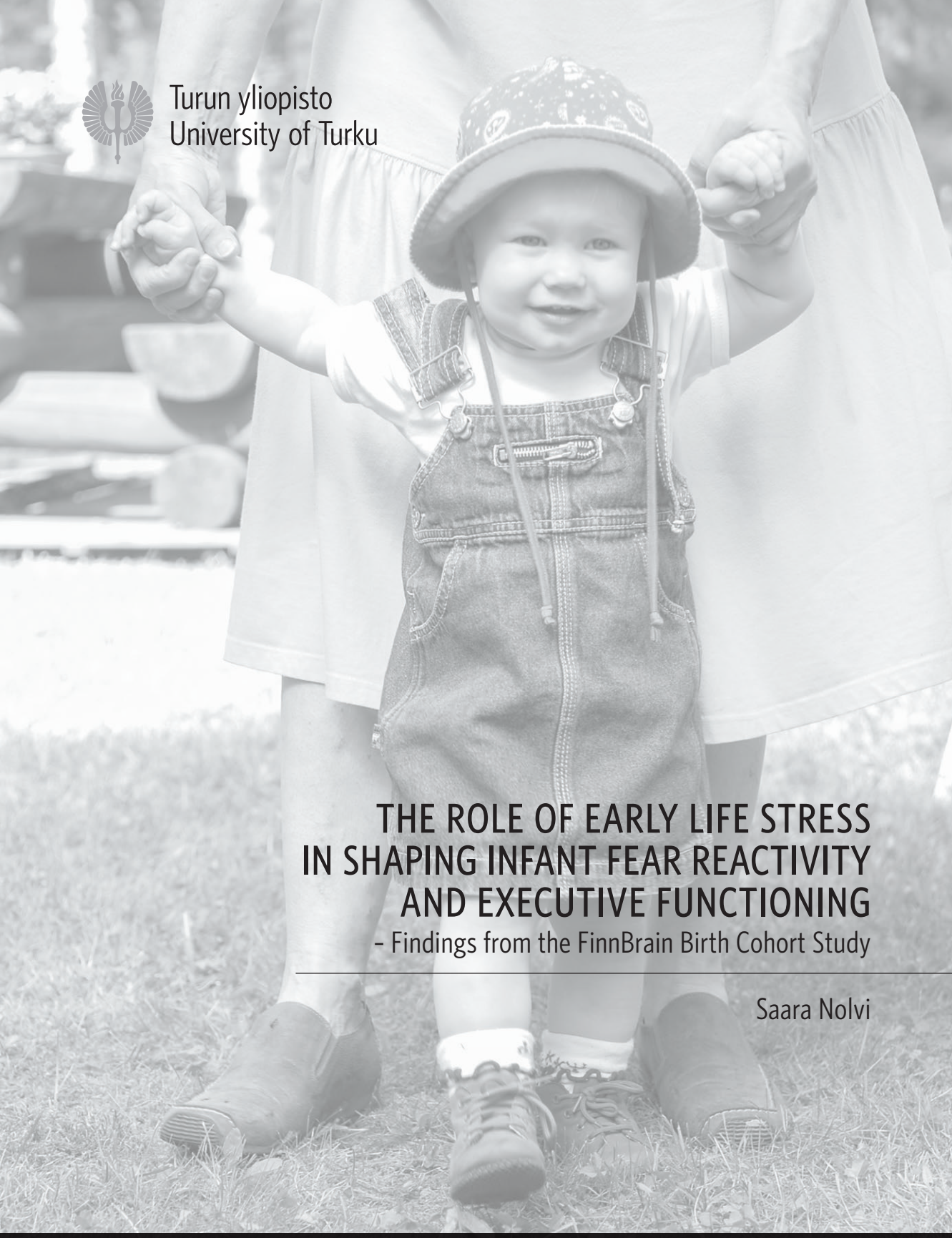

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THE ROLE OF EARLY LIFE STRESS IN SHAPING INFANT FEAR REACTIVITY AND EXECUTIVE FUNCTIONING

– Findings from the FinnBrain Birth Cohort Study

Saara Nolvi

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Tiedättehän, että jos jotakuta säikäyttää kovin usein, hän muuttuu helposti näkymättömäksi.

– Tove Jansson

The wise adapt themselves to circumstances, as water moulds itself to pitcher.

– Chinese Proverb

ABSTRACT

Saara Nolvi

The Role of Early Life Stress in Shaping Infant Fear Reactivity and Executive Functioning – Findings from the FinnBrain Birth Cohort Study

University of Turku, Faculty of Medicine, Institute of Clinical Medicine, Department of Child Psychiatry, Doctoral Programme in Clinical Research, Turku Brain and Mind Center, the FinnBrain Birth Cohort Study

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Early life stress (ELS) measured as the exposure to pre- and postnatal maternal self-reported stress and glucocorticoids reportedly predicts higher child negative emotional reactivity and problems in self-regulation and cognition, including executive functioning (EF). However, to date, there is little research available about the independent effects of maternal pre- and postnatal stress and milk cortisol on infant fear reactivity and EF and their moderation by infant sex.

The aim of this study was to examine the independent effects of pre- and postnatal stress exposure on infant fear reactivity and EF. The study sample comprised 282 (Study I), 391 (Study II), 65 (Study III) and 214 (Study IV) mother-infant dyads from the FinnBrain Birth Cohort Study. The influence of maternal self-reported anxiety and depressive symptoms and the trajectory of symptoms and milk cortisol on infant fear reactivity at 6 and 8 months was examined in Studies I, II and III. The effect of maternal self-reported symptoms on infant EF at 8 months was investigated in Study IV.

The association between maternal self-reported prenatal stress and higher mother-reported infant fear reactivity in both sexes approached significance. Both maternal prenatal stress and milk cortisol concentrations were associated with higher observed fear reactivity in girls. In turn, the trajectory of continuously increasing maternal stress was associated with lower observed fear reactivity in girls. Furthermore, maternal postnatal anxiety predicted poorer EF in girls, while prenatal anxiety predicted a performance difference between girls and boys.

The findings of the present study suggest that different forms of ELS might affect the aspects of infant reactivity and self-regulation, and that these effects are moderated by infant sex.

Keywords: early life stress; prenatal stress; postnatal stress; fetal programming; fear reactivity; self-regulation; executive function; temperament; breast milk cortisol concentration; sex differences

TIIVISTELMÄ

Saara Nolvi

Varhaisen stressialtistuksen yhteydet vauvan pelkoreagoivuuteen ja toiminnanohjauskykyyn – löydöksiä FinnBrain-syntymäkohorttitutkimuksesta

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Lastenpsykiatria, Turun kliininen tohtoriohjelma, Turku Brain and Mind Center, FinnBrain-syntymäkohorttitutkimus

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Varhaisen stressialtistuksen mitattuna altistumisena äidin stressille ja glukokortikoideille on havaittu ennustavan lapsen voimakkaampaa tunnereagointia sekä heikompaa itsesäätelykykyä ja kognitiivista suoriutumista, mukaan lukien toiminnanohjaustaitoja. Kuitenkin raskaudenaikaiselle ja syntymän jälkeiselle stressille sekä rintamaidon kortisolille altistumisen itsenäisiä vaikutuksia vauvan pelkoreagoivuuteen ja toiminnanohjaukseen on tutkittu vain vähän. Lisäksi vain osassa tutkimuksia on otettu huomioon vauvan sukupuolen merkitys stressin ja itsesäätelyn yhteyden muovaajana.

Tämän tutkimuksen tarkoituksena oli selvittää raskaudenaikaisen ja syntymän jälkeisen stressialtistuksen vaikutusta vauvan pelkoreagoivuuteen ja toiminnanohjauskykyyn. Tutkimusotokset sisälsivät 282 (I), 391 (II), 65 (III) ja 214 (IV) FinnBrain-syntymäkohorttitutkimukseen osallistuvaa äiti-lapsiparia. Äidin raportoimien masennus- ja ahdistusoireiden, oireiden kehityskulkujen ja rintamaidon kortisolipitoisuuden yhteyttä vauvan pelkoreagoivuuteen 6 ja 8 kuukauden iässä tutkittiin tutkimuksissa I-III. Äidin oireiden yhteyttä vauvan toiminnanohjauskykyyn 8 kuukauden iässä selvitettiin tutkimuksessa IV.

Äidin raskaudenaikainen oireilu oli lähes merkitsevästi yhteydessä voimakkaampaan äidin arvioimaan vauvan pelkoreagoivuuteen molemmilla sukupuolilla. Äidin raskaudenaikainen oireilu ja rintamaidon kortisolipitoisuus ennustivat voimakkaampaa havainnoitua pelkoreagoivuutta tyttövauvoilla, kun taas seuranta-aikana voimistuva äidin oireilu ennusti tyttöjen keskivertoa vähäisempää pelkoreagoivuutta. Äidin ahdistuneisuus lapsen syntymän jälkeen ennusti tyttöjen heikompaa toiminnanohjauskykyä. Äidin raskaudenaikainen ahdistuneisuus oli lähes merkitsevästi yhteydessä tyttöjen ja poikien suoriutumisen eroon.

Tutkimuksen tulokset tukevat käsitystä erityyppisten varhaisten stressialtistusten vaikutuksesta vauvan tunnereagoivuuteen ja itsesäätelykykyyn. Tulokset viittaavat siihen, että varhaisen stressin ohjelmoivaa vaikutusta ohjaa myös vauvan sukupuoli.

Avainsanat: varhainen stressi; raskaudenaikainen stressi; syntymänjälkeinen stressi; raskaudenaikainen ohjelmoituminen; pelkoreaktiivisuus; itsesäätely, toiminnanohjaus; temperamentti; rintamaidon kortisoli; sukupuolten väliset erot

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ABBREVIATIONS

ELS	Early life stress
EF	Executive functioning
AD/HD	Attention deficit hyperactivity disorder
PFC	Prefrontal cortex
GC	Glucocorticoid
CNS	Central nervous system
HPA	Hypothalamus-pituitary-adrenal (axis)
CRH	Corticotrophin-releasing hormone
ACTH	Adrenocorticotropic hormone
11β-HSD2	11-Betahydroxysteroid dehydrogenase type 2
DNA	Deoxyribonucleic acid
IQ	Intelligence quotient
EPDS	Edinburgh Postnatal Depression Scale
SCL-90	Symptom Checklist -90
PRAQ-R2	Pregnancy Related Anxiety Questionnaire Revised 2
gwk	gestational week
IBQ-R	Infant Behavior Questionnaire Revised
Lab-TAB	Laboratory Temperament Assessment Battery
AFFEX	Affective expression scoring system
A*B*	A-not-B
LGMM	Latent growth mixture modeling
CFI	Confirmatory factor analysis
RMSEA	Root mean square of error of approximation
SRMR	Root mean square residual
GLM	General linear modelling
nlme	Nonlinear and linear mixed effect models
BIC	Bayesian information criterion
AIC	Akaike information criterion
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
CBT	Cognitive-behavioral therapy

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, which are referred to in the text as Studies I-IV. The original publications have been reproduced with the permission of the copyright holders.

I. Nolvi, S., Karlsson, L., Bridgett, D.J., Korja, R., Huizink, A.C., Kataja, E.-L. & Karlsson, H. (2016). Maternal Prenatal Stress and Infant Emotional Reactivity Six Months Postpartum. Journal of Affective Disorders 199, 163-170.

II. Nolvi, S., Bridgett, D.J., Korja, R., Kataja, E.-L., Junttila, N., Karlsson, H. & Karlsson, L. Sensitive Girls? Trajectories of Maternal Pre- and Postnatal Stress, Infant Fear Reactivity and the Moderating Role of Infant Sex. *(Submitted)*

III. Nolvi, S., Uusitupa, H.-M., Bridgett, D.J., Pesonen, H., Aatsinki, A.-K., Kataja, E.-L., Korja, R., Karlsson, H. & Karlsson, L. (2017). Human Milk Cortisol Concentration Predicts Experimentally Induced Infant Fear Reactivity: Moderation by Infant Sex. Development Science 2017 *[Epub ahead of print].* doi: 10.1111/desc.12625

IV. Nolvi, S., Pesonen, H., Bridgett, D.J., Korja, R., Kataja, E.-L., Karlsson, H. & Karlsson, L. (2017). Infant Sex Moderates the Effects of Maternal Pre- and Postnatal Stress on Executive Functioning at 8 Months of Age. Infancy 2017; 1–17 *[Epub ahead of print].* doi: 10.1111/infa.12206

1 INTRODUCTION

The concept of the "Developmental origins of health and disease" is based on the idea that lifespan health and the emergence of disorders or diseases during the lifespan are embedded in an individual's early environment and experience (Barker, 2007; O'Donnell & Meaney, 2017; van den Bergh, 2011; Wadhwa, Buss, Entringer, & Swanson, 2009). Several factors, including early life stress (ELS) exposure, have been identified as potential programmers of later development (e.g. Sandman, Davis, Buss, & Glynn, 2012; van den Bergh, 2011). Early life stress refers to the stress that an individual is exposed to or experiences during the first years of life, including pre- and postnatal periods. For instance, a growing body of literature suggests that pre- and postnatal stress exposure are associated with a later risk for psychiatric symptoms (Bauer et al., 2015; Capron et al., 2015; Kingsbury et al., 2016; Lahti et al., 2017; Pawlby, Hay, Sharp, Waters, & Pariante, 2011; Pearson et al., 2013; Quarini et al., 2016; Van den Bergh et al., 2017).

However, ELS has been linked with outcomes present already during infancy and early childhood. According to recent reviews, ELS predicts higher infant emotional reactivity and less efficient infant self-regulation (Korja, Nolvi, Grant, & McMahon, 2017; Van den Bergh et al., 2017) as well as poorer cognitive development (Kingston, McDonald, Austin, & Tough, 2015; Kingston, Tough, & Whitfield, 2012). These outcomes are mediated by the fronto-limbic brain circuits (Buss et al., 2012; Graham, 2017) that are suggested to be specifically susceptible to stress exposure (Kolb, Harker, Mychasiuk, de Melo, & Gibb, 2017; Posner et al., 2016; Thijssen et al., 2017). In turn, higher negative emotional reactivity and insufficient emotion regulation are risk factors for later disturbances in emotional and behavioral development, such as internalizing symptoms and neuropsychiatric disorders (De Pauw & Mervielde, 2010; Sayal, Heron, Maughan, Rowe, & Ramchandani, 2014). Specifically, early childhood fear reactivity has been identified as a trait that increases the risk for anxiety disorders later in childhood (Clauss, Avery, & Blackford, 2015). Consequently, it is suggested that characteristics of early childhood emotional and cognitive development might mediate the path from ELS to later mental health together with, for instance, genetic dispositions.

However, current evidence is not fully consistent (Bekkhus et al., 2017; Gjerde et al., 2017), and more research is needed about which specific phenotypes of distress and offspring development are related (O'Donnell & Meaney, 2017). Furthermore, an understanding of those developmental trajectories that lead to or protect from later emotional and behavioral disorders is lacking. For instance, it has been suggested that the degree of early life reactivity might also serve as a susceptibility factor defining how vulnerable a child is to early life environmental stress (Pluess

& Belsky, 2011; Slagt, Semon, Deković, & van Aken, 2016). Similarly, it has been suggested that the risk of ELS heightens later in an individual's lifespan upon encountering stressful events and depends on the individual resources to adapt to these events, and for this reason, a moderate level of ELS might be beneficial for later development (Daskalakis, Bagot, Parker, Vinkers, & de Kloet, 2013; Lyons, Parker, & Schatzberg, 2010). Furthermore, an increasing body of work is emerging suggesting that offspring sex moderates the effects of ELS, and that girls and boys may be differentially susceptible to early stress experiences (Glover & Hill, 2012; Sandman, Glynn, & Davis, 2013).

Psychiatric symptoms and disorders are prominent health concerns all over the world (Kessler et al., 2009; Steel et al., 2014). Similarly, psychological distress experienced by the mother is prevalent placing a number of fetuses and infants at risk for ELS (Andersson, Sundström-Poromaa, Wulff, Åström, & Bixo, 2006; Buist, Gotman, & Yonkers, 2011; Sourander, 2016). This underscores the need for a better understanding of ELS influences on early childhood fear and self-regulation and the significance of early self-regulation development for later well-being as well as the moderators of these effects. Such research also has a potential to point out the most relevant targets – and time periods – for prevention and intervention (Glover, 2014).

2 REVIEW OF LITERATURE

2.1 Self-regulation in infancy

Self-regulation refers to the flexibility in regulating emotion, cognition and behavior (Bandura, 1991; Berger, Kofman, Livneh, & Henik, 2007; Gross, 2002; Karoly, 1993). Infant self-regulation knowledge is centered on temperament research studies. In the psychobiological temperament theory proposed by Mary K. Rothbart, two biologically-based, heritable facets of temperament are identified: emotional reactivity and self-regulation/effortful control (Rothbart, 1981; Rothbart & Bates, 2006; Shiner et al., 2012). In the broader perspective, both emotional reactivity and regulation are a part of a larger main concept of self-regulation (Bridgett, Burt, Edwards, & Deater-Deckard, 2015). In this approach, emotional reactivity is referred to as bottom-up self-regulation, and in turn, effortful control is included in the domain of top-down self-regulation. Moreover, effortful control is suggested to overlap with the concept of executive functioning (EF) more commonly used in neuropsychological and neuroscientific research traditions (Bridgett et al., 2015; Nigg, 2017; Zhou, Chen, & Main, 2012). In the current study, both temperament theories and broader self-regulation theory are used in conceptualizing the phenomenon of early self-regulation.

