more pronounced increase in negative dyadic behavior in the reunion episode compared to those with a steeper prenatal maternal cortisol decline. However, in mother-infant dyads with lower diurnal cortisol AUCg levels, the increase in negative dyadic interaction patterns during reunion was more marked than in those with higher maternal diurnal cortisol AUCg levels. Dyads with low cortisol levels showed about twice as much negative dyadic behavior as the more stressed mother-child dyads during the reunion. Taken together, mothers with a steep HPA decline and high cortisol AUCg in pregnancy showed more positive dyadic interaction patterns following the still-face episode.

The significant effects found in the analyses may suggest an advantageous influence of higher prenatal maternal stress levels, supporting the “stress inoculation” theories, but should be considered in detail. Mother-infant dyads with lower maternal prenatal psychosocial stress showed approximately the same amount of mother-infant positive dyadic behavior (IposMpos) in both play episodes. One explanation for the finding that in contrast to the high-stress group, dyads from the low-stress group did not adjust their positive interaction behavior to the second play episode might be that the decrease in positive dyadic behavior resulted from the “still-face” and the subsequent “carry-over” effect. Several studies have demonstrated a change from infant positive behavior in the first play episode to increased infant negative affect during the still-face episode with less gazing to their mother, as well as the “carry-over” effect in the reunion episode, indicating only a partial decrease of negative infant affect compared to the first play episode (Mesman et al., 2009; Montirosso et al., 2010; Weinberg et al., 1999). The separate analyses of infant behavior only showed significant episode effects, while no such effects were found when mother-infant dyadic behavior was analyzed. This could be due to the mothers’ consistent amount of positive behavior in the two play episodes: Consistent maternal positive behavior may have merged with the mother-infant dyadic behavior, thus potentially biasing the existing episode effect for infant behavior. Previous research also failed to find significant changes in maternal behavior in the two play episodes (Montirosso et al., 2010).

A second reason for these findings might be that mothers with higher psychosocial PS are more likely to try to compensate for the experienced stress by paying more attention to their own behavior, such as displaying more positive attention and behavior towards their child. At the same time, however, these mothers might be more vulnerable to current stressors (i.e., still-face episode), resulting in the reported diminished positive dyadic behavior in the reunion episode. Nevertheless, despite the decrease in positive dyadic mother-infant behavior from the first play to the reunion episode, mother-infant dyads with high psychosocial PS still showed slightly more positive dyadic behavior ($M = 3.96$; standard error = 0.47) than those with low psychosocial PS ($M = 3.75$; standard error = 0.47) in the reunion, which puts the significant interaction effect into perspective. When comparing this distinct decrease in positive dyadic behavior in the high psychosocial PS group between the first play episode and the reunion, our results are in line with a previous study (Provenzi et al., 2016) reporting that higher dyadic synchrony in the first play was predictive of more negative infant behavior in the reunion. We agree with the potential explanations speculated by these authors, such as that infants with higher synchrony in normal face-to-face interaction with their caregivers might be more distressed when experiencing the loss of synchrony during the still-face episode, resulting in an increase in negative behavior in the reunion (Provenzi et al., 2016). Nevertheless, positive infant behavior (i.e., smiling, laughing) is discussed as a possible regulator of arousal, which is trained on an everyday basis through the interplay in the caregiver-infant dyad, thus enhancing emotion regulation abilities with every positively overcome challenge of dysregulation and short disruption (Mesman et al., 2009; Tronick & Beeghly, 2011).

With regard to prenatal cortisol measures, the findings also suggested a possible beneficial influence of higher prenatal maternal diurnal cortisol area under the curve levels. Mother-infant dyads with lower diurnal cortisol area under the curve levels before birth displayed significantly more negative dyadic behavior during reunion than dyads with higher levels. In contrast, mother-infant dyads with a steeper ("more healthy") prenatal maternal cortisol decline exhibited less Infant protesting-mother negative dyadic behavior in the reunion than the dyads with a flatter ("less healthy") decline. It seems that a high amount of HPA axis activity over the course of the day might not be particularly detrimental in the last trimester of pregnancy, as long as there is a decline in the cortisol measures over the day. This is in line with previous research reporting beneficial effects of elevated maternal cortisol in late gestation, resulting in accelerated child development, but not in early pregnancy (Davis & Sandman, 2010).

Furthermore, dyads with a prenatally steeper cortisol decline did not significantly differ from those with a flatter decline in the first play episode, but did differ in the reunion episode, suggesting that mother-infant dyads with a steep decline are better at handling current stressors (i.e., still-face episode). These findings support the stress inoculation theories. Moreover, they lead to the assumption that mother-infant dyads with higher levels of prenatal maternal cortisol (AUCg) and a steeper diurnal cortisol decline might have an enhanced resilience to current stress or enhanced stress management strategies, both of which were found to be associated with a steeper cortisol decline (Urizar Jr & Muñoz, 2011).

Mediation analyses examining possible mediating effects of maternal behavior on the relationship between PS and infant behavior in the reunion episode did not reveal significant effects. Thus, they did not confirm the results of previous research revealing a significant influence of maternal responsive behavior on infant positive behavior in the reunion episode (Erickson & Lowe, 2008), highlighting possible postnatal influencing factors.

The present study indicated significant effects of both stress measures (i.e., psychosocial stress and HPA axis activity). These results correspond well with the "match-/mismatch hypothesis", which posits that the offspring benefits from the influence of its early environment if the later environment matches and provides the same demands and resources (Nederhof, 2012; Nederhof & Schmidt, 2012). Mother-child dyads with higher psychosocial PS and higher prenatal maternal HPA axis activity exhibited less negative dyadic behavior when currently stressed six months after birth compared to dyads with less psychosocial PS and less maternal HPA axis activity, suggesting that the environment matches. Contrary to our hypothesis that changes in the HPA axis would affect maternal and infant behavior, as found in previous research (Glover, O'Connor, et al., 2010; Meaney, 2001), no significant effect of prenatal maternal HPA axis activity on dyadic positive mother-infant behavior was found. This might be due to the "still-face" effect and the general decrease in infant positive and increase in infant negative behavior during the still-face episode. In principle, prenatal maternal cortisol can be associated with both infant behavior (Brummelte & Galea, 2010) and maternal caregiving behavior (Baibazarova et al., 2013). However, previous research also reported a lack of associations between self-reported stress and maternal or fetal cortisol levels (Baibazarova et al., 2013). Moreover, the timing of prenatal exposure to maternal cortisol seems to have an important influence on its potential beneficial or detrimental impact (Davis & Sandman, 2010). Referring to Bolten et al. (2013), it has to be conceded that these authors exclusively focused on self-regulation behavior codes of the children, which we did not examine in our study and did not include in the coding of positive and negative dyadic mother-infant behavior.

Furthermore, attenuated cortisol responses were also found to be associated with stress reactivity (Bublitz et al., 2016; Harville et al., 2009; Salacz et al., 2012). Recent research on resilience factors has shown that even severe early life stress was not necessarily linked to a hyper-responsive stress and fear system (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009), although severe adverse early life experiences are still seen as a contributor to adult psychopathology (Levine, 2005). Moreover, the postnatal environment can moderate the relationship between PS and later behavioral outcome, being able to both worsen and reverse the influence of ELS (Mustoe, Taylor, Birnie, Huffman, & French, 2014).

Finally, individual differences need to be taken into account. Research in rodents demonstrated both beneficial and impairing effects of prenatal stress depending on the strain of rats (Rana et al., 2015) or the amount of stress experienced (Mychasiuk, Ilnytskyy, Kovalchuk, Kolb, & Gibb, 2011). Concerning the dosage of stress, DiPietro (2004) argued that the resulting impact of prenatal stress on infants' development could be akin to the relation between arousal and performance reflected in the U-shaped function of the "Yerkes-Dodson law", with a moderate dosage being seen as optimal.

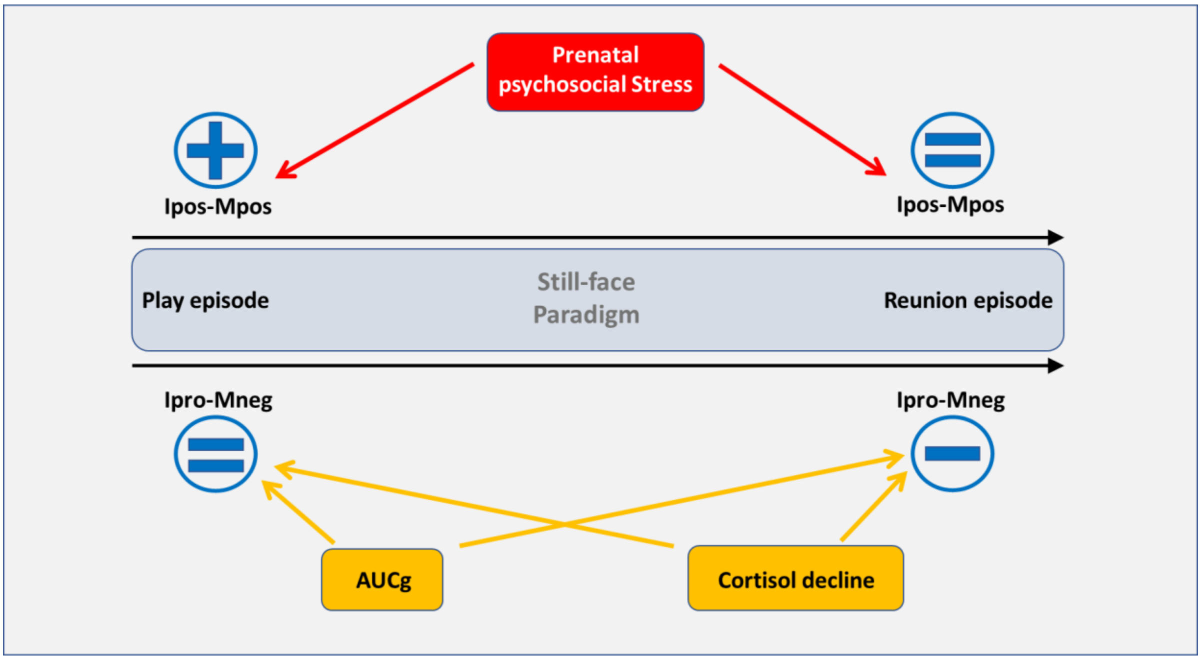
Keeping in mind that the results presented above only showed a snapshot of mother-infant behavior at six months postpartum, further research is needed to identify individual factors and general changes in the impact of PS during infant development. Despite the reports of potentially beneficial influences of prenatal stress exposure, the majority of findings suggesting an impairing influence of early life stress should not be neglected. Furthermore, research on “allostatic load” has suggested that former resilience can turn into proneness to later diseases (McEwen, Gray, & Nasca, 2015). Following the assumption, better survival in stressful and dangerous environments might come at the cost of a shorter lifespan and vulnerability to disorders and diseases later on (Oldehinkel et al., 2014).

Several limitations of the present study need to be taken into account. First, the cortisol data were collected and self-reported by the mothers. For this reason, we set up a strict limitation of outliers. The cortisol measures seem to lie in a normal range expected for mothers-to-be in the third trimester of pregnancy (Jung et al., 2011), possibly less influenced by the reported maternal stress than by the pregnancy itself. Second, the dichotomized stress measurement (extreme-) groups showed an amount of overlapping data for the mother-infant dyadic behavior, defined by means and standard deviations, which has to be taken into account. Third, the study consisted of healthy non-inpatient women. Therefore, it would not be appropriate to compare findings from our sample of pregnant women exposed to rather moderate prenatal maternal stress levels with studies investigating severe event-related prenatal stress in mothers-to-be (i.e.; catastrophes, current psychological disorders needing inpatient treatment). Fourth, prenatal stress can be mediated by influencing factors such as maternal sensitivity, infants’ temperament, coping abilities or attachment quality (Blair, Granger, Willoughby, Kivlighan, & The Family Life Project, 2006; Fuertes, Santos, Beeghly, & Tronick, 2006), none of which were controlled for in the current study. Finally, as our study is the first to attempt to elucidate influences of prenatal stress on mother-infant dyadic behavior, it is therefore of a hypothesis-generating and exploratory nature. Hence, p-values were not post-hoc corrected for multiple testing and the reported results need to be replicated and verified in further independent controlled experiments.

3.6 Conclusion

Mother-infant dyads exposed to higher levels of prenatal psychosocial stress showed more positive dyadic behavior during the play episode, while mother-infant dyads with higher diurnal cortisol and a steeper cortisol decline displayed less negative dyadic behavior during the reunion episode than the respective comparison groups (see Figure 9). Overall, these results support the “*stress inoculation*” theories, which report beneficial effects of prenatal stress

(DiPietro et al., 2006; Ellis et al., 2011; Nederhof et al., 2014) as well as the *"match-/mismatch hypothesis*" (Nederhof, 2012; Nederhof & Schmidt, 2012), contributing to the exploration of resilience and emotion regulation abilities. Nevertheless, with the vast amount of studies reporting impairing influences of prenatal stress, findings of possible positive influences should be taken into consideration but treated with caution and subject to verification. The mixed research findings examining the impact of prenatal stress on infants` development require further research to elucidate the reasons for the conflicting findings.