2.1.1 Emotional reactivity

Infant emotional reactivity is characterized by two broad dimensions being negative and positive emotional reactivity (Garstein & Rothbart, 2003; Shiner et al., 2012). Negative reactivity is defined as a tendency to experience and express negative emotions, such as anger, frustration, fear and sadness (Shiner et al., 2012). Negative reactivity also overlaps with the characterizations of higher infant irritability (Brazelton & Nugent, 1995), more crying (James-Roberts, Conroy, & Wilsher, 1995) and a “difficult” temperament (Chess & Thomas, 1987) as shown in several studies. Positive reactivity, also referred to as surgency, includes the tendency to experience positive emotions, but also high intensity pleasure, approach behaviors and perceptual sensitivity (Garstein & Rothbart, 2003), which in turn predict a later personality trait of extraversion (Evans & Rothbart, 2007). Negative emotional reactivity is also frequently considered as a risk factor for later externalizing and internalizing symptoms, but also neuropsychiatric disorders such as attention deficit/hyperactivity disorder (AD/HD) (De Pauw & Mervielde, 2010; Gutteling, De Weerth, Willemsen-Swinkels, et al., 2005; Nigg, Goldsmith, & Sachek, 2004; Putnam & Stifter, 2005; Sanson, Hemphill, & Smart, 2004; Sayal

et al., 2014). The aspects of reactivity depend on the child's age and maturation. Reactivity emerges relatively early in life, positive reactivity and distress tendencies already around the age of 3 months (Rothbart, 2007); however, fear reactivity can be measured reliably not earlier than during the second half of the first year of life (Carnicero, Pérez-López, Salinas, & Martínez-Fuentes, 2000; Gartstein et al., 2010; Putnam & Stifter, 2005). However, in addition to heredity and maturation, the aspects of temperament are also influenced by experiences (Rothbart, 2011) including parenting (Bridgett et al., 2009; Lengua & Kovacs, 2005) and other environmental factors such as stress. Interestingly, child reactivity tendencies also affect parenting behavior, for instance, high negative reactivity is associated with parent-child interaction difficulties (Stright, Gallagher, & Kelley, 2008) and higher parenting stress (Oddi, Murdock, Vadnais, Bridgett, & Gartstein, 2013). Reactivity tendencies also interact with the child regulatory capacity (Derryberry & Rothbart, 1997). This underscores the interactive nature of self-regulation: the reactive and regulatory functions of a child interact with each other, but the components of child self-regulation also interact with the environment. Moreover, current evidence also shows that negative emotional reactivity might reflect the susceptibility of the infant, thus, infants with higher negative reactivity might be more vulnerable to a non-optimal environment such as negative parenting, but in turn, also greatly benefit from optimal environments (Pluess & Belsky, 2010; Slagt et al., 2016). In other words, the degree of environmental influence on child development might be dependent on infant dispositions, one of which seems to be high negative reactivity.

According to self-regulation theories, reactivity is referred to as bottom-up self-regulation that reflects more automatic processes of regulation facilitated by subcortical brain structures (Bridgett et al., 2015; Buschman & Miller, 2007). In this theoretical approach, reactivity is a regulatory process that facilitates survival by redirecting attention and inhibiting other action (e.g. fear/behavioral inhibition facilitates escape behaviors, and impulsivity facilitates defensive and explorative behaviors) (Gartstein et al., 2010; Nigg, 2017; Rothbart, Ahadi, Hershey, & Fisher, 2001).

2.1.1.1 Fear reactivity

Fear reactivity is an aspect of negative emotional reactivity characterized by experience of distress related to novelty (e.g. novel people, objects or situations). Its extremes are typically referred to as behavioral inhibition or a shy and inhibited temperament type (Kagan, Reznick, & Snidman, 1987). In broader self-regulation theories, especially in the work of Gray (1970; 1987), fear reactivity/behavioral inhibition is regarded as a reactive form of regulation, so-called "overcontrolled"

self-regulation (Aksan & Kochanska, 2004), as it leads to withdrawal, escape or avoidance behaviors in response to a perceived threat.

Fear reactivity represents itself as a distinct behavioral trait from frustration or sadness tendencies (Rothbart, 2011) and has the potential to individually predict anxiety and social anxiety disorders (Baker, Baibazarova, Ktistaki, Shelton, & van Goozen, 2012; Buss, Davis, Hobel, & Sandman, 2011; Clauss et al., 2015; Clauss & Blackford, 2012; Gartstein et al., 2010; Kopala-Sibley et al., 2016; Nozadi, Spinrad, Eisenberg, & Eggum-Wilkens, 2015) as well as conduct disorders (Mills-Koonce et al., 2015) later in life. However, also relations between low fear reactivity and later emotional disturbances have been reported (Beaver, Hartman, & Belsky, 2015; Colder, Mott, & Berman, 2002), while fear may also facilitate positive development such as the development of conscience (Kochanska, 1997).Thus, fear reactivity clearly represents a distinct developmental trajectory, which emphasizes the need to examine it distinctly from overall negative reactivity.

It must be noted that fear reactivity emerges later in development than other facets of reactivity occurring at approximately 6 months of age (Gartstein et al., 2010; Putnam & Stifter, 2005), increasing during the second half of the first year (Carnicero et al., 2000; Rothbart, 1988) and peaking at 4 to 6 years of age (Bridgett et al., 2015). Fear reactivity shows great stability after its development during late infancy (Rothbart, 2011). Still, some stability of fearfulness can be observed already in early childhood (Lemery, Goldsmith, Klinnert, & Mrazek, 1999; Rothbart, Derryberry, & Hershey, 2000). Thus, the assessment and the definition of normative fear is highly dependent on the child's age.

2.1.2 Executive function and other top-down self-regulation processes

In comparison to bottom-up self-regulation, top-down self-regulation refers to the efficiency of executive attention and inhibitory control processes served by cortical structures and corticostriatal areas of brain such as the prefrontal cortex (PFC) (Bridgett et al., 2015; Grossmann, 2013; Heatherton & Wagner, 2011; Hofmann, Schmeichel, & Baddeley, 2012). In broader self-regulation theories, top-down self-regulation covers both effortful self-regulation and executive function (EF), and is a term more commonly used in the fields of neuropsychology and neuroscience (Bridgett et al., 2015). Recent literature states that EF and effortful control are not interchangeable but overlap remarkably, such that EF skills are used in situations that require effortful regulation of emotions and behavior (Nigg, 2017; Zhou et al., 2012). Efficient and flexible EFs are related to better psychosocial, mental and physical health outcomes similarly to other facets of self-regulation,

such as effortful control (Bridgett et al., 2015; Diamond, 2013; Nigg, 2017). In this study, EF is used to reflect early developing self-regulatory skills despite that self-regulation is a broader concept also including other forms of regulation.

Generally, EF is considered to be comprised of three core skills: working memory, inhibition and flexible attention shifting that are needed in planned and goal-directed activities and create a basis for higher-order EF skills such as planning (Best & Miller, 2010; Miyake et al., 2000). A rapid growth in the development of EF core skills is observed in the second half of the first year and first years of life (Best & Miller, 2010; Bridgett, Oddi, Laake, Murdock, & Bachmann, 2013; Diamond, 1985; Diamond & Doar, 1989) simultaneously with the intensive development and differentiation of the prefrontal cortex (e.g. increased synaptic density in dorsolateral PFC; Johnson, 2001; Knickmeyer et al., 2008). The core skills of EF can be measured already from the age of 6 months onwards with A-not-B or delayed response tasks that require all subskills of EF: working memory, inhibition of a prepotent response and attention shifting (Best & Miller, 2010; Diamond & Doar, 1989; Sun, Mohay, & O'Callaghan, 2009). Similarly to rapid EF development, also other indicators of top-down self-regulation are observable from 6 to 12 months of age and can show up as attentional orienting (either towards a stimuli or away from stimuli), self-soothing, communication to the caregiver or inhibition of an action after caregiver denial (Calkins & Johnson, 1998; Grolnick, Bridges, & Connell, 1996; Rothbart, Ziaie, & O'Boyle, 1992; Sheese, Rothbart, Posner, White, & Fraundorf, 2008; Stifter & Braungart, 1995; Stifter & Spinrad, 2002). However, in this study, only EF skills are considered.

Although self-regulation and EF abilities and neural structures underlying them develop remarkably during infancy and toddlerhood, their development continues during an extended period of time until early adulthood (Andersen & Teicher, 2008; Bridgett et al., 2015; Giedd et al., 2014; Grossmann, 2013; Steinberg, 2005), making these abilities especially vulnerable to environmental influences such as stress (Pechtel & Pizzagalli, 2011) and the quality of parenting (Gartstein, Bridgett, Young, Panksepp, & Power, 2013). Furthermore, specifically in young children, different forms of self-regulation are still undifferentiated (Grossmann, 2013; Wiebe et al., 2011) making the assessment of specific functions difficult. These perspectives underscore the age-specific assessment of these functions as well as taking into account the interrelations of developing self-regulation with parenting and environment, including the effects of stress exposure.

2.2 Early life stress

Early life stress (ELS) is the stress that is experienced during the first years of life, including during the pre- and postnatal period that are sensitive periods for central nervous system (CNS) development (Markant & Thomas, 2013; Silberman, Acosta, & Zorrilla Zubilete, 2016; van den Bergh, 2011). Correspondingly, a large body of evidence suggests that ELS affects cognitive, affective and physical development of the offspring (Hedges & Woon, 2011; Pechtel & Pizzagalli, 2011; Van den Bergh et al., 2017; Weinstock, 2008); however, it must be noted that a number of existing studies included in these reviews have also reported negative results concerning prenatal stress and ELS effects. According to the fetal programming model, stress exposure during pregnancy leads to neural adaptations in the offspring, and this way affects offspring postnatal development (Moisiadis & Matthews, 2014a; Sandman, Davis, Buss, & Glynn, 2011).

Although most research has recently focused on fetal programming, similar models of programming have been increasingly applied to early postnatal stress exposure (Catalani et al., 2002; Grey, Davis, Sandman, & Glynn, 2013; Hinde & Capitanio, 2010; Zuloaga, Carbone, Hiroi, Chong, & Handa, 2011). For instance, it has been suggested that prenatal programming prepares the individual for the postnatal environment, and that the adaptations taking place during prenatal life should be matched with the postnatal environment during neonatal period to remain (Lee & Goto, 2013). However, most of the postnatal programming studies have been conducted in animals. Thus, applying the perspective of programming to postnatal environmental influences in humans is relatively novel.

ELS is measured with a myriad of approaches providing evidence for an association between the stress and the child outcomes, most commonly including the exposure to maternal self-reported stress, anxiety or depressive symptoms (e.g. Buss et al., 2011; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003; Rouse & Goodman, 2014), stressful life events (Sarkar et al., 2014), experience of natural disasters (King & Laplante, 2005; Yong Ping et al., 2015), amniotic fluid, maternal saliva or blood glucocorticoid levels during gestation (Baibazarova et al., 2013; Bergman, Glover, Sarkar, Abbott, & O'Connor, 2010; De Weerth, Van Hees, & Buitelaar, 2003; Glynn et al., 2007) and in the recent studies, with breast milk cortisol levels (Grey et al., 2013; Hahn-Holbrook, Le, Chung, Davis, & Glynn, 2016). In the present study, ELS exposure is measured with maternal pre- and postnatal self-reported anxiety and depressive symptoms as well as postnatal breast milk cortisol concentration, so the studies considering these measures of pre- and postnatal stress exposure are emphasized in this literature review.

2.2.1 Fetal and early life programming

In fetal programming models, the classic proposed mechanism by which the fetal CNS is affected by maternal stress is through the glucocorticoids (GCs) that are secreted by maternal hypothalamic-pituitary-adrenal axis (HPA) and the placenta (Cottrell & Seckl, 2009; Moisiadis & Matthews, 2014b). Normally, HPA axis is activated as a response to stressors with the hypothalamus first releasing corticotrophin-releasing hormone (CRH), which in turn triggers the release of adrenocorticotrophin hormone (ACTH) from the pituitary gland. After entering the bloodstream, ACTH stimulates secretion of GCs (mainly cortisol in humans) from the adrenal gland. In turn, cortisol shuts the release of CRH providing a negative feedback loop for HPA axis (Gunnar & Quevedo, 2007).

During gestation, the maternal HPA axis undergoes profound changes, including increasing secretion of CRH and ACTH by placenta (Glynn, Davis, & Sandman, 2013), which also results in a diminished response to stressors (De Weerth & Buitelaar, 2005). These hormones are crucial for the maturation of the fetal organs, but exposure to extreme levels of GC concentrations might permanently affect the development of organs in the offspring. To protect the fetus from these harmfully elevated levels of GCs, the placenta provides a protective mechanism, 11-Betahydroxysteroid dehydrogenase enzyme type 2 (11β-HSD2) that inactivates most of maternal cortisol to biologically inactive form cortisone (e.g. Benediktsson, Calder, Edwards, & Seckl, 1997; Murphy, Smith, Giles, & Clifton, 2006).

The exact mechanisms through which elevated stress affects the fetus despite its protective mechanisms are still not fully understood. However, at least three mechanisms have been suggested (e.g. Rakers et al., 2017; Zijlmans, Riksen-Walraven, & de Weerth, 2015). First, although most of cortisol is inactivated by placental enzymes, 10–20% of maternal cortisol crosses the placental barrier and can have programming influences on organs, including the CNS (Murphy et al., 2006). Moreover, maternal stress levels as well as other environmental factors, such as nutrition (e.g. consumption of glycyrrhizic acid contained by liquorice; Räikkönen et al., 2017; Räikkönen, Seckl, Pesonen, Simons, & Van den Bergh, 2011) can negatively affect 11β-HSD2 activity exposing the fetus to higher levels of maternal cortisol (O'Donnell et al., 2012; Peña, Monk, & Champagne, 2012). Maternal distress has also been reported to alter placental GC sensitivity, which may lead to higher fetal exposure to GCs (Mina, Räikkönen, Riley, Norman, & Reynolds, 2015; Reynolds et al., 2015). Interestingly, these alterations may also be sex-specific (Mina et al., 2015).

A second mechanism considered in fetal programming models is related to placental secretion of CRH. This mechanism occurs via a positive feedback loop causing

increases in both maternal and fetal levels of CRH and cortisol resulting in continuously higher circulating levels of GCs in both the mother and the fetus (Glynn & Sandman, 2011; Majzoub & Karalis, 1999). A third suggested mechanism is indirect and relates to reduced utero-placental blood flow due to increased cortisol and other peptides. The decreased blood flow may lead to insufficient oxygen intake of the fetus affecting organ and CNS development through fetal growth restriction (Wadhwa, Entringer, Buss, & Lu, 2011).

However, research about the HPA axis and cortisol exclusively has not provided consistent and clear findings about how maternal stress is transmitted to the child. Consequently, current studies have searched for other mechanisms of transmission. One of the most central alternative route for above-mentioned mechanisms of programming is suggested to be through genetic inheritance. First, both the child characteristics and prenatal stress experienced by the mother might share the same underlying genotype (Glover, 2011; O'Donnell & Meaney, 2017). Second, offspring susceptibility to stress exposure is shown to be moderated by the genotype of the offspring (Babineau et al., 2015; O'Donnell et al., 2017; Pluess et al., 2011; Velders et al., 2012; Zohsel et al., 2014), although these findings have been inconsistent (Braithwaite et al., 2013). Third, the epigenetic mechanisms in early life programming by stress have been increasingly studied (Cao-Lei et al., 2017; Cruceanu, Matosin, & Binder, 2017). Epigenetics refers to mechanisms by which genetic information is regulated without a change in the DNA sequence. Recent studies suggest that both parental, placental and fetal gene expression can be epigenetically regulated by pre- and postnatal stress exposure (Cao-Lei et al., 2017), and that this regulation depends upon offspring sex (Gröger et al., 2016). Correspondingly, there is evidence that the effects of maternal care on offspring brain and behavior are mediated by changes in the epigenome (Monk, Spicer, & Champagne, 2012), but there is little knowledge about the interactions between epigenetic factors combined with differential stress exposures across development. However, the lack of consideration about the effect on genotype by stress exposure interactions is likely to contribute to the inconsistency of ELS findings.

When considering early life programming more broadly and also after the prenatal period, the sources of stress also include other environmental signals than maternal stress transmitted through HPA axis. Most frequently, postnatal programming has been suggested to happen via parental caregiving or parent-child interaction that mediates parental stress. In accordance with this idea, the caregiving provided by parents with high levels of stress is shown to be inadequate and affect child development independent of parental stress (Field, 2010, 2011; Grant et al., 2009). However, in animals, prenatal stress exposure effects may be reversed by the high quality of postnatal caregiving or environmental enrichment (Del Cerro et al., 2010; Koo et al., 2003; Lemaire, Lamarque, Le Moal, Piazza, & Abrous, 2006; Morley-

Fletcher, Rea, Maccari, & Laviola, 2003). There is some evidence for this also in humans (Kaplan, Evans, & Monk, 2008; Sharp, Hill, Hellier, & Pickles, 2015), but overall, the research about interactions between pre- and postnatal environment remains scarce. Similarly, the differential mechanisms of pre- and postnatal stress and its continuity have been studies in animals. It is suggested, for example, that the adaptations taking place during the prenatal period would have to be matched with the postnatal environment, and that a mismatch between these environments would predict poorer outcomes (Lee & Goto, 2013) or that both pre- and postnatal stress exposures would have additive (Lee, Kim, & Goto, 2016) and differential (Wen et al., 2017) effects on offspring development, but currently, these perspectives would need to be validated in further studies.

Moreover, in recent studies, there has been a shift from considering only GCs to other mechanisms of fetal programming such as inflammatory cytokines, telomere biology, epigenetic clocks and the intestinal microbiome (Beijers, Buitelaar, & de Weerth, 2014; Entringer, Buss, & Wadhwa, 2015; Howerton & Bale, 2012; Rakers et al., 2017; Spencer & Meyer, 2017; Van den Bergh et al., 2017). Consequently, although not considered in this study, taking into account the broad spectrum of biological mechanisms of ELS seems a prominent future direction for all early programming studies and may provide insight into why some individuals are affected by maternal stress and GCs, whereas others are not.

However, it must be noted that there are several limitations in the current understanding of the biological mechanisms. The models or theories tested usually arise from animal studies, where an accurate controlling of stress moderators is possible. However, the generalizability of the findings and translational paradigms from animal studies to humans is limited (Bolton, Molet, Ivy, & Baram, 2017; Graignic-Philippe, Dayan, Chokron, Jacquet, & Tordjman, 2014). Second, especially with regard to the most novel stress biology mechanisms (e.g. gut microbiome), the normative associations between a set of biomarkers and behavior at a certain age is not known, which complicates the interpretation of the findings. Further, as the effects of stress exposure likely reflect the interaction of several biological systems (Beijers et al., 2014), more advanced and multilevel analytical methods are needed to enable simultaneous assessment and complex interactions between these systems.

2.2.2 Lactocrine programming

As already reviewed, the concept of GC programming has been applied to also postnatal stress influences. In animal studies, it is demonstrated that increasing

postnatal cortisol levels synthetically can affect infant brain, cognition and behavior (Casolini et al., 1997; Catalani et al., 2000), and that these associations may be sex-specific (Farrell, Holland, Shansky, & Brenhouse, 2016; Gobinath, Workman, Chow, Lieblich, & Galea, 2016). In turn, breast milk is one of the most prominent postnatal biological exposures for the developing infant, including also GCs that are transferred to milk from maternal plasma. This has led to the hypothesis that bioactive components in milk, including GCs, could affect infant CNS and behavior, described by the terms lactocrine programming/signaling (Bartol, Wiley, & Bagnell, 2008) or lactational programming (Grey et al., 2013; Hinde & Capitanio, 2010).

Supporting the transmission of maternal stress to child via milk, the level of GCs in milk follows the diurnal cortisol rhythm (van der Voorn et al., 2016) and is fairly highly correlated (r = .60–.70) with maternal plasma cortisol (Patacchioli et al., 1992). The idea that milk cortisol reflects maternal stress levels is also supported by the fact that in contrast to the prenatal period, maternal plasma cortisol levels gradually decline to normal pre-pregnancy levels during the postnatal period (Chrousos, Torpy, & Gold, 1998; Mastorakos & Ilias, 2003). However, some confusion is caused by the notion that lactation might suppress maternal cortisol response to stressors (Altemus, Deuster, Galliven, Carter, & Gold, 1995; Heinrichs et al., 2001; Heinrichs, Neumann, & Ehlert, 2002), which may affect the variance of milk GCs and thus, the interpretation of milk GC findings.

The exact mechanisms of how GCs in milk potentially affect offspring development are unclear. However, in animal studies, biologically active factors in milk are shown to cross the intestinal epithelial barrier of the offspring, which may provide the route to the programming of offspring brain and behavior (Angelucci, Patacchioli, Chierichetti, & Laureti, 1983; Melnik et al., 2016). However, breastfeeding may also affect maternal hormonal levels such as oxytocin (Dawood, Khan-Dawood, Wahi, & Fuchs, 1981) and affect maternal behavior (Hart et al., 2004), which in turn may have implications for maternal interaction with the child. Overall, the number of studies considering both mechanisms and behavioral outcomes of lactation is very small emphasizing the need for further research on this topic.

2.2.3 Maternal pre- and postnatal anxiety and depressive symptoms

In a large proportion of the studies assessing pre- and postnatal stress effects, stress is measured using maternal self-reports of anxiety and depressive symptoms or the diagnostic information regarding maternal emotional state. Anxiety and depressive

symptoms are common during pre- and postnatal periods with prevalence estimates ranging from 10 to 20% (Andersson et al., 2006; Buist et al., 2011; Heron et al., 2004; Pearson et al., 2013). Maternal pre- and postnatal anxiety and depressive symptoms are also relatively consistently linked with child developmental outcomes (Kingston et al., 2015, 2012; Korja et al., 2017) as well as lower quality of parental caregiving, which in turn has adverse effects on child development (Field, 2010). As a natural consequence, they are also considered as a feasible ground for clinical prevention and intervention (Glover, 2014; Kaplan et al., 2008). However, not all studies report an association between ELS and child development (Erickson, Gartstein, & Dotson, 2017; Korja et al., 2017; Van Batenburg-Eddes et al., 2013) suggesting that the association is dependent of both the phenotype of maternal distress and child outcome as well as moderating factors such as child sex, genetic makeup and postnatal events (O'Donnell & Meaney, 2017). Further, as already noted, there is evidence that postnatal caregiving may counteract the effects of prenatal adversity (Del Cerro et al., 2010; Lemaire et al., 2006; Sharp et al., 2015), which emphasizes the need to research both exposure to pre- and postnatal stressors, moderators such as sex as well as genetic susceptibility in early life programming studies.

Furthermore, it is suggested that the existing associations between the pre- and postnatal maternal psychological state and child outcomes are explained by a correlation between maternal emotional stress and changes in maternal-fetal-placental stress biology (e.g. Cottrell & Seckl, 2009; Wadhwa et al., 2011) that would lead to CNS programming and in turn, behavioral alterations in the offspring. Indeed, a number of studies indicate that prenatal mood is associated with alterations in HPA-axis functioning (Glynn et al., 2013; Seth, Lewis, & Galbally, 2016). However, several have found no association between maternal psychological state and glucocorticoid measures (Rothenberger, Resch, Doszpod, & Moehler, 2011; Sandman et al., 2011; Seth et al., 2016; Voegtline et al., 2013; Zijlmans et al., 2015). This suggests that either biological mechanisms other than cortisol might be underlying the association between prenatal stress and child outcome, or that phenotypes of maternal stress profoundly differ in how they are associated with the biomarkers of stress (for instance, see Seth et al., 2016 on transient and chronic depression and cortisol responses). In conclusion, glucocorticoids and maternal symptoms seem neither to be interchangeable nor equal in terms of predicting the outcomes (O'Donnell & Meaney, 2017), and they should not be handled as equal in terms of prenatal and early life stress exposure.

2.3 Early life stress and infant fear reactivity

2.3.1 Maternal pre- and postnatal stress and infant emotional reactivity

Maternal prenatal stress, anxiety and depressive symptoms are relatively consistently associated with higher infant overall negative reactivity (Henrichs et al., 2009; Korja et al., 2017; Pesonen, Räikkönen, Strandberg, & Järvenpää, 2005; Rouse & Goodman, 2014) and irritability and lower rhythmicity, which are components of a "difficult temperament" (Austin, Hadzi-Pavlovic, Leader, Saint, & Parker, 2005; Della Vedova, 2014). Similarly, maternal postnatal stress is linked with a higher overall negative reactivity in a number of studies (Emerson, Bradley, Riera, Mayes, & Bechtel, 2014; Feldman et al., 2009; Henrichs et al., 2009; McMahon, Barnett, Kowalenko, Tennant, & Don, 2001; Pesonen et al., 2005).

Still, not all studies have found a link between maternal prenatal mental health and negative reactivity (Bhat et al., 2015; Kaplan et al., 2008; Korja et al., 2017). Furthermore, no clear pattern of whether anxiety or depressive symptoms differ in their potential to predict infant emotional reactivity exists; rather, significant results have been reported using all measures (Glover, 2014). There is evidence that different phenotypes of maternal perinatal stress might be linked with different outcomes of the infant overall (O'Donnell & Meaney, 2017). Thus, still more understanding is needed about what aspects of reactivity are predicted by prenatal stress, and whether different forms of maternal distress are equivalent in predicting infant negative reactivity.

To our knowledge, little research exists also on fear reactivity, which is a specific aspect of negative reactivity important for child future outcomes. To date, a handful of studies have reported an association between maternal prenatal stress and infant fear reactivity after controlling for postnatal stress (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Davis et al., 2004; Henrichs et al., 2009; Möhler, Parzer, Brunner, Wiebel, & Resch, 2006). Similarly, postnatal stress has been reported to predict higher fear reactivity and increases in infant fear in some studies (Feldman et al., 2009; Gartstein et al., 2010; Pauli-Pott, Mertesacker, & Beckmann, 2004; Sugawara, Kitamura, Toda, & Shima, 1999). However, most of the studies in the field have either focused on pre- or postnatal stress. Likewise, most studies about prenatal stress have not examined the independent effects of stress or continuity of stress during these periods, and almost all postnatal stress studies lack the controlling of earlier prenatal stress exposure.

Still, to date, three studies that have examined stress exposure during both periods were found. First, in two of these studies, more chronic stress was associated with higher overall negative reactivity. Pesonen et al. (2005) found that prenatal stress

predicted both higher overall negative reactivity and fearfulness, but not other aspects of negative reactivity, but only if the child was exposed to continuous stress from pre- to postnatal period. This suggests that continuity of stress might be important in defining whether prenatal stress has any effects on infant emotional reactivity. In a similar manner, Henrichs et al. (2009) reported that postnatal stress was linked with irritability-related aspects of emotional reactivity, whereas higher fearfulness was predicted by only prenatal anxiety. Furthermore, in the study from Stapleton et al. (2012), prenatal stress was not directly associated with fear reactivity; rather, postnatal stress mediated the association between prenatal stress and fear reactivity. Earlier studies in animals (Lee & Goto, 2013; Lee et al., 2016) and the ones using other outcomes than fear (Diego, Field, & Hernandez-Reif, 2005) also underscore the importance of considering pre- and postnatal and continuous stress exposures in offspring development.

To summarize, surprisingly few studies have used longitudinal approaches in researching maternal stress and infant fear. However, existing studies propose that continuity, change and the timing of maternal stress (pre- or postnatal) might be central in determining whether stress has an effect on infant fear reactivity.

2.3.2 Maternal pre- and postnatal blood or saliva cortisol and infant emotional reactivity

Relative to studies using self-reports of stress as a predictor of infant emotional reactivity, far fewer studies have found similar links between prenatal cortisol levels and higher infant overall negative reactivity (Zijlmans et al., 2015). There are studies that show, in an expected direction, that higher cortisol concentration during gestation predicts higher negative reactivity (Davis et al., 2007; Davis, Glynn, Waffarn, & Sandman, 2011; De Weerth et al., 2003). In line with these studies, two have reported a link between maternal prenatal cortisol or catecholamine levels and higher infant observed fear reactivity specifically (Buitelaar et al., 2003; Davis et al., 2007). However, several studies have not found an association between prenatal glucocorticoids and infant reactivity tendencies (Baibazarova et al., 2013; Rothenberger et al., 2011; Zijlmans et al., 2015). A number of explanations for the inconsistency in these findings have been provided including the lack of sufficient moderators in the analyses (Zijlmans et al., 2015).

In animal studies, the exposure to postnatal GCs is linked with altered behavioral responses (Casolini et al., 1997; Catalani et al., 2000). However, to our knowledge, no studies have been conducted with an aim to link postpartum exposure to glucocorticoids (e.g. corticosteroid medication) and infant emotional reactivity, except

one study that focused on maternal cortisol and the moderating role of breastfeeding (Glynn et al., 2007). In conclusion, the evidence for a link between maternal pre- and postnatal cortisol and infant reactivity tendencies is currently scarce.

2.3.3 Milk cortisol concentration and infant emotional reactivity

There is a paucity of studies considering milk as a programmer of early behavior. However, studies in rhesus macaques show that heightened milk cortisol concentrations are associated with higher offspring negative emotional reactivity and less impulsivity in both sexes (Dettmer et al., 2017; Hinde, Skibiel, Foster, Rosso, & Sally, 2015), with more confidence in boys, but not in girls (Sullivan, Hinde, Mendoza, & Capitanio, 2002) and the higher frequency of social behavior in girls but not in boys (Dettmer et al., 2017). To date, only two studies considering milk cortisol effects and behavior have been conducted in humans. In the first study, levels of maternal cortisol were associated with higher infant fear reactivity only in breastfed infants (Glynn et al., 2007) suggesting that breastfeeding played a role in transmitting glucocorticoid effects on infant behavior. In the second existing study, higher milk cortisol concentration was positively associated with infant fear reactivity and sadness in infant girls (Grey et al., 2013).

In conclusion, current literature suggests that milk glucocorticoids might potentially affect infant emotional responses, including fear reactivity, but overall the state of evidence for this association in humans is limited underscoring a need for further examination about the role that milk plays in programming early behavior.

2.4 Early life stress and infant executive functioning

Both maternal self-reported prenatal and postnatal stress are reportedly associated with poorer cognitive development, measured as mental developmental index or intelligence quotient (IQ) (Davis & Sandman, 2010; Grace, Evindar, & Stewart, 2003; Henrichs et al., 2011; Ibanez et al., 2015; Keim et al., 2011; Kingston et al., 2015, 2012; Kingston & Tough, 2013; Tarabulsy et al., 2014). Beyond cognitive development, prenatal stress is also associated with top-down self-regulation behaviors during infancy, including poorer emotion regulation (Babineau et al., 2015; Bolten et al., 2013) and alterations in attentional control (Gutteling, De Weerth, & Buitelaar, 2005; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2002; Lin, Crnic, Luecken, & Gonzales, 2014). Although EF can be considered as cognition, there is a remarkable overlap between EF and top-down emotion regulation (Zhou et al., 2012) with the same underlying neural structures

(Grossmann, 2013). Thus, it could be hypothesized that ELS might affect EF performance as early as in infancy. Relatively few studies have, however, focused on EF specifically, and no studies exist on ELS and EF during infancy. One study indicates that maternal prenatal anxiety is associated with poorer childhood executive functioning, specifically inhibitory control and working memory from 6 to 9 years of age (Buss et al., 2011). Another two studies provided evidence about maternal prenatal anxiety and poorer performance in EF tasks in later childhood or adolescence (Mennes, Stiers, Lagae, & Van den Bergh, 2006; O'Donnell et al., 2017); in the latter, however, the effects were moderated by the COMT genotype of the child.

Further, a couple of studies have linked postnatal maternal depression in toddlerhood to poorer EF later in childhood (Hughes, Roman, Hart, & Ensor, 2013; Jensen, Dumontheil, & Barker, 2014). Similarly, a number of studies confirm that general adversity in early life is linked with poor EF in childhood (Blair et al., 2011; Bos, Fox, Zeanah, & Nelson, 2009; Pollak et al., 2010). However, to our knowledge, none of the studies of postnatal stress have accounted for the prenatal exposure to stress.

Interestingly, not all studies suggest that ELS exposure predicts poorer cognitive/EF performance. In a couple of studies, prenatal stress exposure is associated with better cognitive performance (Davis & Sandman, 2010; DiPietro, Novak, Costigan, Atella, & Reusing, 2006; Ellman et al., 2008; Keim et al., 2011). Similarly, some studies suggest that children with early postnatal stress might show improved learning and memory compared to those with no ELS (Frankenhuis & de Weerth, 2013). This has been suggested to result from beneficial effects of moderate levels of stress, given that some amount of GC exposure is necessary for child development and tissue maturation (Amiel-Tison et al., 2004; Moisiadis & Matthews, 2014a). Furthermore, the potential of moderate stress to promote resilience in the condition of facing later life challenges similar to those experienced earlier has been introduced in prior research (Daskalakis et al., 2013; Lyons et al., 2010).

Another emerging hypothesis from the field of affective neuroscience is based on the findings that exposure to severe early life maltreatment/stress exposure may lead to *both* heightened anxiety *and* earlier maturation of self-regulation and brain circuits responsible for regulatory functions (Gee et al., 2013; Humphreys et al., 2012; Silvers et al., 2016; Tottenham, 2014). Hence, in the case of severe early (postnatal) stress exposure, earlier or more efficient regulation of emotion might be an adaptation to an environment that elicits anxiety (Gee et al., 2013). These findings underline the view that outcomes of stress are not necessarily impairments

as such but rather adaptations (Daskalakis et al., 2013; Frankenhuis & de Weerth, 2013), even though they might impair individual functioning in other occasions.

Overall, pre- and postnatal stress are related to poorer cognitive development in several studies and to poorer EF and emotion regulation in some studies. However, due to a limited amount of research conducted during early childhood as well as the mixed findings in current literature, no conclusions can be drawn about infant EF after exposure to pre- or postnatal stress.

2.5 Sex differences in early life programming

Beyond the main effect of ELS, it is suggested that infant sex might moderate the effect of stress on later development. For instance, the viability-vulnerability tradeoff theory describes the possibility that females and males would be differentially susceptible to prenatal stress exposure (Sandman et al., 2013). Sandman et al. (2013) proposed that as a response to prenatal stress, females would show higher neural plasticity and behavioral adaptiveness, whereas males would invest in more gross developmental outcomes, such as tissue growth. This would also result in a higher variation of neural plasticity in female offspring, while in terms of plasticity, males would represent a more homogeneous group in postnatal life. From a slightly different perspective, Glover and Hill (2012) have suggested that females and males would benefit from different emotional strategies in adapting to early stress exposure (i.e. males would benefit from impulsivity and aggression, whereas females would benefit from heightened reactivity to threat).