Legend: IposMpos: Infant positive-mother positive, IproMneg: Infant protesting-mother negative, AUCg: Area under the curve with respect to ground.

Figure 9: Summary of the present findings.

3.7 Appendix Study II

3.7.1 Appendix SII A1: Inclusion and exclusion criteria of video data

Several video sets had to be excluded due to technical problems of the filmed material (i.e., light and sound overexposure, missing sequences, early ending; n = 8) and outliers in infant behavior assumed as disturbed due to interfering circumstances (i.e., sleepiness and >80% infant protesting behavior; n = 28; cf. baseline of 10% negative infant behavior reported by Ginger and Calkins (2004), leaving 164 mother-infant pairs for statistical data analysis.

3.7.2 Appendix SII A2: Assessment of the stress indices

Mothers-to-be (N = 410) were assessed in the last trimester of pregnancy using a structured interview and a series of questionnaires in order to collect information concerning a broad range of environmental and sociodemographic risk factors, prenatal medical risk factors, general medical characteristics, and psychosocial risk factors. Eight main stressor variables derived from eight different questionnaires were selected to represent a variety of prenatal adversities, yielding three different dimensions of stress: a) maternal psychopathology (primarily depressive and anxiety symptoms); b) perceived stress; and c) socioeconomic and psychosocial stress. The composite score of psychopathology was derived from three questionnaires (Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987); State-Trait Anxiety Inventory (STAIT/S) (Spielberger, Gorsuch, & Lushene, 1970); Anxiety Screening Questionnaire (ASQ) (Wittchen & Boyer, 1998), and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), indicating current depression or anxiety disorder. The composite score of perceived stress was derived from the Perceived Stress Scale (PSS) (Cohen et al., 1983) and the Prenatal Distress Questionnaire (PDQ) (Yali & Lobel, 1999). The composite measure of socioeconomic and psychosocial stress was obtained from the Life Experiences Survey (LES) (Sarason et al., 1978), which scores for negative life events, and the inverted score of the Social Support Questionnaire (Soz-U) (Fydrich et al., 2007). Furthermore, the interview scores for the categories living without a partner, encouragement through partner, separation(s) in the last year, daily arguments, physical conflicts within the preceding 12 months, the composition of the household (e.g. rooms per person), no academic qualification, no professional education, monthly income per household less than 1,750 Euro, and debt were included in the psychosocial stress axis (positively-impacting data were inverted; for detailed records, see Dukal et al. (2015)). In addition, an “adversity score” was calculated by summing up the number of dichotomous stressful prenatal adverse conditions and environmental circumstances. To obtain a homogeneous composite measure of prenatal stress, a principal components analysis (PCA) was performed. This involved the eight main stressor variables and the total adversity score as a ninth main variable. This analysis yielded a first principal component (PC1), which explained about 60% of the common variance.

3.7.3 Appendix SII A3: Results of mediation analyses

Mediation analysis (considering the covariates gender, parity, maternal age and video setting) investigating the possible mediating role of positive maternal behavior between PS and positive infant behavior in the reunion play indicated that psychosocial PS was not a significant predictor of infant positive behavior (b = .007, SE = .091, p = .940) or of maternal positive behavior during reunion (b = -.023; SE = .061, p = .710). Furthermore, maternal positive behavior did not significantly predict infant positive behavior in the reunion episode (b = -.137, SE = .091, p = .137). Tests for direct and indirect effect as well as total effects were nonsignificant (all p > .05), suggesting that neither mediator effects nor a predictor-outcome relationship can be assumed. The same applied for the mediation analysis considering further covariates (i.e., breastfeeding, perinatal complications, perceived current stress (PSS), Apgar score five minutes after birth, and maternal depression).

Mediation analyses testing the role of negative maternal behavior in the relation between maternal cortisol AUCg and infant negative behavior indicated that AUCg was not a significant predictor of infant negative behavior (b < .001, SE < .001, p = .138) or of maternal negative behavior (b < .001, SE < .001, p = .197). Further, maternal negative behavior was not a significant predictor of infant negative behavior in the reunion (b = -.126, SE = .075, p =.095). Moreover, tests for total and indirect effects indicated no significance (all p > .05). The same applied for the mediation analysis considering all covariates (all p > .05).

3.8 Declarations

3.8.1 Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg and the Ethics Committee of the Medical Association of Rhineland-Palatinate and conducted in accordance with the Declaration of Helsinki. All mothers provided written informed consent prior to enrolment in the study.

3.8.2 Consent for publication

All mothers participating in the still-face situation gave their written consent to the filming and later pseudonymized analyses.

3.8.3 Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

3.8.4 Competing interests

Michael Deuschle and his research group received speaker and consulting fees from BristolMyers Squibb, Lundbeck Otsuka Pharma, and Servier. Michael Deuschle is a national coordinator and principal investigator of phase II and III trials for Lilly Pharma and Roche. The remaining co-authors have no competing interests to declare.

3.8.5 Funding

The study was supported by a grant of the ERA-Net Neuron and by the Dietmar-Hopp-Foundation.

3.8.6 Authors' contributions

Each author made a substantial contribution to the conception and design of the study, and to the interpretation of the data. ML, MD and MR conceptualized and designed the study. MG, IACW, VP, and BS recruited the pregnant mothers and collected the biomaterials and behavioral data. JS performed ICEP coding on still-face videos. BK and MG calculated the early life stress scores. IACW, CJ, MD and ML calculated and interpreted the behavioral data. IACW was responsible for the preparation of the manuscript. All authors read and approved the final manuscript.

3.8.7 Acknowledgements

The authors thank the midwives, physicians and the families for their participation. A special thank-you to Henrike Otto, who helped to gather the data.

4 GENERAL DISCUSSION

4.1 Summary of the present findings

In **Study I**, in which the first play episode of the still-face paradigm was investigated, the findings provided evidence of an impact of psychosocial prenatal stress on mother-infant dyadic behavior during normal mother-infant play. Mother-infant dyads with more psychosocial PS in pregnancy showed significantly more positive dyadic behavior (i.e., IposMpos) than did the less stressed dyads. The same was found for perceived maternal prenatal stress, but the effect vanished when analyses were computed taking into account all covariates. Thus, the evidence was considered as restricted. No other stress index (i.e., psychopathological PS, cortisol decline and cortisol AUCg) reached significance in predicting mother-infant dyadic play behavior. Furthermore, mediation analyses were computed to examine the possibility that the relationship between PS and infant behavior might be mediated by maternal behavior, but failed to show a significant mediation effect. Moreover, no direct or total effect reached significance (Wolf et al., 2017).