Both these theoretical perspectives are evolutionarily grounded, suggesting that males and females might have an advantage in different early life programming. In line with these theories, current evidence suggests that in girls, prenatal stress exposure is related to increased negative/fear reactivity or anxiety proneness (Braithwaite, Pickles, et al., 2017; Braithwaite, Murphy, Ramchandani, & Hill, 2017; Quarini et al., 2016; Sandman et al., 2013) mediated by sex- and timing-specific changes in amygdala size and brain microstructure (Buss et al., 2012; Kim et al., 2016; Wen et al., 2017). By contrast, some other studies show that prenatal stress is associated with delayed neuromotor and cognitive development or less negative reactivity only in boys (Braithwaite, Pickles, et al., 2017; Braithwaite, Murphy, et al., 2017; Ellman et al., 2008; Sandman et al., 2013). Similar findings have been reported in a number of animal studies, and the possible neurobiological mechanisms of sex-specific neural adaptations during gestation have been presented in the review of Weinstock (2007). Moreover, recent work has suggested that similar sex-specificity might also apply to postnatal stress influences (Farrell et al., 2016; Gobinath et al., 2016; Grey et al., 2013; Hahn-Holbrook et al., 2016;

Zuloaga et al., 2011) including back-transformation of prenatal effects by an optimal postnatal environment (Sharp et al., 2015). For instance, breast milk cortisol concentration is reported to predict mother-reported fear reactivity only in girls but not in boys (Grey et al., 2013) and certain immunoreactivity alterations in the amygdala occurring only in females (Zuloaga et al., 2011).

However, although these sex-specific adaptations are hypothesized to be beneficial in the short-term, they might predispose an individual to emotional or behavioral problems later in life. This is in line with the studies that show an association between maternal prenatal stress and AD/HD-like deficit only in boys (van den Bergh et al., 2006) and depressive or anxiety symptoms only in girls (Quarini et al., 2016; Sandman et al., 2013). Similarly, they fit with the higher overall prevalence of anxiety and depressive disorders in women in relation to men in adolescent and adult populations (Costello et al., 2003; Salk, Hyde, & Abramson, 2017), whereas the prevalence of neurodevelopmental and neuropsychiatric disorders is higher in men in comparison to women (Bryson & Smith, 1998; Fombonne, 2009; Leonard & Wen, 2002; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

It must be noted that some studies have also yielded contradictory results. For instance, some authors report that prenatal stress is related to increased fear only in boys (Henrichs et al., 2009) or externalizing symptoms only in girls (de Bruijn, van Bakel, & van Baar, 2009). Further, some have not found differences in susceptibility between boys and girls (e.g. Pesonen et al., 2005). Moreover, because of the relative paucity of the studies reporting sex-specificity as a response to ELS, more research is warranted to strengthen the theoretical hypotheses generated by theories of Sandman et al. (2013) and Glover and Hill (2012).

2.6 Summary of the current literature

Several studies have showed that pre- and postnatal stress are related to infant emotional reactivity and early childhood cognitive development or self-regulation. However, there are some gaps in the current literature. First, only a small section of studies has systematically examined specific aspects of emotional reactivity to determine which phenotypes are related to ELS. Specifically fear reactivity, despite its ability to independently predict later anxiety disorders, has been scarcely studied. Second, with regard to top-down self-regulation, no studies currently exist about ELS effects on infant or early childhood EF. Third, studies of postnatal stress have quite seldom adopted the view of early life programming but rather treated postnatal stress as a predictor of alterations in parenting behavior or mother-child interactions. Consequently, relatively few studies of either pre- or postnatal stress have focused on independent effects of stress experienced during both periods.

Fourth, the field concentrating on lactocrine programming is novel. Some studies suggest that milk glucocorticoids have a potential to steer behavioral development, but more studies are needed to strengthen the findings in the field. Fifth, a state of the research concerning moderating role of infant/fetal sex is currently mixed, although the need for systematically examining moderating role of sex has been communicated in the literature (Zijlmans et al., 2015). Thus, more research is needed to validate the hypothesis that infant sex could moderate early life programming effects.

3 AIMS OF THE STUDY

The aim of the current study was to extend the current state of literature by examining whether pre- and postnatal stress exposure are independently related to infant fear reactivity and executive functioning. Moreover, the aim was to investigate the effects of milk cortisol concentration on infant fear reactivity as well as whether ELS effects are moderated by infant sex. Specifically, the aims of this thesis were:

1. To study whether maternal self-reported prenatal anxiety, depressive and pregnancy-specific anxiety symptoms are associated with aspects of mother-reported infant fear reactivity at 6 months in contrast to other aspects of emotional reactivity (Study I).

2. To study the relations between trajectories of maternal self-reported pre- and postnatal stress and infant fear reactivity at 6 and 8 months and whether these associations are moderated by infant sex. In order to do this, the trajectories of maternal pre- and postnatal anxiety and depressive symptoms were first explored (Study II).

3. To determine whether breast milk cortisol concentration at 2.5 months is associated with higher infant fear reactivity at 6 and 8 months, and if infant sex has a moderating effect on this association (Study III).

4. To investigate the associations between maternal pre- and postnatal self-reported anxiety, depressive and pregnancy-specific anxiety symptoms and infant executive function performance at 8 months as well as if infant sex moderates the association between ELS and EF (Study IV).

4 MATERIALS AND METHODS

4.1 Study design and participants

The sample of the present study consisted of mother-infant dyads participating in the larger FinnBrain Birth Cohort Study. The FinnBrain Study is a pregnancy cohort that aims to prospectively study the effects of ELS, including prenatal stress, on child neurodevelopment and health and identify biomarkers for later psychiatric and somatic illnesses (www.finnbrain.fi). All the families living in the area of Southwest Finland Hospital District and the Åland Islands in Finland were invited to participate in the study. The recruitment took place during the first trimester ultrasound visit at gestational week 12 through personal contact by a research nurse. Overall, 66% of the invited families gave written informed consent for their participation and on behalf of their child. Generally, the overall population of the Cohort resembled the source population in Finland, although the prevalence of younger, multiparous and smoking women in the cohort as well as the number of preterm births was lower than among all deliveries in Turku University Hospital (see more detailed characteristics and the description of the cohort in Karlsson et al., 2017). The data for the present study was gathered between December 2011 and June 2016.

Most mother-infant dyads in the current study belonged to the FinnBrain Focus Cohort Study that was a nested case-control study within the main cohort. The Focus Cohort consisted of mothers with high or low prenatal stress who were invited to more intensive follow-up during the pre- and postnatal period. To determine the criteria for the Focus Cohort, the questionnaire data of the first 500 participating mothers was used to establish cut-points for highest and lowest 20th percentile of maternal prenatal stress. More specifically, three questionnaires were used in defining maternal prenatal stress, one measuring depressive symptoms (Edinburgh Postnatal Depression Scale, EPDS), one measuring overall anxiety (Symptom Checklist -90 anxiety subscale) and one assessing pregnancy-specific anxiety (Pregnancy-Related Anxiety Questionnaire Revised 2, PRAQ-R2). The cut-points were $\geq$12 and $\leq$ 6 for the EPDS, $\geq$10 and $\leq$ 4 for the SCL-90 anxiety subscale and $\geq$ 34 and $\leq$ 25 points for PRAQ-R, respectively. The participating mother was qualified as a "case" if she scored above the selected cut-point in at least two different questionnaires or twice in the same questionnaire during pregnancy. Correspondingly, the criterion for being a control was to remain below the lower cut-point in all the pregnancy assessments. Moreover, all mothers who reported the use of serotonin reuptake inhibitors (SSRIs) during the gestation were included as cases.

This procedure resulted in two groups, controls with low prenatal stress (27% of the whole cohort) and "cases" with high prenatal stress (20 % of the whole cohort). Furthermore, the current study also included a small group of mothers that were initially candidates for the Focus Cohort and had participated in a neurocognitive assessment during pregnancy. However, these mothers ended up having moderate rather than high or low levels of stress at the end of the pregnancy. Also, some mother-infant dyads were used to enrich the dataset because the infants had participated in pre-existing neonatal brain scans. Moreover, the inclusion criterion for Studies I-IV was that parents stated that their infant had no known CNS abnormalities. The number of participants and the number of cases, controls and mothers with moderate stress in each study are presented in the Figure 1.

Of all mother-infant dyads in the Focus Cohort, 908 (74.0%) were contacted for the purpose of inviting them for the visit. Altogether, a visit was scheduled for 490 (54.0% of those contacted) mother-infant dyads of which 427 (47.0% of those contacted) finally participated in some part of the 8-month visit. Of those contacted, the mothers who took part in the visit were older ($T = 2.81$, $p = .005$), more highly educated (χ^2 [2] = 15.61, $p < .001$) and earned higher income (χ^2 [2] =11.89, $p = .003$) than the ones who abstained (with no answer to several phone calls or orally refused to participate). The mothers who abstained might also have reported more smoking during pregnancy (χ^2 [1] = 3.42, p = .06) and experienced more anxiety and depressive symptoms during the beginning of pregnancy (T = 2.49–2.93, p = .004 to .013) and anxiety symptoms during the third trimester (T = –1.87, p = .06) in comparison to their participating counterparts. However, the associations in maternal symptoms did not remain when using non-parametric group comparisons. There were no other differences in prenatal or postnatal anxiety or depressive symptoms among the mothers who participated and the mothers who did not participate in the visit.

The characteristics of mother-infant dyads in each Study are displayed in Tables 1 and 2, and the percentage of mothers who have experienced symptoms exceeding the clinical cut-offs in each study are shown in Table 3. In Study I, the sample consisted of a Focus Cohort subsample of those mothers who had returned the prenatal and 6-month questionnaires about symptoms of depression and anxiety as well as the 6-month-questionnaire of infant emotional reactivity by the end of March 2014. Mothers who did not return the 6-month questionnaires in the Focus Cohort overall were more likely to be younger ($T = 2.04$, $p = .042$), have a lower educational level (χ^2 [3] = 23.91, $p < .001$) and a higher level of depressive ($T = –3.83$, $p < .001$) and anxiety ($T = –2.832$, $p = .005$) symptoms. There were no differences between the responders and non-responders in terms of parity. Data for this study was gathered between December 2011 and March 2014.

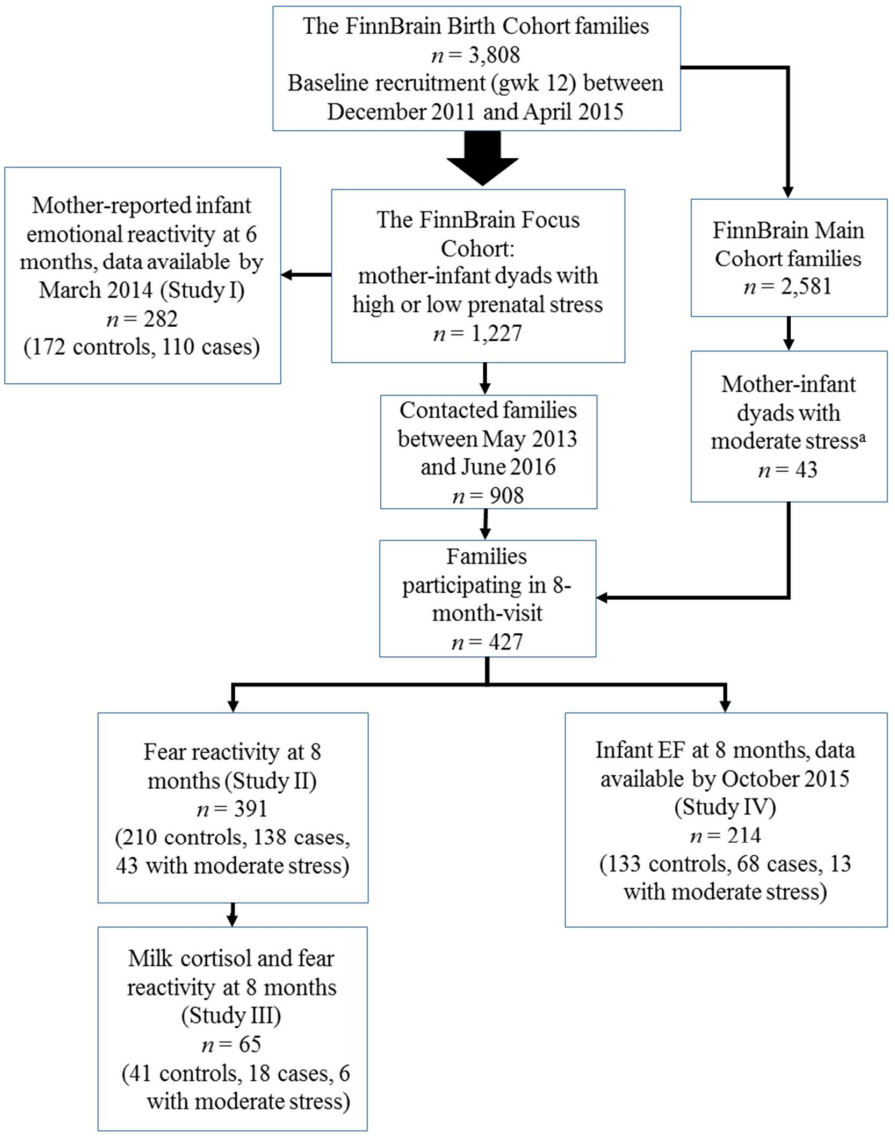

Figure 1. Flow chart of mother-infant dyads participating the present study. The inclusion criteria are described in more detail in the text. EF = Executive function. [a]These were mother-infant dyads from the main cohort that had taken part in the pre-existing child brain scans or maternal neurocognitive assessment during pregnancy and were used to enrich the 8-month dataset.

The sample of Study II was comprised of the mother-infant dyads where the mother had returned symptom questionnaires used in the assessment of pre- and postnatal stress in at least one time point out of five (gwk: 14, 24, 34, 3 months

and 6 months) and the infant participated in an 8-month observational assessment of fear reactivity. Of the initial 412 mother-infant dyads who had participated the specific fear assessment, 17 experiments were excluded either due to not receiving parent permission of the specific fear task (6 infants) or other problems related to the test situation resulting in a sample of 395 infant fear assessments (96% success rate). Out of this population, 391 mother-infant dyads had complete pre- and postnatal stress data (one assessment point) needed in the analysis. Furthermore, in this study, mother-reported fear reactivity assessed 6 months postpartum was available from 329 infants and multiple imputation in SPSS was used to handle the missing data throughout the analysis (Little & Rubin, 2002; Schafer & Graham, 2002). The mothers who did not respond to 6-month questionnaires were less educated (χ^2 [1] = 6.62 to 9.60, *p*'s ranging from .010 to .002), but no differences were found with regard to age, income or prenatal anxiety or depressive symptoms. Data for this study was gathered between March 2012 and June 2016. There was an overlap of 17% in participants of Studies I and II.

In turn, the sample of the Study III was a part of the sample in Study II. The sample of Study III included the mother-infant dyads that took part in both milk sample collection at 2.5 months of infant's age as well as infant 8-month fear reactivity assessment. Of the initial 76 mother-infant dyads, one was excluded due to postnatal corticosteroid medication of the mother and one due to exceptionally high milk cortisol concentration (i.e. 5.8 higher than the average of the sample). Moreover, complete data needed in the analysis was available from a final population of 65 mother-infant dyads. At time of the analysis, there was no available information about the differences between the mothers who gave the milk sample and the mothers who did not participate in milk sample collection. Data was gathered between May 2013 and June 2016.

In Study IV, the sample was comprised of mother-infant dyads that participated in the infant 8-month EF assessment between March 2012 and October 2015 and provided prenatal and 6-month questionnaires concerning maternal self-reported depressive and anxiety symptoms. Of initial 303 experiments, 18 measurements were excluded due to reasons related to testing situation, such as infant's language, restlessness or difficulty at baseline evaluation, experimenter error or recording failure resulting in a sample of 285 mother-infant dyads (94% success rate). Moreover, 214 (75%) of the remaining mother-infant dyads had complete data needed in the analyses. In this sample, the mothers who did not return 6-month questionnaires were slightly younger (T [283] = –1.866, p = .06) and less educated (χ^2 [1] = 9.110, p = .003) than those mothers who returned the questionnaires. However, the groups did not differ in terms of maternal pre- or postnatal symptoms, maternal smoking during pregnancy, monthly income or parity.

Table 1. The descriptive statistics of mother-infant dyads participating in Studies I-IV

	Study I (*n* = 282)			Study II (*n* = 391)			Study III (*n* = 65)			Study IV (*n* = 214)		
	%	M (SD)	Range	%	M (SD)	Range	%	M (SD)	Range	%	M (SD)	Range
Maternal characteristics												
Age		31 (4)	19–41		31 (4)	19–45		31 (4)	23–45		31 (4)	19–42
Monthly income after taxes												
Less than 1000 euros[a]	25			18			15			19		
More than 1000 euros	75			82			85			81		
Education												
High school/voc. or lower	34			27			12			26		
University/polytechnics or higher	66			73			88			74		
Parity (primiparous)	48			56			55			55		
Infant and gestation characteristics												
Length of gestation		39.7	27–42		39.9	35–43		40.0	36–42		40.0	35–43
Sex (boys)	55			54			57			53		
Age in months[b]		6[c]			8.1	7.2–9.1		8.1	7.2–8.7		8.1	7.6–8.6

[a]The monthly income of under 1000 euros reflects living close to or below the poverty level in Finland (Statistics Finland, 2015)
[b]At observation and calculated from expected due date; [c]infant outcome was assessed using 6-month questionnaires.

Table 2. The level of maternal self-reported stress in Studies I-IV and breast milk cortisol concentration in Study III.

	Study I (*n* = 282)		Study II (*n* = 391)		Study III (*n* = 65)		Study IV (*n* = 214)	
Stress measure (theoretical range)	Mdn (Q_1, Q_4)	Range	Mdn (Q_1, Q_4)	Range	Mdn (Q_1, Q_4)	Range	Mdn (Q_1, Q_4)	Range
Depressive symptoms (EPDS, 0–30)								
Average across pregnancy	2.7 (1.7, 7.7)	0–21.7					2.9 (1.5, 6.3)	0–15.5
Gwk 14	3.0 (1.0, 8.0)	0–27	4.0 (1.0, 7.0)	0–22			3.0 (1.0, 6.0)	0–19
Gwk 24	3.0 (1.0, 7.0)	0–22	3.0 (1.0, 7.0)	0–25			3.0 (1.0, 5.0)	0–18
Gwk 34	3.0 (1.0, 6.8)	0–26	3.0 (1.0, 7.0)	0–20			3.0 (1.0, 6.3)	0–19
3 months			3.0 (1.0, 6.0)	0–19	3.0 (1.0, 6.0)	(0-15)		
6 months	3.0 (1.0, 6.0)	0–22	3.0 (1.0, 7.0)	0–23			3.0 (1.0, 7.0)	0–22
Overall anxiety (SCL-90, 0–50)								
Average across pregnancy	1.3 (0.3, 5.3)	0–26.7					1.3 (0.3, 4.8)	0–26.7
Gwk 14	2.0 (0.0, 4.0)	0–40	2.0 (0.0, 4.0)	0–24			1.0 (0.0, 4.0)	0–40
Gwk 24	2.0 (0.0, 5.9)	0–40	2.0 (0.0, 5.6)	0–28			1.0 (0.0, 5.0)	0–40
Gwk 34	1.0 (0.0, 5.0)	0–40	1.1 (0.0, 4.0)	0–33			1.0 (0.0, 4.0)	0–26.7
3 months			1.0 (0.0, 3.3)	0–24	1.00 (0.0, 3.0)	(0-15)		
6 months	0.0 (0.0, 3.0)	0–23	1.0 (0.0, 4.0)	0–28			1.0 (0.0, 3.1)	0–24
Pregnancy-specific anxiety (PRAQ-R2, 10–50)								
Average across pregnancy	21.0 (17.0, 26.0)	10–43.5					21.3 (17.5, 25.1)	10–40.5
Gwk 24	21.0 (17.0, 26.0)	10–46					21.0 (17.0, 25.0)	10–42
Gwk 34	21.0 (16.0, 27.0)	10–42					22.0 (17.0, 26.0)	10–42
Breast milk cortisol concentration, nmol/l					3.5 (2.4, 5.6)	(1.4–13.1)		

Overall, the demographic characteristics of the substudies resembled the characteristics of the FinnBrain Birth Cohort Study families in terms of maternal age. infant sex and length of gestation (described in Karlsson et al., 2017). The sample of Study I resembled the source population also in terms of education and income, and it had even more multiparous mothers than in the source population. Instead, there was a slightly lower amount of multiparous mothers and mothers with the lower income or lower education in the Studies II, III and IV, and the sample of Study IV had a remarkably higher education and income level than in other studies.

Table 3. The percentage of mothers exceeding the cut-offs of the clinical measures across assessments in each study. The cut-points are shown for EPDS (≥12) and SCL-90 anxiety subscale (≥10).

Symptoms	I (*n* = 282)	II (*n* = 391)	III (*n* = 65)	IV (*n* = 214)
Depressive (EPDS)				
Gwk 14	7.5	7.3		6.6
Gwk 24	9.6	8.5		6.5
Gwk 34	5.8	8.4		5.6
3 months		3.2	3.1	4.2
6 months	3.4	6.0		3.7
Anxiety (SCL-90)				
Gwk 14	11.8	8.1		6.1
Gwk 24	15.0	13.7		8.4
Gwk 34	9.7	9.7		8.4
3 months		6.4	6.2	8.9
6 months	5.6	7.5		6.1

4.2 Methods

4.2.1 Procedure

The procedures in Studies I-IV are presented in Figure 2. Maternal self-reported stress was gathered with electronic and postal questionnaires at five time points during the early second trimester (gestational week [gwk] 14), late second trimester (gwk 24) and third trimester (gwk 34) and 3 and 6 months postpartum using the EPDS and SCL-90. Moreover, the PRAQ-R2 was used in the assessment of prenatal stress at gestational weeks 24 and 34. In Study III that focused only on postnatal stress exposure, mothers gave a breast milk sample at 2.5 months and reported their anxiety and depressive symptoms at 3 months. Infant fear reactivity was assessed at 6 months in Studies I, II and III and in a laboratory visit at 8 months in Studies II and III. Infant executive functioning, which was in focus of Study IV, was measured in the laboratory when the infant reached the age of 8 months.

Background information, including demographic statistics, is based on maternal self-reported data gathered in first trimester. Data on infant sex, birth weight, birth date and length of gestation is drawn from hospital records and complemented with data from Finnish National Birth Register (www.thl.fi).

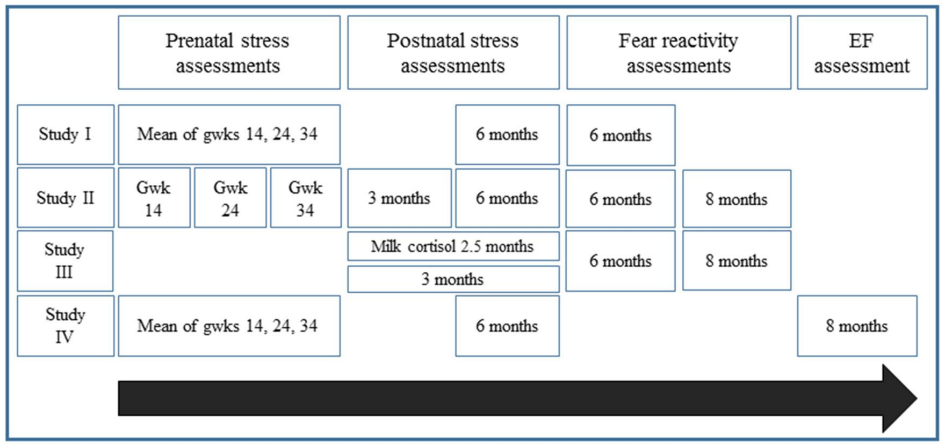

Figure 2. Design of the current study

4.2.2 Early life stress

In the current study, ELS was measured as both maternal self-reported psychological stress, including depressive, anxiety and pregnancy-specific anxiety symptoms during pre- and postnatal period and breast milk cortisol concentration at 2.5 months. The specific measures used are described below.

4.2.2.1 Maternal pre- and postnatal self-reported stress

Maternal prenatal stress was measured at gestational week 14 using Edinburgh Postnatal Depression Scale (the EPDS) and Symptom Checklist -90 anxiety subscale (the SCL-90) and at gestational weeks 24 and 34 using the EPDS, the SCL-90 and the Pregnancy-Related Anxiety Questionnaire Revised 2 (PRAQ-R2). The EPDS is a widely used instrument for assessing both prenatal and postnatal depression (Bergink et al., 2011; Cox, Holden, & Sagovsky, 1987; Rubertsson, Börjesson, Berglund, Josefsson, & Sydsjö, 2011). It consists of items ranging from 0 to 3 with higher scores indicating higher depressive symptoms. The anxiety scale of SCL-90 is a valid measure of overall anxiety symptoms in both clinical and general population settings (Derogatis, Lipman, & Covi, 1973; Holi, 2003) and consists of 10 items that are rated from 0 to 5. The PRAQ-R2, a revised version of PRAQ-R, is validated for use in both nulliparous and multiparous women (Huizink et al., 2015; Huizink, Mulder, Robles de Medina, Visser, & Buitelaar, 2004). The PRAQ-R consists of ten items rated from 1 to 5 with higher scores indicating higher pregnancy-specific anxiety. The PRAQ-R includes three factors measuring fear of giving birth, fear of fetal health and concerns about own appearance. In this study, the sum of all items was used as a measure of pregnancy-specific anxiety.

Maternal postnatal stress was measured using the EPDS and SCL-90 anxiety scale described above 3 and 6 months postpartum. All the instruments measuring maternal self-reported stress demonstrated good to excellent internal consistency in the current study (Cronbach's α for EPDS = .83–.89, .86–.90 for SCL-90 anxiety scale and .85–.91 for PRAQ-R2, respectively). In the final analyses, all instruments were used as continuous measures, either reflecting the mean of symptoms throughout the pregnancy or sum of postnatal symptoms 6 months postpartum. Only exceptions are Studies II and III. In Study II, three trajectory classes were formed based on the course of depressive and general anxiety (SCL-90) sums during pre- and postnatal period. In Study III, a standardized sum of maternal anxiety and depressive symptoms at 3 months was used in the analyses.

4.2.2.2 Breast milk cortisol concentration

One breast milk sample per participating mother was collected during a visit to the FinnBrain Birth Cohort Research Site 2.5 months postpartum. The study nurse was present during the data collection. To avoid error caused by circadian variation in the cortisol concentrations of milk (van der Voorn et al., 2016), the majority (90%) of the samples were collected between 10 am and 4 pm. However, not all participants were able to extract the sample in the instructed time frame, so sample collection time (continuous, in minutes) was taken into account in the analyses.

The mothers were told to feed the baby from the right breast 1.5–2 hours prior to study visit, but breastfeeding from the left breast was allowed according to the infant needs. Mothers wore latex gloves and expressed 10 ml of front milk from the right breast using manual expression (Pundir et al., 2017). Breast milk was collected in sterile cups, and immediately transferred into tubes in the laboratory. Milk samples were stored in a –70 °C freezer. Prior to processing, milk was thawed and gently mixed for 1 minute. Cortisol was extracted from milk using dichloromethane and assays were analyzed using validated luminescence immunoassay method (IBL International, product RE62111) described previously in detail by Grey et al. (2013). Assays were carried out at the Finnish Institute of Occupational Health.

4.2.3 Infant fear reactivity

4.2.3.1 Parent-reported fear reactivity

At 6 months of age, mothers rated their infants' emotional reactivity including fear reactivity. The Infant Behavior Questionnaire Revised (Garstein & Rothbart, 2003) in Study I and its Short Form (Putnam, Helbig, Gartstein, Rothbart, & Leerkes, 2014) in Studies II–IV were used to measure mother-reported emotional reactivity and fear. The IBQ-R is a widely used and a reliable measure for assessing infant temperament between the ages 3 and 12 months. The original IBQ-R consists of 191 items, whereas Short Form of IBQ consists of 91 items, comprising three broad dimensions and fourteen subscales. The parent assesses infant behavior during the past week or past two weeks on a scale from 1 to 7. Higher scores on each scale refer to higher level of certain temperament characteristic.

In Study I, two broad dimensions of reactivity and their subscales were used to measure infant emotional reactivity: Surgency/Positive Affectivity (including subscales Activity Level, Smiling and Laughter, High Intensity Pleasure, Perceptual Sensitivity, Approach and Vocal Reactivity) and Negative Affectivity (including

subscales Distress to Limitations, Fear, Sadness and Falling Reactivity), which is referred to as Negative Reactivity in the current study. In Studies II and III, we only focused on the subscale Fear under the broad dimension Negative Reactivity. In Study I, the emotional reactivity subscales demonstrated adequate to good internal consistency (Cronbach's alphas ranging from .68 to .89), and the Fear subscale demonstrated good internal consistency throughout the studies (Cronbach's α = .83–.88).

4.2.3.2 Observed fear reactivity

At 8 months of age, infant fear reactivity and EF were assessed in the laboratory during a visit with a total duration of 1–1.5 hours. In addition to measures described in this study, the visit included an eye movement tracking task, two other temperament observations and a free play situation of mother and the infant, always administered in the same order. The behavioral assessment of fear reactivity was conducted using Masks episode from the Laboratory Temperament Assessment Battery Prelocomotor (Lab-TAB; Goldsmith & Rothbart, 1999), which is a standardized battery for the laboratory-based assessment of infant temperament. In Masks episode, infants are exposed to four masks (A theater mask, Old man, Chucky, Gas mask; see Figure 3) always presented in a fixed order and ranging from lower to higher in intensity. The masks are presented for 10 seconds each, with a 5-second interval in between and through a curtain hanging on a plastic, textile-covered booth that separates the experimenter and the infant (see depiction on the task setting in the Lab-TAB prelocomotor manual cited above).

Four indicators of fear reactivity, escape behaviors (on a scale from 0 to 3), infant facial fear (0–3), bodily fear (0–3) and fearful vocalizations (0–5) were coded in response to presentation of each mask following the Lab-TAB instructions and AFFEX guidelines (Izard, Dougherty, & Hembree, 1983). The coders were psychologists or psychology master students, who received a reliability training prior to actual coding. The coders had to reach the reliability level of 80% in each of the fear indicators in eight training videos that were previously coded by a team of three experienced Lab-TAB coders. After receiving the training, 10% of the coded videos were reliability coded by the researcher, and the coders received feedback for their coding. The coders also had a possibility to discuss about unclear situations and code them together with the researcher.

The associations between infant reactivity on each indicator in each of the masks and the composite variable of the indicators of reactivity were examined. The behavioral indicators of fear were moderately to highly correlated (*r*'s ranging from

.45 to .79 in Study II and from .63 to .84 in Study III), but due to a weaker correlation of escape behaviors to other indicators of fear, only facial, bodily and vocal indicators of fear were included in the composite variable in Study III. For the use in analyses, the composite was calculated by creating an averaged sum variable of indicators. In calculating the sum, the logarithm-transformed and standardized (*z*-score) indicators were used to reach normal distribution. The indicators of fear reactivity showed high internal consistency (Cronbach's α = .89 in Study II and .88 in Study III) and inter-rater reliability (Mean of Cohen's Kappa for the full scale = .79, inter-rater *r* = .95–.98). Further, caregiver behavior during fear observation was assessed (0 = severe interference, 1 = mild interference, 2 = no interference) to control for the effect of parent behavior during the task on infant reactivity.

Figure 3. The masks showed for the infant in the Lab-TAB Masks episode that was used to assess observed infant fear reactivity

4.2.4 Infant executive functioning

The modified A*B* task (the delayed response task) was used to assess infant executive functioning. The A*B*/delayed response task requires infant to hold and update spatial locations in mind and inhibit a prepotent response (Diamond, 1985; Sun et al., 2009). In comparison to the classic A*B* task (e.g. Wolfe & Bell, 2007), a fixed order of object hidings is used in the delayed response task, an approach that is regarded as equivalent in terms of its ability to assess infant EF (Diamond & Doar, 1989).

During the task, infants were seated in their mother's lap in front of a table. The testing instrument was a board with a midline located 20 cm from the edge and two hiding locations (two blue cups) marked with X's separated by 11 cm on either side of the midline (Figure 4). The midline of the board was matched with the

infant's position in the mother's lap and corrected whenever needed. During experimental trials, the toy was hidden in one of the two locations. After the toy was hidden, the infant's gaze was brought to the midline by asking "(Infant's name), Where's the toy?" The direction of the infant's reaching after his/her gaze was brought to midline was scored either as correct or incorrect. All reaching behaviors initiated within 8 seconds were scored as reaching.

Stimuli were presented in a fixed pattern on three delay levels reflecting task demands for working memory (0 seconds, 2 seconds and 4 seconds). There were 6 trials in each delay level. For instance, in the delay of 0 seconds, the hidings started from the right (R-L-L-R-R-L). Infants were allowed to continue to the next delay if they scored correctly in 3 of the 6 trials, which was based on the observation that one-third of the infants reached in less than 6 trials in each delay level. The duration of administering each delay was approximately five minutes resulting in a duration of 5 to 15 minutes for the entire task depending on to which delay infant was able to proceed.

The procedure was video recorded and infant performance was coded by both the experimenter and afterwards by a trained coder. If there was a disagreement between the coder and the experimenter on infant scores, the average of the coder and experimenter scores was calculated. If a disagreement involved the decision to move to the next level of delay, the coder evaluation based on the video recording was used in the final scoring. Inter-rater agreement between the raters was 81%, and in 82% of the disagreements and rater assessments were within one point of each other. All trials where the infant showed some reaching behaviors, and at least the first 3 trials were presented, were included in the dataset. The response to each trial (0 = incorrect, 1 = correct) was used as an outcome in the analyses reflecting the probability of the correct choice across all trials in relation to predictors. As infant performance relied greatly on the difficulty of the trial, and task difficulty also reflects task duration, the delay level was controlled for in the analyses.

Figure 4. The modified A*B* task setting

4.2.5 Background factors

In all studies, preliminary analyses were conducted to investigate whether maternal age, education, monthly income after the first trimester of gestation, number of prior deliveries, infant sex, infant age from expected due date, length of gestation or birth weight were associated with dependent variable. Information on maternal education, monthly income, age and number of prior deliveries were acquired along with maternal responses to the first questionnaire at gestational week 14. Similarly, information on maternal smoking was gathered with questionnaires at gestational weeks 14 and 34 during the index gestation, and a sum variable of maternal smoking during the pregnancy was calculated (0 = no smoking, 1 = smoking either during early or late gestation or both). Moreover, information on infant sex, birth weight and the length of gestation was drawn from hospital records after children in the sample were born and complemented with the data from Finnish National Birth Register when available.

Eventually, in Study I, information about maternal education and infant sex were used as covariates in the analyses in addition to postnatal stress. In Study II, infant sex and maternal education, maternal income, the number of prior deliveries, maternal age and caregiver behavior during fear observation were used as covariates in the final models. In Study III, based on the preliminary analyses, only infant sex along with maternal psychological distress, sample collection time and caregiver behavior during fear observation were included in the final model. In Study IV, as there were no association between infant EF performance and maternal smoking during pregnancy, only maternal education, infant sex and infant age from expected due date were included as covariates in the final model.