In **Study II**, the aim was to elucidate the impact of prenatal stress on behavior during the still-face paradigm. The mother-infant dyadic behavior in the first play episode of the still-face paradigm was compared with that in the reunion episode following the stressful still-face episode. The findings provided evidence for the "still-face" and "carry-over" effect, with mother-infant dyads in both the high- and low-stress groups showing decreasing positive and increasing negative dyadic behavior in the reunion episode. Furthermore, mother-infant dyads with higher psychosocial prenatal stress showed significantly more positive dyadic behavior (i.e., IposMpos) in the first play episode, but not in the reunion episode. Here, the positive behavior of the dyads with high prenatal stress decreased to approximately the same level as the dyads with low prenatal stress.

Significant results also emerged for physiological stress dimensions: Mother-infant dyads with a prenatally flat diurnal cortisol decline and low diurnal cortisol AUCg levels showed a significant, distinctive increase in negative dyadic behavior (i.e., IproMneg) in the reunion episode. As in Study I, the analyses showed that maternal behavior was not a significant mediator between prenatal stress and infant behavior (Wolf et al., 2018).

The findings of Studies I and II support the "stress inoculation" theories, according to which more psychosocial prenatal stress is related to more positive mother-infant dyadic behavior, and a steeper cortisol decline and higher cortisol AUCg levels are related to less negative dyadic behavior.

4.2 Integration into previous research

One big advantage of the present prospective studies lay in the availability of longitudinal data, covering the time span from late pregnancy until six months postpartum. A second advantage was the investigation of both psychological and physiological stress indices in mothers-to-be. A third strength was the assessment of behavioral data via behavioral observations of the mother-child interactions, instead of exploring mother and infant characteristics in the maternal assessment or via questionnaires. As previous studies found that mothers tend to describe child behavior, the mother-infant relationship and child temperament according to their current mood, a critical range of possible bias in maternal evaluation can be assumed, especially in mothers with symptoms of depression or anxiety (Atella, DiPietro, Smith, & James-Roberts, 2003; Pauli-Pott, Ries-Hahn, Kupfer, & Beckmann, 1999). Contrary to the vast amount of findings reporting an impairing influence of prenatal stress on the infant, as well as research on mother-infant behavior (Angelidou et al., 2012; Davis & Sandman, 2012; Gardener et al., 2009; Glover, 2011; Juruena, 2014), the present results showed higher psychosocial PS to be related to more positive mother-infant dyadic behavior. For example, de Weerth and colleagues (2003) reported that more negative facial expressions, crying, and fussing in 5-month-old infants during routine mother-child interaction were related to higher prenatal maternal cortisol levels at the end of pregnancy. However, it should be noted that de Weerth et al. collected their data from a filmed routine mother-infant interaction (e.g. a bathing situation) rather than from a standardized paradigm such as the still-face paradigm as employed in the present study. Nevertheless, like in our study, the authors recruited their participants from a healthy, non-inpatient population, suggesting a normal range of maternal stress, comparable to that found in our studies. In terms of the power of the sample, our investigation of 164 mothers-infant dyads seems to be more powerful than the sample investigated by de Weerth and colleagues, which comprised 17 mothers and their infants. Nevertheless, other studies investigating prenatal psychopathological stress and infant behavior also reported negative associations between prenatal stress and positive mother-infant behavior. In view of the previously reported impairing associations between prenatal stress and infant behavior, the present results should be interpreted with caution. In particular, research focusing on maternal depression found more negative matching synchrony states in mother-infant behavior (Field et al., 1990), as well as generally more negative affective behavior during mother-infant interaction (Campbell, Cohn, & Meyers, 1995; Cohn et al., 1990). Moreover, Field and colleagues (1994) reported that infants' development and emotional regulation capacities was more strongly impaired by parental depression and the resulting emotional unavailability than by physical separation from a parent. In addition, maternal anxiety was found to be related to infant cortisol responses during the still-face procedure (K. A. Grant et al., 2009). Another study reported that maternal prenatal anxiety predicted infant negative emotional reactivity (Nolvi et al., 2016). However, in contrast to objective observations during the still-face paradigm as in the present study, the infant data were obtained by maternal reports, which limits the generalization of the findings/ puts the findings into perspective. Interestingly, in the present analyses, the stress dimension "psychopathological stress" failed to reach significance in the analysis of the first play situation and in the comparison between the first play episode and the reunion episode. This may be attributable to the fact that the present findings rely on a sample of non-inpatient mothers-to-be without extremely high stress, while the previous studies focusing on inpatients or catastrophe-related studies did include such extreme stress (Baibazarova et al., 2013; Reck et al., 2011). Another reason for the discrepant findings might lie in the investigation of mother-infant dyadic behavior instead of infant behavior separately. However, contrary to the assumption that mothers would show as much positive behavior in the reunion episode as in the first play episode, regardless of the infant affect, which should have been represented through the infant protesting-mother positive dyad, no significant associations with prenatal psychopathological stress were found.

Notably, the stress dimension "perceived stress" also failed to show significant results, with the exception of the first play episode. The significant effect disappeared after including additional covariates in the ANCOVA analyses, which puts the significant effect into perspective. Previous research found perceived stress to be a difficult factor to investigate due to conceptual and methodological difficulties and its relation to other risk factors or life events (Kingston, Heaman, Fell, Dzakpasu, & Chalmers, 2012). Only a small number of previous studies have focused on perceived stress and infant behavior. For example, negative infant reactivity was found to be predicted by prenatal maternal perceived stress (Huizink et al., 2002). However, other findings, for example by Leung and colleagues (Leung et al., 2010), who reported a positive association between prenatal perceived stress and infant stress reactivity in response to a frustration task, cannot be compared to the present findings due to the postnatal data assessment. Another study explored prenatal perceived stress after rocket attacks, which is related more to traumatic experiences rather than the normal range of stress and daily hassles assessed in the present sample (Wainstock, Anteby, Glasser, Shoham-Vardi, & Lerner-Geva, 2013). Nevertheless, our results seem to be along the same lines as the findings of Austin and colleagues, reporting also no association between perceived stress and infant temperament when investigating maternal depression and anxiety simultaneously (Austin, Hadzi-Pavlovic, Leader, Saint, & Parker, 2005). In methodological terms, previous studies have often assessed perceived stress in relation to life events, while the present model categorizes life events into the “psychosocial stress” dimension. In sum in the presented analyses, no significant findings emerged for perceived stress. Moreover, to date, few studies have focused on maternal perceived stress during pregnancy and child behavior. Thus, further perceived stress models and future research are warranted in this regard.