4.2.6 Statistical analyses

In Study I, the association between prenatal stress and aspects of infant reactivity were assessed by comparing high and low prenatal stress groups. Furthermore, a linear regression analyses for both negative and positive emotional reactivity as well as those subcomponents, where there had been a significant difference between high and low prenatal stress groups, were run to control for the effect of maternal education and infant sex. Both prenatal depressive, overall anxiety and pregnancy-specific anxiety symptoms were included in the final step of the regression models as separate predictors to examine whether there were differences in the potential of different symptoms to predict infant emotional reactivity and specifically, fear reactivity.

In Study II, latent growth mixture modeling (LGMM) in Mplus 6.0 (Muthén & Muthén, 1998-2011) was used to identify maternal pre- and postnatal stress (anxiety and depressive symptoms) trajectories. For this purpose, the validity of factor structures of the EPDS and SCL-90 were first examined with longitudinal confirmatory factor analysis. The fit of the models was evaluated using χ^2-test, the root mean square error of approximation (*RMSEA*; values close to .06 indicating a good fit of the model), the comparative fit index (*CFI*; values close to .90 reflecting adequate fit) and the standardized root mean square residual (*SRMR*, values below .08 indicating a good fit) (Hu & Bentler, 1999; Steiger, 1990). The longitudinal factor model of the EPDS showed acceptable fit with the data, [χ^2 (1054) = 1785.905, $p < .001$, *CFI* = .91, *RMSEA* = .042, *SRMR* = .062] when errors of consecutive items (1 and 2, 4 and 5, 8 and 9) were allowed to correlate. Similarly, the longitudinal factor model of the SCL-90 anxiety subscale showed acceptable fit with the data, [χ^2 (1045) = 1728.654, $p < .001$, *CFI* = .90, *RMSEA* = .041, *SRMR* = .059] when errors of item pairs with similar content (3 and 6, 5 and 10) and errors of consecutive item pairs (7 and 8, 1 and 2) were allowed to correlate.

For the evaluation of model class solutions, Bayesian and Akaike Information Criteria (lower values indicating better model; Muthén & Muthén, 1998-2011; Nylund, Asparouhov, & Muthén, 2007), entropy values (values closer to 1.0 indicating higher confidence of classification; Ramaswamy, Jedidi, & DeSarbo, 1993) and posterior class probabilities were used. Furthermore, the theoretical fit and interpretability of the results were used in choosing the best model. After the evaluation of these indices, three-class models of both anxiety and depressive symptoms were selected (see Results section for more details concerning the class solution). Due to the high correlation of anxiety and depressive trajectories, the two solutions describing maternal anxiety and depressive symptoms were combined into one three class solution describing maternal stress (see Results section). One-way ANOVA in SPSS 22.0 was used to study differences between the classes with regard to mother-reported and observed infant fear reactivity. Moreover, multifactorial ANCOVA was used to examine differences between the classes and infant sex by class interactions after controlling for maternal age, education, monthly income, parity and caregiver behavior.

In Study III, linear regression analyses were used to study the association between milk cortisol concentration and mother-reported and observed infant fear reactivity. For observed fear reactivity, linear mixed modeling in R program using Nonlinear and linear mixed models (nlme) package (Pinheiro et al., 2016; R Core Team, 2016) was utilized to examine the association between milk cortisol and infant fear reactivity after controlling for mask type (i.e. the effect of mask intensity and the task duration on fear reactivity). In addition to confounding factors, including sample collection time, caregiver behavior and maternal self-reported

stress and the main effects of infant sex and milk cortisol, sex by milk cortisol interaction was added in the final model. Furthermore, simple slope analyses were conducted for interaction slopes.

In Study IV, the effect of pre- and postnatal stress on infant EF performance was studied using Spearman correlations, a logistic regression analysis and general linear modeling (GLM) function of R program (R Core Team, 2016). The frequency of correct choice (0 = incorrect, 1 = correct) across the whole dataset was used as a dependent variable to reflect probability of the correct choice. Based on preliminary set of models, there were observable associations only between maternal overall anxiety and infant EF but no associations between maternal pre- or postnatal depressive symptoms or pregnancy-specific anxiety and infant EF. Consequently, maternal pre- and postnatal overall anxiety were used as predictors in the model. In the second step of the model, after controlling for the task difficulty (delay), infant age, maternal education and the main effect of prenatal anxiety and infant sex, an interaction of prenatal anxiety and infant sex was added in the model. In the third step of the model, the postnatal anxiety and infant sex by postnatal anxiety interaction were added into the model.

In all statistical analyses of the present study, findings at a significance level $p < .05$ (or with 95% confidence interval) were regarded as significant. Accordingly, findings at a level $p < .10$ were treated as approaching significance. In case that the dependent variables were not normally distributed, variables were transformed with a usual logarithm transformation (Tabachnick & Fidell, 2007) with an exception of Study IV where a non-parametric approach was used. In terms of attrition analyses, if the dependent variable did not follow normal distribution but the association between variables was linear, both parametric and non-parametric test methods were used to test the differences. If the results were similar, parametric indices were reported. In cases of different results, non-parametric indices were reported.

4.2.7 Ethical considerations

The present study and the FinnBrain Birth Cohort Study are approved by the Ethics Committee of the Hospital District of Southwest Finland. Informed consent was gathered from all participating families. For the part of the data drawn from National Birth Register, a register-keeping organization gave their permission to use the data in this study according to the Finnish data protection legislation. All subjects were informed about the confidentiality of the study as well as their voluntary participation and a right to interrupt the testing without any specific reason. Moreover, with regard to testing situations used in Studies II-IV, experimenters were

trained to recognize when infant or the mother were not ready for the task, and in this case, the session was interrupted. The Finnish legislation was followed in all phases of the study.

5 RESULTS

5.1 Maternal pre- and postnatal stress and infant fear reactivity

5.1.1 Parent-reported fear reactivity in contrast to other aspects of infant emotional reactivity

In Study I, there was a significant difference between mothers with high prenatal stress and low prenatal stress in their ratings of aspects of infant emotional reactivity (Table 4). Mothers with high prenatal stress rated their infants higher in overall negative reactivity and all its subscales (Fear, Sadness, Distress to Limitations, Falling Reactivity). Moreover, infants of mothers with high prenatal stress were rated higher in overall positive reactivity and its aspects: Perceptual sensitivity and Vocal reactivity. Similar results were evident when correlations among indices of maternal prenatal stress – overall anxiety symptoms, depressive symptoms and pregnancy-specific anxiety symptoms – and aspects of emotional reactivity were examined.

With regard to background factors, mothers with high prenatal stress were also more likely to have lower education (χ^2 [3] = 13.47, p = .004) and lower income (χ^2 [3] = 9.23, p = .026) in comparison to mothers with low prenatal stress, but there were no differences in age, infant gestational age or sex. Moreover, infant girls were rated higher in fear (T [271] = –3.554, p < .001). Consequently, maternal education and infant sex were controlled for in the regression models.

Table 4. The means and mean differences between the case group (infants exposed to high maternal prenatal stress) and the control group (infants exposed to low prenatal stress)

	Mean (SD)			
	Cases	Controls	*T* (df)	*p*
Negative emotional reactivity	3.09 (0.64)	2.76 (0.60)	4.28 (279)	.000
Distress to limitations	3.42 (0.88)	3.04 (0.80)	3.69 (279)	.000
Fear reactivity	2.69 (0.97)	2.34 (0.98)	3.31 (271)	.001
Sadness	3.46 (0.99)	3.10 (0.90)	3.05 (277)	.003
Falling reactivity	5.23 (0.78)	5.43 (0.73)	2.21 (279)	.030
Positive emotional reactivity	4.93 (0.64)	4.69 (0.68)	2.97 (280)	.003
Activity level	4.57 (0.75)	4.42 (0.76)	1.62 (280)	.106
Smiling and laughter	4.78 (1.18)	4.54 (1.08)	1.76 (277)	.079
High intensity pleasure	6.08 (0.71)	5.99 (0.74)	0.94 (274)	.351
Perceptual sensitivity	4.05 (1.13)	3.60 (1.25)	3.10 (280)	.002
Approach	5.66 (0.66)	5.48 (0.83)	–1.54 (272)	.124
Vocal reactivity	4.51 (0.98)	4.23 (1.03)	2.28 (280)	.023

After controlling for maternal postnatal stress, infant sex and maternal education, the associations between maternal prenatal stress and infant positive reactivity and its subscales disappeared. In turn, maternal pregnancy-specific anxiety positively predicted infant overall negative emotional reactivity even after controlling for confounders and other maternal prenatal symptoms. When more fine-grained aspects of negative emotional reactivity were studied, it was found that indices of prenatal stress were not related to ratings of infant Distress to Limitations or Sadness, although the association between pregnancy-specific anxiety and sadness approached significance ($p = .08$). In turn, pregnancy-specific anxiety was negatively related to infant Falling Reactivity, and positively related to higher infant Fear at the trend level ($p = .057$). In addition to pregnancy-specific anxiety, infant sex was also a significant predictor of fear, as girls were rated higher in fear than boys.

In other words, infants of mothers with pregnancy-specific anxiety were more negatively reactive, specifically, more fearful and less efficient to recover from negative emotions (see the final steps of the regression models in Table 5). Indices of prenatal stress explained 2% of the variance of fear and 6% of the variance in falling reactivity and overall negative reactivity.

Table 5. The association between maternal prenatal stress and mother-reported infant negative reactivity and its aspects of fear reactivity and falling reactivity after controlling for confounding factors (Step III of the regression model)

	Negative reactivity	Fear reactivity	Falling reactivity
Predictor	*β*	*β*	*β*
Maternal education	0.11	0.02	–0.02
Infant sex	0.12	0.26***	0.01
EPDS at 6 months	0.03	0.01	–0.00
SCL at 6 months	0.02	0.13	0.10
Prenatal EPDS mean	0.15	0.06	–0.13
Prenatal SCL mean	0.00	–0.01	0.07
PRAQ-R2 mean	0.20**	0.15†	–0.22**
Adjusted R^2	0.10**	0.10***	0.04*
ΔR^2 of prenatal stress	0.06**	0.02†	0.06**

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, † $p < 0.10$

5.1.2 The trajectories of maternal pre- and postnatal stress

In Study II, the maternal prenatal stress measured as maternal anxiety and depressive symptoms was not associated with infant observed fear reactivity. The only associations found were the ones between maternal anxiety in gestational week 14

and parent-reported fear (r = .12, p = .03) and maternal anxiety at 6 months and parent-reported fear (r = 0.11, p = 0.048).

Consequently, the trajectories of maternal pre- and postnatal stress were first studied using latent growth mixture modeling in order to be able to differentiate between the trajectories of pre- and postnatal stress, and later, whether the trajectory of stress affects infant fear reactivity. Based on the inspection of model fit indices, models slightly improved until 5-class solution with regard to both depressive and anxiety symptoms (Table 6). However, in both instances, the 4- and 5-class solutions were not notably better than 3-class solution, and the number of cases in 4- and 5-class solutions was too low to conduct further interaction analyses. Consequently, three-class solution of both anxiety and depressive symptoms were selected. In both solutions, the trajectories were named "Prenatal symptoms" "Low and stable symptoms" and "Continuously increasing symptoms" (see Figure 5AB).

Table 6. The latent growth mixture model fit indices

EPDS						
No. of classes	*LL* index	*AIC*	*BIC*	Entropy	N	The probability for class membership
1	–4883.017	9786.034	9825.721	1	391	1
2	–4800.612	9627.223	9678.817	.87	300/91	.98/.92
3	–4767.89	9567.780	9631.279	.87	53/299/39	.86/.97/.87
4	–4750.880	9539.760	9615.165	.90	3/70/285/33	1.00/.86/.97/.85
5	–4729.476	9502.951	9590.263	.89	12/78/261/30/10	.86/.86/.97/.86/.95
SCL-90						
No. of classes	*LL* index	*AIC*	*BIC*	Entropy	N	The probability for class membership
1	–4831.607	9683.213	9722.900	1	391	1
2	–4717.337	9460.674	9512.267	.96	354/37	1.00/.92
3	–4651.943	9335.886	9399.385	.94	56/307/28	.91/.99/.93
4	–4624.424	9286.848	9362.253	.94	25/55/22/289	.92/.90/.93/.98
5	–4572.4608	9195.216	9294.434	.95	17/57/17/9/276/15	.92/.92/.96/.94/.97/.91

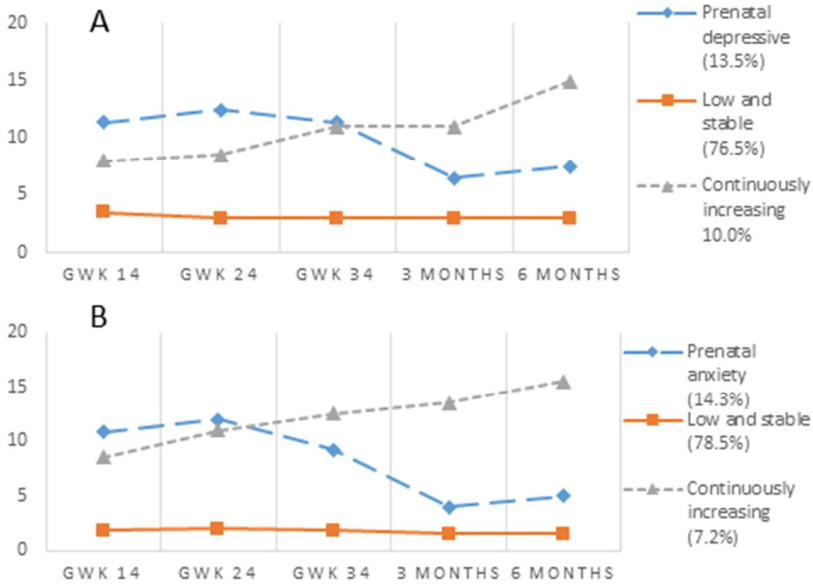

Figure 5. The latent trajectories of maternal pre- and postnatal anxiety and depressive symptoms

The trajectories of depressive symptoms (Figure 5A) were not related to any background factors in preliminary analyses. By contrast, the trajectories of anxiety symptoms (Figure 5B) were associated with maternal monthly income (χ^2 [4] = 11.303, p = .023), maternal age (F [2,388] = 5.666, p = .004) and parity (χ^2 [4] = 5.256, p = .072). Mothers with continuously increasing anxiety were more likely to earn below the poverty level (less than 1000 euros per month). Additionally, when compared to mothers with low and stable symptoms, both mothers with prenatal and continuously increasing anxiety were less likely to earn more than 2000 euros per month. They were also younger and more likely to be primiparous than mothers with low and stable symptoms.

The trajectories of depressive and anxiety symptoms were highly correlated (χ^2 [4] = 226.516, $p < 0.001$). Based on the correlation as well as on the fact that the results were similar regardless of whether the trajectory of anxiety or depressive symptoms was used as a predictor of fear, the trajectories were combined to reflect overall maternal stress, now named “Low and stable stress” (70.6%), “Prenatal stress” (18.9%) and “Continuously increasing stress” (10.5%). The combined trajectories were not related to any of the background factors.

5.1.3 The trajectories of pre- and postnatal stress and infant fear reactivity

In Study II, boys and girls differed from each other in mother-reported fear (T [329] = – 2.756, p = .006) and observed indicators of fear, thus, escape behaviors, facial fear and fearful vocalizations (T [389] = –2.005 to –2.933, p = .004 to .046) but not in bodily fear (T [389] = – 0.131, p = .896). Other background factors were not associated with infant fear reactivity with one exception; caregiver interference during the observation was associated with higher infant fear reactivity (F [2, 390] = 10.222, p < .001).

The means of fear reactivity within each stress trajectory in Study II are showed in Table 7. When compared to the findings of the Study I, similar results were obtained concerning mother-rated infant fear reactivity. There was a near-significant difference between maternal stress trajectories with regard to mother rating of fear reactivity (p = .06). More accurately, mothers with prenatal stress rated their infants higher in fear reactivity compared to mothers with low and stable stress. However, after accounting for confounders, the statistical significance of the model weakened (p = .098), and there was no evidence for stress trajectory by infant sex interaction (Table 8). Effect size was similar to Study I, as stress trajectory explained 2% of the variance in mother-reported fear.

Table 7. One-way group comparisons between maternal trajectories of stress during pre- and postnatal period and infant fear reactivity

The aspect of reactivity	The means of reactivity by the maternal trajectory of stress in pre- and postnatal period (Mean, SD)				
	Low and stable (n = 276)	Prenatal (n = 74)	Continuously increasing (n = 41)	F^b	p
Observed fear reactivity	3.51 (2.07)	3.76 (2.34)	3.33 (2.48)	0.737	.48
Reported fear reactivity[a]	0.34 (0.20)	0.40 (0.19)	0.37 (0.20)	2.941	.06

[a]Log-transformed values based on the imputed dataset are showed for mother-reported fear.
[b]Indices reported are based on the statistical analyses that used logarithm-transformed variables.

Similarly, there were no significant differences between the trajectories in observed infant fear reactivity (Table 7). However, the results of factorial ANCOVA showed that stress trajectory by infant sex interaction significantly predicted observed infant fear reactivity (Table 8). That is, after controlling for maternal education, income, parity and age, caregiver behavior in the test situation and the main effects of maternal symptom trajectory and infant sex, infant girls of mothers with prenatal stress showed elevated fear reactivity in contrast to boys, who were slightly lower than average in fear reactivity (Figure 6). Moreover, infant girls of mothers with continuously increasing stress showed decreased fear reactivity. Interaction of stress trajectory and infant sex explained 3% of the variance in infant fear responses.

Table 8. The factorial analysis of covariance for the effects maternal pre- and postnatal stress trajectory on observed and parent-reported infant fear reactivity

The predictor	*F* and *p* values and η^2 for each predictor of fear reactivity			
	Observed fear reactivity	η^2	Reported fear reactivity	η^2
Intercept	3.564*	.01	13.341	.04
Child sex	0.134	.00	3.440	.01
Income	1.806	.01	0.530	.00
Education	0.182	.00	0.106	.00
Parity	2.091	.00	0.572	.00
Maternal age	1.925	.00	0.638	.00
Caregiver behavior	8.913***	.05		
Trajectory of symptoms	0.918†	.00	2.477†	.02
Trajectory by infant sex	5.445**	.03	0.722	.00
Model effect size (R^2)	0.10***		0.06†	

*** $p < .001$, ** $p < .01$, * $p < .05$, † $p < .10$

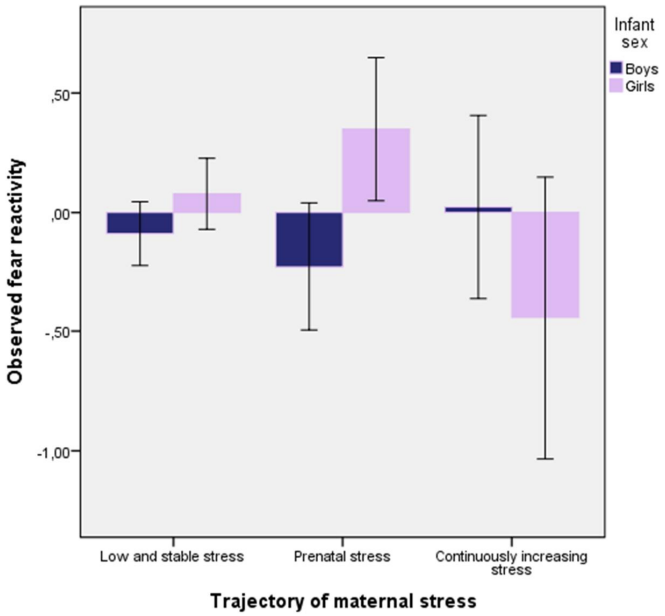

Figure 6. The association between maternal stress trajectory and observed standardized fear reactivity in girls and boys (error bars represent the confidence interval of 95%)

5.2 Breast milk cortisol concentration and infant fear reactivity

The means of infant fear reactivity in Study III are displayed in Table 9. Fear reactivity corresponded to that reported in other studies that used Mask task in measuring observed fear of 8-month-old infants (Gartstein & Marmion, 2008). However, in contrast to some previous studies, level of fear reactivity was not associated with infant sex in this sample, and parent-reported and observed fear reactivity did not correlate with each other.

When both sexes were included in the zero-order analyses (Table 10), breast milk cortisol concentration was not associated with mother-reported fear or observed infant fear reactivity. Furthermore, milk cortisol was neither associated with maternal postnatal psychological distress nor infant sex. However, caregiver behavior was related to fear reactivity during masks 3 and 4. Beyond the correlations showed in the table, milk cortisol was also not related to maternal prenatal distress (*r*'s ranging –.14 to .08, *p*'s ranging from .26 to .97).

Table 9. The descriptive statistics (raw scores) of parent-reported and observed infant fear reactivity in Study III

Infant fear reactivity (theoretical range)	Overall, mean (range)	Means by stimuli			
		Mask 1	Mask 2	Mask 3	Mask 4
Fear composite	3.11 (0–7.50)	1.53	2.01	3.12	4.73
Bodily (0–3)	1.19 (0–2.75)	0.71	0.89	1.55	1.63
Facial (0–3)	1.10 (0–2.25)	0.57	0.72	1.45	1.66
Vocal (0–5)	0.82 (0–2.50)	0.25	0.40	1.12	1.44
Parent-reported (1–7)	2.42 (1.00–5.17)				

Next, the analyses were conducted separately for girls and boys. A positive correlation between milk cortisol and observed fear reactivity was found in girls but not in boys. After adjusting the associations for sample collections time, the associations between milk cortisol and fear disappeared; nevertheless, this was mainly explained by an inverse association between sample collection time and fear reactivity and not by a link between milk cortisol concentration and sample collection time as hypothesized. Consequently, the main effect of sample collection time was controlled for in the subsequent analyses.

After controlling for sample collection time, the main effect of infant sex, maternal psychological distress at 3 months and variation of responses to each mask stimulus, there was an interaction between infant sex and milk cortisol in predicting observed infant fear reactivity (Table 11). Milk cortisol was positively associated with fear reactivity in girls (β of simple slope analysis = 0.36, p = .04) but not in boys (Figure 7).

Table 10. The zero-order associations between milk cortisol concentration and fear reactivity and the confounding factors in the whole sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Fear reactivity (IBQ)															
2. Fear reactivity (lab)	.07														
3. Mask 1	.07	.70**													
4. Mask 2	.16	.80**	.62**												
5. Mask 3	–.03	.91**	.51**	.59**											
6. Mask 4	.07	.91**	.48**	.60**	.82**										
7. Milk cortisol[a]	.08	.15	.18	.15	.08	.09									
In girls	–.05	.44*	.32	.43*	.20	.39*									
In boys	.19	–.13	.02	–.19	–.04	–.18									
8. Sample coll. time	–.18	–.32*	–.23†	–.35**	–.25*	–.26*	–.22†								
9. Postnatal distress	.25†	–.12	–.08	–.09	–.10	–.12	–.06	–.00							
10. Depressive	.27*	–.13	.00	–.06	–.14	–.14	–.13	.05	.91**						
11. Anxiety	.19	–.10	–.14	–.10	–.04	–.08	.02	–.05	.90**	.63*					
12. Maternal age	–.06	–.08	–.14	.07	–.00	–.10	–.11	.16	–.12	–.02	–.20				
13. Gestational weeks	.14	–.00	.05	.10	–.03	–.01	–.10	.05	.05	.08	.01	–.10			
14. Birth weight	.12	.13	.14	.13	.12	.09	–.15	.09	.07	.05	.08	–.01	.45**		
15. Infant age (IBQ)	.15	–.20	–.10	–.03	–.20	–.23†	–.06	.06	.02	.14	–.12	.13	.59**	.11	
16. Infant age (lab)	.01	.10	.15	.13	.03	.03	.11	.05	.10	.17	–.00	–.02	.08	.19	.18
The partial correlations between milk cortisol and fear after adjusting for sample collection time															
Milk cortisol	.06	.08	.09	.08	.13	.09									
In girls	–.07	.29	.16	.32	.01	.28									
In boys	.17	–.15	.02	–.23	–.05	–.20									

** $p < .01$, * $p < .05$, † $p < .10$

Table 11. The linear mixed effect model for milk cortisol and standardized observed infant fear reactivity: moderation by infant sex (n = 65)

		Effect sizes (β) for the overall and stimulus-related standardized infant fear reactivity[a]				
	T value[b]	Overall	Mask 1	Mask 2	Mask 3	Mask 4
Intercept	–3.85***					
Caregiver behavior (in contrast to: severe interference)						
Mild interference	–1.43	–0.15				
No interference	–2.17*	–0.18				
Sample collection time	–4.08***	–0.02				
Maternal psychological distress	–1.54	–0.00				
Infant sex (girl)	–3.34***	–0.20				
Milk cortisol	–1.77†	–0.05	–0.03	–0.04	–0.06	–0.08
Milk cortisol by sex (girl)	3.83***	0.16	0.12	0.15	0.18	0.20

*** $p < 0.001$, * $p < 0.05$, † $p < .10$

[a]Effect sizes are shown for the standardized overall and stimulus-related infant fear reactivity and log-transformed milk cortisol along with the parameter estimates

[b]*T* value is shown for the overall effect across the stimuli

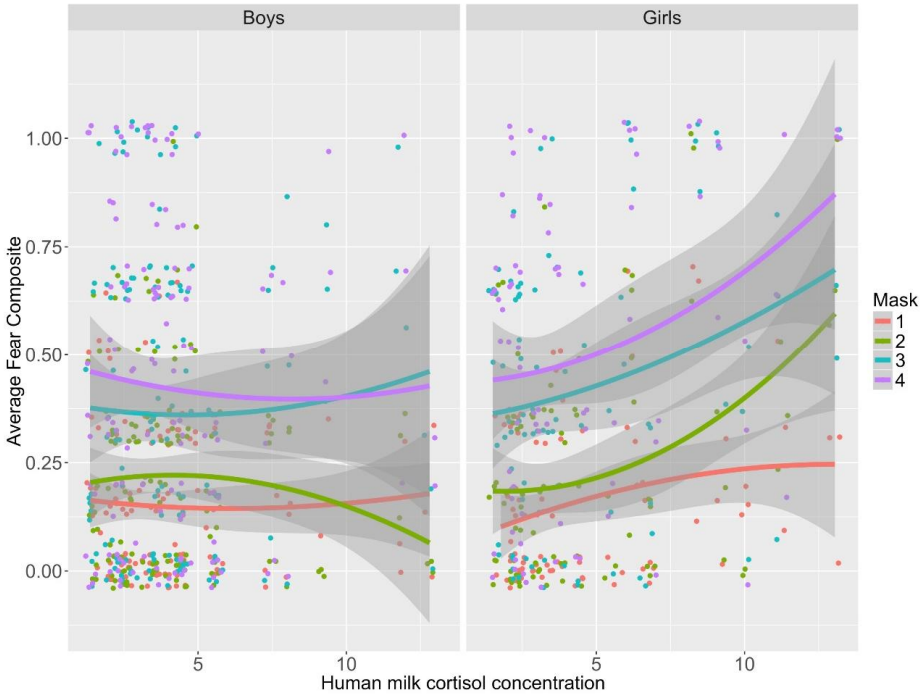

Figure 7. The association between breast milk cortisol and experimentally-induced infant fear reactivity (standardized values) in boys and girls separately using the mask type (the stimulus intensity) as a grouping variable

5.3 Maternal pre- and postnatal stress and infant executive functioning

The levels of infant EF performance for the entire sample and for boys and girls separately are showed in Table 12. Of all experiments, 29 (14%) were discontinued early at 0 or 2 second delays most typically due to infant exhaustion, restlessness or fussiness occurring during the experiment. In zero-order analyses, infant performance was not associated with infant sex or any of the background variables. Infant EF was also not associated with maternal pre- or postnatal anxiety, depressive or pregnancy-specific anxiety symptoms. However, there was a trend towards a negative correlation between postnatal overall anxiety and infant EF ($r = -.13$, $p = .06$).

Furthermore, when examining relations between EF, stress and background factors in girls and boys separately, there was a negative association between postnatal anxiety and EF only in girls ($r = -.22$, $p = .028$). Infant age was also positively associated with performance only in boys ($r = .20$, $p = .034$). In a set of preliminary models conducted, only prenatal and postnatal overall anxiety showed potential interactions with infant sex in predicting EF; there were no interaction effects when using maternal depressive or pregnancy-specific anxiety as predictors. Based on this observation, the association between postnatal anxiety and EF in girls, as well our aim to control for both pre- and postnatal exposure, overall anxiety in both periods was included in the regression model.

Table 12. Descriptive characteristics for the infant EF, measured as performance in the modified A*B* task including mean of correct recall and mean probability of correct recall out of six trials conducted (*N* = 214)

Task difficulty		Percentile		Infant sex	
		25th	75th	Boys	Girls
0 second delay	N = 214 (100 %)			N = 114	N = 100
Reaching (SD)[a]	5.3 (1.2)	5	6	5.3 (1.2)	5.2 (1.3)
Mean score (SD)[b]	2.8 (1.4)	2	4	2.9 (1.5)	2.8 (1.4)
Mean prob. (SD)[c]	.47 (0.24)	.33	.67	.48 (0.24)	.46 (0.24)
2 second delay	N = 116 (54 %)			N = 68	N = 48
Reaching (SD)	4.8 (1.5)	4	6	4.9 (1.5)	4.7 (1.4)
Mean score (SD)	2.7 (1.3)	2	3.75	2.6 (1.3)	2.8 (1.4)
Mean prob. (SD)	.45 (0.22)	.33	.63	.44 (0.22)	.47 (0.23)
4 second delay	N = 57 (27 %)			N = 30	N = 27
Reaching (SD)	4.2 (1.8)	3	6	4.6 (1.6)	3.7 (1.9)
Mean score (SD)	2.5 (1.4)	1.25	3.5	2.7 (1.4)	2.2 (1.3)
Mean prob. (SD)	.41 (0.23)	.17	.58	.46 (0.23)	.36 (0.22)
Overall	N = 214 (100 %)			N = 114	N = 100
Reaching (SD)	8.9 (1.8)	5	12	9.3 (4.9)	8.5 (4.7)
Mean score (SD)	4.9 (3.9)	2	7.6	5.1 (3.9)	4.7 (3.8)
Mean prob. (SD)[d]	.27 (0.21)	.11	.42	.28 (0.22)	.26 (0.21)

[a]The mean of trials where infants reached the cup
[b]The mean sum of correct choice
[c]The mean probability (frequency) of correct choice per six possible trials in each delay
[d]The mean probability (frequency) of correct choice per eighteen possible trials during the experiment

The results of logistic regression analysis are showed in Table 13. After controlling for task difficulty, infant age and maternal education, maternal prenatal anxiety had a negative effect on EF performance. Also, there was a trend towards anxiety and infant sex interaction in predicting EF (see Step 2 of the model). In other words, the association between prenatal anxiety and EF was negative in boys, but this effect was counteracted by infant sex so that this association was not evident for girls. After adding the postnatal anxiety in the model (Step 3), the trend towards an interaction of prenatal anxiety and infant sex remained. After controlling for postnatal stress, prenatal anxiety predicted EF performance in opposite directions for girls and in boys, thus, girls were better than boys in the presence of prenatal stress exposure. However, there was no evidence for an independent effect of prenatal anxiety on performance in either girls or boys (Figure 8A).

In the final step of the model, there was a significant interaction between postnatal anxiety and infant sex in predicting infant EF. Thus, maternal postnatal anxiety predicted poorer EF performance in girls but not in boys (Figure 8B). Additionally,

Figure 9 shows the difference of predicted mean probabilities between girls and boys based on the fitted model. That is, in the presence of very high maternal prenatal anxiety (score > 21) but no postnatal anxiety, girls performed better than boys within a 95% confidence interval. However, at even lower levels of postnatal anxiety (scores ranging from 3 with no prenatal exposure to 25 when prenatal anxiety score = 10), girls performed worse than boys within the 95% confidence interval.

These results were replicated with a sample where experiments that were discontinued early due to infant fussiness were excluded (N = 185). In this sample, the interaction between postnatal anxiety and infant sex remained (β = –2.05, p = .04, OR = 0.93 [0.88, 0.99]). Moreover, the interaction between prenatal anxiety and infant sex was significant in predicting infant EF, thus, there was a difference in performance between boys and girls (β = 2.08, p = .04, OR = 1.05 [1.00, 1.11]).

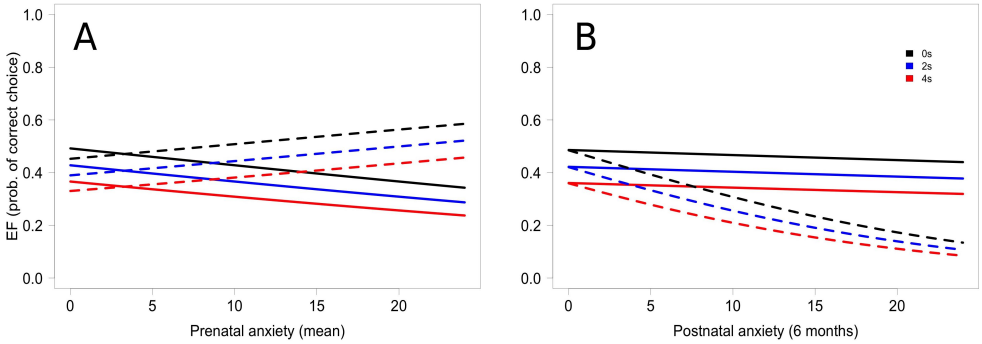

Figure 8. The fitted logistic regression curve showing the influence of the total prenatal and postnatal general anxiety to infant performance in EF task. (A) Prenatal anxiety has a positive influence on the performance of girls (dashed line) in contrast to boys (solid line). (B) The curves are fitted at the observed anxiety median (= 1)

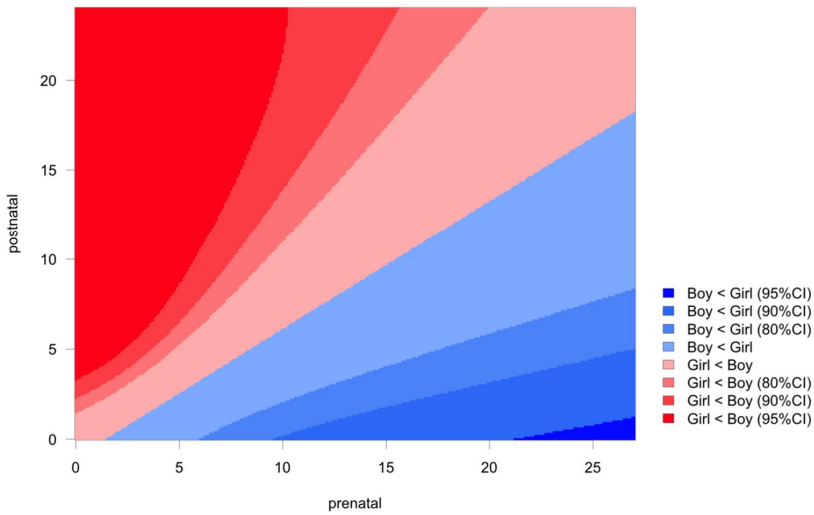

Figure 9. The difference of the predicted mean probabilities of boys vs. girls based on the fitted model evaluated at a range of pre- and postnatal anxiety scores

Table 13. The logistic regression model for infant executive function at 8 months: the association between pre- and postnatal maternal anxiety and infant performance (N = 214)

	Step 1		Step 2		Step 3		
	Effect size[b]	*β*	Effect size[b]	*β*	Effect size[b]	*β*	OR (CI 95 %) for Step 3
	0.006		0.060		0.254		
Intercept		–1.75†		–2.51*		–1.88†	0.03 (0.00, 1.17)
Task difficulty		–4.00***		–4.00***		–4.50***	0.88 (0.83, 0.93)
Infant age[a]		1.69†		2.50*		1.87†	1.57 (0.98, 2.53)
Infant sex (Girl)		–0.61		–1.78†		–0.65	0.93 (0.76, 1.15)
Maternal education		–0.34		–0.28		–0.28	0.97 (0.77, 1.21)
Prenatal anxiety (SCL)				–2.60**		–1.26	0.97 (0.94, 1.01)
Prenatal anxiety x infant sex (Girl)				1.85†		1.97†	1.05 (1.00, 1.10)
Postnatal anxiety (SCL)						–0.35	0.99 (0.95, 1.03)
Postnatal anxiety x infant sex (Girl)						–2.21*	0.93 (0.88, 0.99)

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, † $p < 0.10$; [a]from expected due date, [b]for the whole model, McFadden (Pseudo-*R*)

5.4 Summary of the results

The summary of associations found in Studies I-IV is presented in Figure 10. To conclude, maternal prenatal stress predicted higher mother-reported fear reactivity (Studies I and II) but also higher overall negative reactivity and less efficient recovery from negative emotions in the entire sample (Study I). In Studies II-IV, the main findings were sex-specific. Maternal prenatal stress predicted higher observed fear reactivity (Study II) and better EF performance (Study IV) in girls in contrast to boys. Second, breast milk cortisol concentration predicted higher fear reactivity only in girls but not in boys (Study III). Third, indices of high postnatal or continuously increasing maternal stress predicted both decreased infant fear reactivity (Study II) and poorer EF performance (Study IV) in girls.