By contrast, the dimension “psychosocial stress” (which was defined by maternal life events, perceived social support, current relationship situation, educational level and living circumstances such as the current job situation and household income) showed significant associations with positive mother-infant dyadic behavior, both in the first play episode and in the stress group x play episode interaction. The decrease in positive behavior in the reunion episode was hypothesized beforehand to be a result of the still-face effect, and was reported as a “carry-over effect” in previous studies (Mesman et al., 2009). Yet, for the psychosocially stressed group of mothers, the still-face episode might be especially challenging, resulting in a diminished ability to resume the play situation. Furthermore, the results only provide a brief insight into the mother-infant interaction, and leave scope for speculations about the everyday mutual engagement. If a mother wanted to show her best maternal caretaking qualities and thus showed more positive behavior than usual, her infant might have been positively surprised, potentially also resulting in more positive behavior of the infant in response to the high quality and quantity of positive stimuli. Moreover, mothers with high psychosocial prenatal stress might be prone to react more strongly to additional current stress, leading to the decline in positive mother-infant behavior.

Contrary findings of associations between psychosocial maternal stress during pregnancy and later higher insulin responses in young adults may suggest that the present findings should be treated with caution and tested in longitudinal studies (Entringer et al., 2009).

Furthermore, higher prenatal HPA axis activity (i.e. AUCg) was found to be related to less negative dyadic mother-infant behavior. This is in contrast to previous studies, which reported that higher prenatal maternal cortisol was associated with more infant crying and fussing during a bath session (de Weerth et al., 2003). In addition, a previous study showed that the prenatal maternal HPA axis activity predicted the infants’ HPA response to an acute stressor at the age of 17 months (O'Connor, Bergman, Sarkar, & Glover, 2013). As the infant sample in the latter study was older, there is room for speculation about the possibility of an effect onset in older infants. Nevertheless, our findings are in line with previous research, reporting ab association of elevated prenatal HPA axis activity in late pregnancy with accelerated infant development, but no such association in early pregnancy (Davis & Sandman, 2010). Contrary findings of an impairing influence of higher prenatal cortisol levels on infant development (Huizink et al., 2003) emphasize the need for further research on prenatal cortisol exposure, including different timing during gestation and possible sensitive developmental windows.

Concerning the maternal behavior, the assumption that mothers contribute to the training of their infants' emotion regulation capacities in everyday interaction (Beeghly & Tronick, 2011; DiCorcia & Tronick, 2011) led to the investigation of maternal behavior as a possible moderating factor between prenatal stress and mother-infant dyadic behavior. However, mediation analyses revealed no significant moderating effect of maternal behavior. Therefore, a probable redefinition of maternal comforting and soothing behavior, as well as the separate investigation thereof in future studies, would contribute to the exploration of this hypothesized moderating factor.

In terms of further influencing factors of mother-infant interaction, earlier research reported that infant temperament might also be shaped by maternal cortisol levels during late pregnancy, with a negative impact of high prenatal cortisol levels (de Weerth et al., 2003). This defines infant temperament itself as a potential outcome of prenatal stress exposure, or at least leads to the assumption that it can interact with risk status (Tarabulsy et al., 2003). In turn, this leaves the problem of which problem came first and which is acting as a moderator. Moreover, it has been suggested that infants might influence the maternal behavior to a greater degree than vice versa, depending on the infant's contribution and responsiveness (Van Egeren et al., 2001). In sum, human studies bring with them a vast amount of possible interdependencies between various influencing factors, which can hardly all be controlled for.

Furthermore, the highly standardized still-face paradigm was chosen in order to assess behavioral data, as well as the ICEP coding system due to its specificity, having been developed to identify emerging behavior during the still-face paradigm (Mesman et al., 2009; Reck et al., 2011; Tronick et al., 2005). Due to the relevance of dyadic interactive processes in infant development, we chose to investigate mother-infant dyadic behavior rather than maternal and infant behavior separately. Previous authors defined such processes as learning processes, as well as an indicator of early development in the first months of life (Blehar et al., 1977; Gekoski et al., 1983). The definition of the present mother-infant dyadic behavior was oriented to the construct of "matching states" as defined by Tronick and Cohn (Tronick & Cohn, 1989). Many studies have tried to focus on the overall amount of a behavioral category, such as "infant positive behavior" (Mesman, Linting, Joosen, Bakermans-Kranenburg, & van Ijzendoorn, 2013). However, few studies have examined the amount of time for which the mother-infant dyad shows a certain mutual behavior, such as Tronick and Cohn's "matching states" (Müller et al., 2015; Tronick & Cohn, 1989). Additionally, the analysis of the quantitative amount of observable behavior according to the ICEP coding system constitutes a clearly interpretable measurement without the need for any artificial categorical systems. Contrary to previous research (Pesonen et al., 2005), the current study did not include maternal perception of the child temperament assessed via the Infant Behavior Questionnaire (IBQ). Instead, the unbiased dyadic behavioral coding by a certified ICEP coder was preferred. According to the study design, mother-infant dyadic behavior categories were chosen as the outcome variable, as previous studies considered mother-infant interaction as a learning process and a marker of effective emotion regulation, as well as an important objective of infant development in the first year of life (Blehar et al., 1977; Conradt & Ablow, 2010; Gekoski et al., 1983). Therefore, mother-infant interaction was not considered as a moderating factor for other developmental outcome measures. Furthermore, previous research found that mother-infant interaction depended both on the infant's contribution and responsiveness and on maternal availability, sensitivity and responsiveness, suggesting the need to control for these potential influencing factors in future studies (Braungart-Rieker, Garwood, Powers, & Wang, 2001; Van Egeren et al., 2001). In particular, Grant and colleagues demonstrated a moderating role of maternal sensitivity between prenatal stress and infant reactivity during the still-face procedure (K.-A. Grant, McMahon, Reilly, & Austin, 2010).

Concerning the presented theories on stress experience and stress impact, our findings are in line with stress inoculation models. So far, inoculation hypotheses have been explained by "hit" theories, but have not been empirically tested up to now. Compared to the sensitization models, which have long been a focus of research, the newer approaches need to be investigated in extended future research. The present study contributes to match-/mismatch theories, or the PAR model (see Chapter 1.7.3). For example, in their study on the impact of early stress exposure in rats, Chaby and colleagues (2015) emphasized the importance of taking into account the impact of context on behavior and performance, suggesting dependencies of the context in the framework of the Yerkes-Dodson law. The present study suggests first, the possibility of a beneficial influence of prenatal stress if the stressor is moderate, and non-traumatic, and second, that the beneficial influence on development seen in the first months might also be a precursor of later negative outcomes, predicted in the same line by match-/mismatch hypotheses or the PAR model.

4.3 Methodological limitations and implications for further research

Mother-infant dyadic behavior was assessed according to percentage of time in which mother and infant showed the respective behavior we had established for the three dyads (e.g., both positive, infant protesting-mother positive, infant protesting-mother negative). While most previous studies focused on the overall amount of a behavioral category, only a small number of studies have investigated the amount of a certain mutual behavior within the mother-infant dyad. We chose to investigate dyadic behavior due to the targeted manner in which it can to describe what happens between mother and child. The definition of the dyadic behavior categories was oriented to the “matching states”, which represent a part of the “synchronous behavior” construct and were reported in previous literature (Tronick & Cohn, 1989). Although “synchrony” has been assessed in various ways by past research, Leclère et al. (2014) proposed in their review to assess “synchrony” in behavior according to frequencies, mean durations, latencies of specific behavior relations, proportions, percentage of time gazing at each other, or correlations between mothers’ and infants’ behaviors. This restricts the comparability between different studies, but leads to the assumption that the present study also addresses the research field of synchronous behavior. Furthermore, the present approach of analyzing the quantitative amount of observable dyadic behavior was realized by using the behavioral coding according to Tronick’s “Infant and Caregiver Engagement Phases” (ICEP), which is a clearly interpretable measurement without the need for any artificial categorical systems. Other authors also included the maternal perception of the infant behavior, for example by using the Infant Behavior Questionnaire (IBQ) (Pesonen et al., 2005).

Particularly with respect to interdependencies of mother-infant behavior, one might suggest that both mother and infant are capable of shaping the dyadic behavior. This gives rise to the assumption that infant behavior is not completely independent of the mother’s behavior and vice versa. Furthermore, it should be mentioned that the infant’s temperament might impact the outcome of infant behavior in the still-face paradigm. At the same time, previous findings revealed that high maternal cortisol levels in pregnancy were associated with a negative impact on infant temperament (de Weerth et al., 2003), suggesting infant temperament as both an outcome of prenatal stress exposure and as a possible factor in the interaction with the risk status (Tarabulsy et al., 2003). This leads to a chicken-and-egg problem for the evaluation of infant temperament and its impact on current behavior. Interestingly, Van Egeren and colleagues (2001) hypothesized that infants have a greater degree of influence over the maternal behavior than vice versa. This suggestion further compounds the difficulty of correctly interpreting mother-infant behavior while considering all possible influencing or moderating factors.

The present study relies solely on the unbiased dyadic behavioral coding by a certified ICEP coder. However, the operationalization of the dyadic behavior leads to a deterministic dependency of maternal behavior and mother-infant behavior, and leaves no possibility to conduct a mediation analysis with maternal behavior as supposed mediator and maternal-infant dyadic behavior as outcome variable. The computed mediation analyses investigated the possibility that maternal positive behavior is a mediator of the relationship between psychosocial PS and infant behavior, and showed no significant mediation effects. Future research should include other maternal parameters, such as sensitivity and responsiveness, in mediation analyses.

Participation in the still-face paradigm was voluntary, and the mothers were able to choose whether they wished to be filmed at their homes or in the lab. This led to 73.2% (120 dyads) of the still-face procedures being filmed in participants' homes and 26.8% (44 mother-infant dyads) in the lab, distributed equally across the two extreme groups (i.e. high and low general adversity group) of the video sample. This was not taken into account as a potential influencing factor in the first study. Consequently, to avoid missing a possibly important influencing factor, further analyses were carried out before the second study in order to test the influence of the video setting. The analyses revealed no significant difference between the lab and home group for IposMpos dyadic behavior (first play phase: $F(1,161) = 1.563$; $p = .213$; Reunion play: $F(1,161) = .779$; $p = .379$), but did show significant differences in IproMpos (first play phase: $F(1,161) = 16.697$; $p < .001$; reunion play: $F(1,161) = 5.188$; $p = .024$) and IproMneg dyadic behavior (first play phase: $F(1,161) = 6.487$; $p = .012$; reunion play: $F(1,161) = 9.902$; $p = .002$). Therefore, the factor of video setting (i.e. lab vs. home) was added to the RM-ANCOVA as a further control variable, as well as in the post-hoc tests and mediation analyses.

The present studies focused only on the first play episode and the reunion episode but not on the still-face episode itself as the specific characteristics of the still-face episode make it impossible to investigate dyadic behavior. The still-face episode requires the mother-infant dyadic behavior to be interrupted, with the mother sitting quietly in front of the infant, not looking at or touching him/her. Many previous studies have investigated the still-face episode, which is the essential part of the paradigm. The evaluation during the still-face part itself remains a task for future research. In this respect, the investigation of infants' signs of responsiveness could be of interest. As some research groups used their own coding scheme to define responsiveness (Bigelow & Power, 2014; Braungart-Rieker, Garwood, Powers, & Wang, 2001), a general consensus regarding responsiveness coding seems to be currently lacking. Accordingly, there are problems in terms of direct comparability of studies and the differing ways in which responsiveness is conceptualized.

Further, to answer the question regarding infant behavior as a potential outcome variable, the present conceptualization was based on the assumption that mother-infant behavior can be seen as a milestone in the first months of the infant's development, as discussed in chapter 4.2. Nevertheless, we conducted several one-way ANCOVAs to investigate the possible influence of maternal behavior (DV: IposMpos dyad, IV: prenatal stress (psychopathological PS, perceived PS, and psychosocial PS separately), covariates: maternal age, gender, parity; considering maternal behavior (negative and neutral) as additional covariate). The results confirmed the significant effect of psychosocial PS ($F(1,155) = 10.622$, $p = .001$, partial $\eta^2 = .064$) on IposMpos. Moreover, when controlled for maternal behavior, perceived PS had a significant effect on IposMpos ($F(1,155) = 5.727$, $p = .018$, partial $\eta^2 = .036$). However, no significant effect emerged for psychopathological PS ($p > .05$). Furthermore, in all three ANCOVAS, no maternal behavior covariate showed a significant effect. As already mentioned, however, the present construct of mother-infant behavior results in a deterministic dependency of dyadic behavior and maternal behavior. Therefore, the findings of these analyses were considered to be restricted. Here too, an independent measurement of maternal behavior (such as the suggested maternal sensitivity), as seen for example in previous research (Braungart-Rieker et al., 2001), would be highly advantageous for future research.

The conceptualization of the stress measures, with a distinction divided between psychological and psychophysiological stress, and within these a subdivision into two extreme groups (i.e., high and low), was chosen in order to achieve more distinct differences in the behavior analyses. The psychological stress dimension, with its division into psychopathological, perceived and psychosocial stress, was assessed using data from the maternal prenatal assessment and questionnaires. Therefore, the psychological stress measures might be more prone to bias by maternal evaluation than the physiological stress measures, which were assessed via the HPA axis activity. Despite the high correlation between the psychological stress dimensions, they were considered as discrete dimensions which are able to influence each other. Thus, the saliva samples for the measurement of the HPA axis activity were collected by the mothers, and although they were provided with printed instructions, incorrect collection could not be ruled out. Therefore, we chose a strict limit for outliers, as seen in past research (Hellgren et al., 2013), meaning that several participants were excluded from our original sample. Moreover, we decided to investigate only the two extreme groups of the 100 most or least psychologically stressed participants, resulting in a sample of 200 mother-infant dyads for the investigation. Due to technical problems, such as lack of sound or early ending, several videos could not be taken into account in the current sample.

Notably, despite the high intercorrelations of the stress dimensions, maternal prenatal perceived stress did not show any significant effect, either in the first play episode, or in the reunion episode. A possible reason for this might be a difference between the perceived stress dimension or estimated stress level construct and the HPA axis activity measures. Nevertheless, in previous research, maternal perceived stress during pregnancy was found to be moderately strongly associated with cortisol measures (La Marca-Ghaemmaghami & Ehlert, 2015). Moreover, the authors pointed out the importance of perceived emotional support for the perception of maternal stress and 11ß-HSD2 activity. This also raises the question of which factors contribute to the generation of the maternal perceived stress, and if they do not contribute to the body's physiological stress response, how they can be evaluated. Possible influencing factors might be thinking styles, coping abilities and evaluation, as well as problem-solving strategies. These factors are known to be stand-alone psychological constructs, and they are linked to numerous other human perceptions and behavior, but not exclusively to the stress perception. By contrast, psychopathological stress, if defined based on the diagnosis of current psychopathological disorders as in the present study, can be assumed to be a stable and comparable construct. The present definition of psychosocial stress also comprised comparable features, such as the net income or the size of current living space.

When evaluating the concept of three stress dimensions, it has to be taken into account that the investigated stress factors are only measured according to their definition. This gives rise to the question of whether three highly correlated stress dimensions should be investigated separately or whether a global stress factor would present a broader picture. We decided on the threefold stress axes due to their differing manifestations. For example, while psychopathological stress, such as current depression, might correlate with social status, this is not necessarily the case. The same applies for the correlation of the two axes with perceived stress.

Given that postnatal stress can also be an important factor influencing mother-infant behavior, we added the Perceived Stress Scale (PSS), administered six months after birth, as a covariate in the computed ANCOVAs and mediation analyses. As prenatal stress (i.e. psychosocial stress, cortisol AUCg, cortisol decline) still reached significance when considering current postnatal stress, the results of the preliminary ANCOVAs were confirmed.

Concerning the classification of stressors, the present study distinguished between the prenatal, perinatal and postnatal period. However, some types of stressors may be difficult to classify into the given episodes. For example, psychosocial maternal PS (such as income or living space) does not end with birth. Further, new constellations of stressors can arise in the perinatal period, which tend to be investigated in the postnatal period, such as birth complications impacting the later infant’s health. In general, as underlined by previous literature, the key factor for sensitive periods during pregnancy is time (O'Connor, 2003). Little is known about the exact time windows of fetal development and their possible relation to beneficial or impairing effects, in interaction with cortisol exposure. To define all of these stressors as early life stress seems to be a good solution for the incorporation of a broad range of possible factors. Nevertheless, concerning the investigation of sensitive periods and their vulnerability to influence from particular stressors, future research needs to be as clear and detailed as possible investigating the onset and offset of stressors.

Regarding the HPA system activity, we chose the diurnal AUCg levels as well as the diurnal cortisol decline as markers of prenatal stress. In general, previous research termed impairing, high amounts of maternal HPA levels as “adverse fetal environment” (Seckl & Meaney, 2004; Welberg & Seckl, 2001). The cortisol decline provides information about the diurnal process of the maternal HPA response, which itself was shown to be associated with fetal programming (Benediktsson et al., 1997). Moreover, past research acknowledged the pattern of the diurnal cortisol decline as an important indicator of the influence of maternal psychology on the function of the HPA axis (Kivlighan et al., 2008). As several studies reported that the cortisol levels are generally heightened in late pregnancy, the separate investigation of morning or evening cortisol levels was seen as favorable than the measurement of the diurnal cortisol decline. As pointed out by Obel and colleagues (Obel et al., 2005), the effect of prenatal stress on the HPA axis response would likely be apparent through elevated evening cortisol levels, resulting in a flatter diurnal cortisol decline. This is supported by findings from samples of depressed pregnant women (O'Connor et al., 2014) and women with high stress during pregnancy (Suglia et al., 2010), which reported associations with blunted prenatal diurnal cortisol decline. A further limitation of the present study lies in the lack of infant cortisol parameters before and after the still-face paradigm. It would have been useful to investigate the relationship between these measures in the context of prenatal stress and the different still-face episodes.

Concerning the statistical analyses in general, as the present work aimed to analyze the current behavioral data using one-way ANCOVAs and RM-ANCOVAS, the division into high-and low-stress groups as well as high- and low-HPA axis activity groups was highly beneficial. Furthermore, by conducting analyses of covariance, we were able to draw conclusions regarding the influencing factor of prenatal stress, rather than conclusions regarding associations, as would be gained from regression models. Moreover, repeated measures ANCOVAs allowed the comparison of the two play episodes. The selected covariates, such as parity and maternal age, were chosen due to their ability to impact the mother-infant dyad and due to their inclusion in previous studies (Kivlighan et al., 2008; Vleugels, Eling, Rolland, & Graaf, 1986). As there is a vast amount of possible influencing factors, it is not possible to take all of them into account in a human study. However, as Schneider (Schneider, 1992) already criticized, human studies are prone to methodological problems, such as failure to control for postnatal infant variables or the failure to identify or control for general mediating or moderating factors, which may lead to inconsistencies. Nevertheless, the investigation of human mother-infant dyadic behavior cannot be replaced by only investigating animal interactive behavior. Therefore, although it is not possible to control for every postnatal influencing factor, human research that includes a huge sample of participants, and uses a clearly defined paradigm and preferably an observation under laboratory conditions, would be best placed to provide insights into interdependencies.

4.4 Conclusion and clinical implications

The present study presents results on the possible influence of moderate prenatal stress (as opposed to traumatic stressors) on the mother-infant dyadic behavior at six months after birth. Contrary to a vast number of previous findings, the present study reported higher prenatal stress levels to be associated with more positive mother-infant behavior. To seek an answer to the question of why some individuals seem to be better at handling adverse situations, life events or disease, the research on resilience factors has attempted to elucidate the current state of art. Compared to previous research, which defined “resilience” as a consequence of exposure to stress instead of the common definition of resilience as a psychological trait (Troy & Mauss, 2011), the definition of the “inoculation” theories seem to go along the same lines. The authors speculate that better emotion regulation abilities are the key factor of resilience. However, it has to be kept in mind that this previous research focused on adults rather than young infants, and the findings showed beneficial influences of cognitive emotion regulation capacities on coping with major stressors, which cannot be assumed for children in their first months of life. Other research reported increased amygdala reactivity following stress, which possibly contributes to vulnerability as well as to resilience factors (Yamamoto et al., 2017). Nevertheless, this notion can also be relevant for the mother-child interaction, as the focus did not lie solely on concrete maternal behavior relevant for children's emotion regulation, such as soothing. Furthermore, the observation of such maternal behavior would require long-term investigations of mother-infant dyads over longer play phases. Furthermore, according to Yamamoto and colleagues, in individuals with ELS experience, resilience might be fostered by the reactivation of the amygdala, such as by practicing mindfulness meditation, as reported by previous research (Desbordes et al., 2012; Yamamoto et al., 2017).

Research in rodents suggested that the antecedents of resilience may lie in the alteration of epigenetic mechanisms in early developmental stages (Roth & David Sweatt, 2011). The authors proposed that the current research state of the art indicates similar mechanisms in humans.

Despite the lack of results indicating an impairing impact of prenatal stress on the mother-infant dyad, the vast body of research reporting contrary results should not be neglected. Therefore, the present thesis underlines the need for further research on the concrete mechanisms of ELS and its impact in order to create possible therapy programs or mother-infant training interventions. For example, concerning the aforementioned maternal abilities of sensitive and responsive behavior towards the infant, preventive programs for mothers who are thought to experience problems with their own emotion regulation skills, such as the "Parenting Skills for Mothers with Borderline Personality Disorder", have been reported to be useful interventions (Renneberg & Rosenbach, 2016). As other researchers have already mentioned, in the developing world, mothers may be exposed to harsher levels of stress (Talge et al., 2007); thus, a more general preventive program, starting with prenatal classes, might sensitize the mothers to possible problems following high stress (Rieger & Heaman, 2016). With regard to a general reduction of prenatal stress, previous studies found a beneficial effect of meditation practice on psychosocial stress and stress-induced physiological reactions such as the immune response (Pace et al., 2009). Moreover, possible factors contributing to stress perception and HPA axis activity, such as perceived emotional support (La Marca-Ghaemmaghami & Ehlert, 2015), might constitute a further focus, for example of support groups or voluntary "godmother" programs for pregnant women who do not have a sustainable emotional support network.

Although the study at hand presents results suggesting a beneficial influence of prenatal stress on the mother-infant dyadic behavior, the intention is not to support a conclusion that mothers should experience stress in pregnancy. With regard to the match-/mismatch models, it should be kept in mind that benefits in one area might be at the expense of diseases in another area later on, if no match is possible.

On the other hand, with the prediction of harsher circumstances for future mothers, the present findings can also be seen as a small, reassuring hint that not all prenatal stress results in impairing child outcome.

Likewise, as previous authors reported that methylation patterns might be reversed by positive parenting or beneficial mother-infant interaction, later mother-infant training can contribute to changing methylation patterns and preventing, for example, a possible disease onset in the child later in life (Haselbeck et al., 2013; McGowan & Szyf, 2010).

Despite the limitations of the presented study, the results provide a valuable insight into mother-child dyadic behavior and its relations to prenatal stress. Future work in this research area should also compare longitudinal data from mother-infant interaction in different development stages, such as early infancy, kindergarten, school age, and puberty, focusing on possible long-term implications.

5 SUMMARY

Early life stress is known to influence mothers and consequently also the infant pre-, peri-, and postnatally. Both stress sensitization and inoculation theories have speculated about the conflicting previous findings of beneficial as well as impairing influences of early life stress. Findings of an impact on infant development, behavior and later vulnerability for cognitive and emotional problems, physical diseases and mental disorders, suggested the need to identify possible pathways between early life stress and infant outcome. Suggested underlying processes, such as fetal programming, were discussed. The present thesis focused on the possible impact of prenatal maternal stress on mother-infant dyadic behavior in a standardized observation paradigm, i.e. the still-face paradigm. Study I aimed to illuminate the prospective influence of psychological and physiological stress during pregnancy on mother-infant dyadic behavior in the first play episode of the still-face paradigm. In Study II, both the first play episode and the reunion episode were investigated.

In **Study I**, the first play episode of the still-face paradigm was investigated. The findings provided evidence of an impact of psychosocial prenatal stress on mother-infant dyadic behavior during the normal mother-infant play, as it was expected for the first play episode. Mother-infant dyads with more psychosocial PS in pregnancy showed significantly more positive dyadic behavior then the less stressed dyads. The same was found for perceived maternal prenatal stress, although the effect vanished when analyses were conducted including all covariates. Hence, the findings were considered as providing only restricted evidence. No other stress index (i.e., psychopathological PS, cortisol decline and cortisol AuCg) reached significance in predicting mother-infant dyadic play behavior. In Study II, the impact of prenatal stress on mother-infant dyadic behavior in both play situations of the still-face paradigm was investigated. The dyadic behavior in the first play episode was compared with that in the reunion episode. The results provided evidence for the “still-face” and “carry-over” effect, with mother-infant dyads in both the high- and low-stress groups showing decreasing positive and increasing negative dyadic behavior in the reunion episode. Here too, mother-infant dyads with higher psychosocial prenatal stress showed significantly more positive dyadic behavior in the first play episode, but not in the reunion episode. In the latter episode, the positive behavior of the dyads with high prenatal stress decreased to approximately the same level as that of the dyads with low stress.

In **Study II**, significant results emerged for physiological stress dimensions, with mother-infant dyads with a prenatally flat diurnal cortisol decline and low diurnal cortisol

AUCg levels showing a distinctive, significant increase in negative dyadic behavior in the reunion episode. Mediation analyses run in both studies showed that maternal behavior was not a significant mediator between prenatal stress and infant behavior. The present findings contribute to inoculation theories on the impact of stress. Nevertheless, both studies provide merely a glimpse into the complex relationship of early life stress factors, maternal and environmental factors, and the infant's development. Taken together, given the vast amount of studies reporting an impairing impact of prenatal stress on the infant, the present results should be interpreted with caution. The results add further support to the idea of individual resilience factors, suggesting that some individuals are not influenced by stressors or even benefit from them. Future research should focus on the underlying mechanisms, such as early programming, sensitive time periods in infant development, as well as possible influencing factors, in order to contribute to the explaining the mixed results, and to inform the creation of preventive programs for mothers and infants.

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