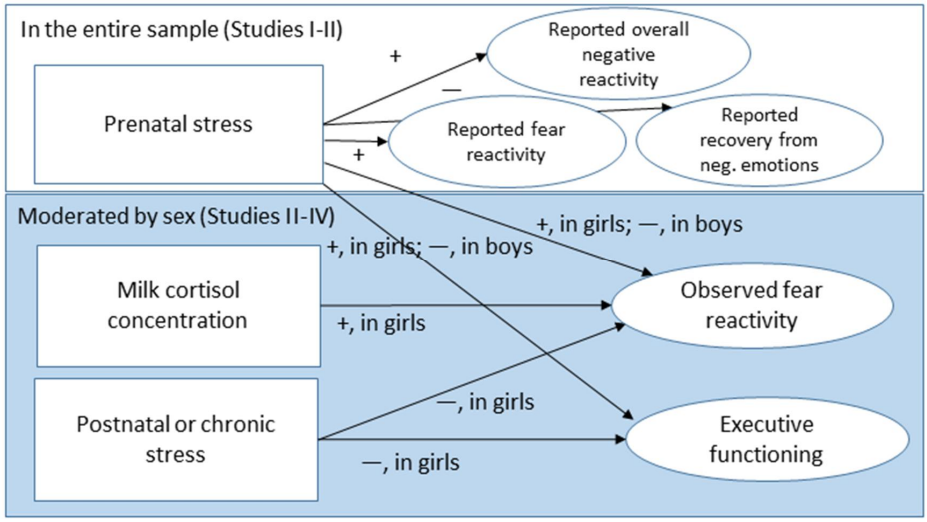

Figure 10. The summary of the main findings of the present study. The effects of pre- and postnatal stress exposure on infant self-regulation measured as fear reactivity and executive functioning

6 DISCUSSION

In the present study, we examined whether maternal self-reported pre- and postnatal stress were associated with infant fear reactivity that reflects bottom-up self-regulatory processes. Second, we tested if breast milk cortisol concentration was associated with infant fear reactivity. Third, we looked at if maternal pre- and postnatal stress were associated with infant executive function, an indicator of top-down self-regulation. Finally, we explored stress by sex interactions, with an expectation that early life stress (ELS) effects would depend on infant sex.

6.1 Maternal pre- and postnatal stress and infant fear reactivity

It was found that higher maternal prenatal stress was associated with higher infant fear reactivity in Studies I and II. More specifically, maternal pregnancy-specific anxiety predicted higher mother-reported infant fear reactivity along with higher overall negative reactivity and lower infant recovery from negative emotions, but not in other aspects of infant emotional reactivity. In Study II, we first identified three trajectories of maternal pre- and postnatal stress, "Low and stable stress" (70.6% of all mothers), "Prenatal stress" (18.9%) and "Continuously increasing stress" (10.5%) that corresponded to the existing studies of trajectories of maternal perinatal symptoms (Christensen, Stuart, Perry, & Le, 2011; Mora et al., 2008; Vänskä et al., 2009). The trajectory of prenatal stress predicted higher observed infant fear reactivity only in girls. Similarly to the findings of Study I, there was a trend-level finding such that mothers with prenatal stress rated their infants higher in fear reactivity in contrast to mothers with low and stable stress, and this rating was not dependent on infant sex.

Overall, these findings are in line with the previous studies (Bergman et al., 2007; Davis et al., 2004; Henrichs et al., 2009; Pesonen et al., 2005), and strengthen the perception that prenatal stress predicts higher distress to novelty in infancy, although this association might be moderated by other factors such as infant sex. This could indicate that prenatal stress programs infant behavior towards higher wariness and sensitivity to threat, which might be evolutionarily adaptive predisposition in stressful environments, especially for girls (Glover, 2011; Glover & Hill, 2012). However, simultaneously, higher fear reactivity can place the child at risk for later anxiety or other emotional problems (Buss & McDoniel, 2016; Clauss et al., 2015; Kiel, Premo, & Buss, 2016), which are, however, also primarily more prevalent in girls (e.g. Salk et al., 2017).

Our initial hypothesis based on earlier literature was that there would be a positive association between maternal postnatal or chronic stress and infant fear (Gartstein et al., 2010; Pauli-Pott et al., 2004; Pesonen et al., 2005; Stapleton et al., 2012). However, in the current study, continuously increasing maternal stress that peaked during the postnatal period was unexpectedly associated with lower, not higher, observed fear reactivity in infant girls at 8 months of age. Only Henrichs et al. (2009) have reported partially similar findings as in their study postnatal stress was associated with irritability-related aspects of emotional reactivity but not specifically fear, which was instead related to prenatal stress.

There can be several explanation for this finding. First, one possibility is that prolonged postnatal stress exposure might be associated with delayed cognitive and neural maturation (Davis & Sandman, 2010; Diego et al., 2005; Ellman et al., 2008). The delays in maturation might also reflect on the development of fear reactivity, which typically emerges between 6 and 12 months of age (e.g. Carnicero et al., 2000; Putnam & Stifter, 2005; Rothbart, 1988). Second, even though we were not able to include an assessment of parenting in the current study, it can be hypothesized that lower fear reactivity is an adaptation to non-optimal parenting behaviors or parent-infant interaction situations, where the infant does not receive the required support and as a result, might inhibit external emotional reactions (Righetti-Veltema, Bousquet, & Manzano, 2003). For instance, earlier studies have reported more depressed infant behavior as a response to chronic pre- and postnatal depression (Diego et al., 2005).

Building on this line of reasoning, it can be hypothesized that infants who experience elevated stress, including parental psychological distress or negative parenting, are exposed to more frequent stress-provoking situations, which might result in habituation and eventually, to inhibition of external reactivity. For instance, it has been reported in animal studies that for the offspring exposed to repeated maternal separations in novel environment, a novel stressful stimulus is not enough to trigger stress reaction (Daskalakis et al., 2011). What is more, a growing body of recent evidence suggests that severe ELS might be associated with both elevated anxiety *and* precocious development of self-regulation, especially inhibitory control, and neural networks underlying such regulatory functions (Gee et al., 2013; Humphreys et al., 2012; Thijssen et al., 2017; Tottenham, 2014). Further, regardless of the explanation, there is evidence that not only higher but also lower fear reactivity might be indicative of risk for later disorders reflecting abnormal development of socialization (Beaver et al., 2015; Colder et al., 2002). Thus, both low and high fear reactivity may be risk factors for self-regulation development. However, further research is needed to follow the development of high and low fear infants to address this hypothesis.

On the other hand, both findings on prenatal stress and mother-rated fear in Studies I and II were at trend-level indicating that prenatal stress does not strongly affect maternal ratings of infant fear. The findings of the Study I further suggest that pregnancy-specific anxiety might have some unique influence on maternal ratings of infant emotional reactivity and emotion regulation. This is in line with recent views that pregnancy-specific anxiety might be a distinct predictor of some child outcomes, such as decreased gestational age (O'Donnell & Meaney, 2017), or associate with certain maternal characteristics and cognitive skills (Kataja et al., 2017; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993).

This raises the question whether anxiety, and pregnancy-specific anxiety specifically, and maternal ratings of infant affectivity actually are a consequence of the shared genetic makeup (Glover, 2011). For instance, it is possible that maternal pregnancy-specific anxiety reflects underlying maternal negative reactivity that is specifically observable due to major life event (pregnancy) and then inherited by her infant. Maternal genetic reactivity might also lead to a mismatch between pre- and postnatal environments, which is a known risk for offspring development and the potential cause of higher offspring reactivity (see for instance Daskalakis et al., 2013; Lee et al., 2016; and Nederhof & Schmidt, 2012). In turn, general anxiety and depressive symptoms might reflect more general and predictable stress in contrast to pregnancy-specific anxiety tapping an entirely different type of early life adversity and may even promote adaptation to environment in some cases. Thus, more research on the specific phenotypes of maternal prenatal stress and the interaction with genetics and postnatal environment is needed.

Overall, the findings of the present study propose that maternal self-reported stress, measured as depressive and anxiety symptoms, affects infant fear reactivity, and that pre- and postnatal stress have unique, and possibly opposite, effects on infant fear responses. The findings suggest that the course of stress might be important in predicting patterns of infant reactivity. This might be related to the different mechanisms of early life programming during pre- and postnatal period as well as the continuity of the stress exposure which should be more thoroughly researched in future studies. However, even though in line with the earlier studies (Henrichs et al., 2009; Huizink, Medina, Mulder, Visser, & Buitelaar, 2003; Pesonen et al., 2005), effect sizes for maternal pre- and postnatal stress and infant fear reactivity in our study were modest, and maternal stress explained only 2–3% of the variance in infant fear responses. This warrants the cautious interpretation and transfer of the results into practical use. Furthermore, more proximal characteristics of fetal and infant environment, such as the mother-infant interaction, might be prominent underlying factors in observed and parent-rated infant behavior. These moderating and mediating factors should be researched in more detail in future studies.

6.2 Breast milk cortisol concentration and infant fear reactivity

In Study III, we examined the association between breast milk cortisol concentration at 2.5 months and infant fear reactivity at 8 months. No main effect of milk cortisol on infant fear reactivity was found. In turn, there was an interaction between infant sex and milk cortisol such that higher milk cortisol predicted higher observed fear reactivity in girls but not in boys. However, no association was found between milk cortisol concentration and mother-reported fear reactivity unlike evidence found in the only previous study investigating this subject in humans (Grey et al., 2013). Furthermore, maternal postnatal or prenatal self-reported stress were neither associated with milk cortisol nor infant fear reactivity.

Our findings are partially in line with earlier studies showing an association between maternal postnatal cortisol or breast milk cortisol concentrations and offspring emotionality (Glynn et al., 2007; Grey et al., 2013; Hinde et al., 2015; Sullivan et al., 2002). Thus, our results provide some support for the view that infants exposed to higher levels of maternal glucocorticoids (GCs) via breast milk might be programmed towards showing higher fear reactivity later during infancy. The concept of lactocrine programming was established by Bartol et al. (2008), but to our knowledge, this study is one of the first to examine lactocrine programming of behavior in humans. As a continuum to prenatal programming, lactocrine programming is suggested to have an evolutionary background, steering infant development to respond appropriately to environmental challenges. In accordance with this view, higher fear reactivity could provide survival advantages in a stressful environment, but later on, predispose the child to anxiety disorders (Buss, 2011; Clauss & Blackford, 2012; Glover, 2011; Kopala-Sibley et al., 2016).

However, given that we regard higher milk cortisol as a measure of higher postnatal stress, our finding does not correspond to the findings of Study II that higher postnatal stress was associated with lower fear reactivity. Instead, both infant girls exposed to prenatal stress and infants exposed to milk cortisol had higher fear reactivity in our study, even though prenatal stress was not associated with milk cortisol concentration in a smaller sample. Also in some prenatal stress studies, maternal self-reported stress and maternal cortisol have shown opposite effects on infant development (Davis & Sandman, 2010), and in a large number of studies, maternal cortisol and psychological distress do not correlate (Seth et al., 2016). Due to the small sample size in Study III, we were not able to analyze and take into account the trajectory of maternal stress when examining breast milk cortisol effects, and consequently, the association between these two different predictive patterns remains unclear. It is possible that the course of prenatal stress is associated with maternal postnatal (milk) cortisol, and that cortisol levels are more sim-

ilar in mothers who have prenatal rather than increasing postnatal stress. For instance, milk composition is shown to be regulated by several factors, including infant sex and socioeconomic situation (Fujita et al., 2012; Hinde, 2009; Powe, Knott, & Conklin-Brittain, 2010), suggesting that individual and environmental factors can further affect the programming function of milk. This possibility must be delineated in future studies. Moreover, the sample sizes in Studies II and III were profoundly different, which might partially explain the difference in results concerning postnatal milk cortisol and maternal postnatal stress, thus, the effect seen in Study II might be lacking because of insufficient statistical power.

Even though ELS is a risk factor for later emotional development, there are also other possibilities for interpretation that might explain the findings of Study III. For instance, ELS has also been regarded as an accelerator of development (DiPietro et al., 2006; Ellman et al., 2008; Keim et al., 2011). Correspondingly, GCs are known to aid in the maturation of tissues during prenatal development, and in animals, synthetic GCs are shown to lead to enhanced learning (Casolini et al., 1997; Catalani et al., 2000). Moreover, as already reviewed, severe ELS or insensitive parenting has been linked with precocious development of both anxiety tendencies and self-regulatory function (Gee et al., 2013; Silvers et al., 2016; Thijssen et al., 2017). Interestingly, a combination of fear reactivity and better cognitive skills at a certain stage of infancy (Graham et al., 2015) has been found to predict later internalizing symptoms, especially if the child has been insecurely attached to the caregiver (Graham, 2017).

Consequently, it could be hypothesized that higher or moderate fear reactivity can also be a sign of earlier maturation in the context of stress exposure not only a risk trait *per se*. In Study III, this could be a plausible alternative explanation because the mothers in the sample of this study were more likely to have higher education, higher SES and relatively low levels of psychological distress in comparison to the mothers in Studies I-II and IV. This might indicate that mothers in the sample of Study III might have had a more normally functioning HPA axis, given that high levels of psychological distress are sometimes linked with alterations in HPA axis responses and cortisol concentrations (Glynn et al., 2013). Consequently, in Study III, rather normative (moderate) levels of stress exposure were related to higher fear reactivity, in other words, normative or even advanced emotional development. However, as we found no relation between maternal distress and milk cortisol, this explanation remains speculative at best.

Further, the relative highly educated and less stressed sample might also partially explain why milk cortisol was not associated with mother-reported fear as in earlier studies (Glynn et al., 2007; Grey et al., 2013). This is strengthened by the obser-

vation that mother-reported and observed fear might reflect different facets of fearfulness. Mother-reported fear might cover more consistent extreme reactions of fear, whereas observed fear reactivity might actually measure normal neural reactivity indicating normal development and neural maturation. Also other factors might explain the differences in results in the current study and the study of Grey et al. (2013). Grey et al. (2013) measured concurrent milk cortisol and fear reactivity in early infancy, while in the current study, fear reactivity was measured later in infancy. Fear reactivity is generally recommended to be observed during its emergence in the second half of the first year. Thus, fear reactivity rated at 3 months and observed at 8 months probably reflect a different developmental stage of fear. In addition, Grey et al. used the original long version of IBQ-R, whereas in this study, mother-reported fear was measured with a short version of IBQ-R. Finally, it must be underscored that the mothers in the sample of the Study III had an exceptionally higher education and monthly income in comparison to other samples and the source population, which might have skewed the results to reflect stress levels of normative sample rather than highly stressed sample. This could also support the view that fear reactivity in this sample might reflect normative development or maturation instead of adaptation to high levels of environmental stress.

Furthermore, recent studies indicate that both baseline level of fear, development of fear and regulation of fear might be important in determining whether fear behaviors reflect normal development or risk trajectory (Buss & McDoniel, 2016; Ursache, Blair, Stifter, & Voegtline, 2013). For instance, Buss and colleagues (2011; 2017) have proposed that especially early "dysregulated fear", thus, fear reactivity to low-threat stimuli, would be predictive of later anxiety. Thus, whether the fear response is maladaptive or not might depend on the context and the intensity of the fear stimuli. In Study III, we calculated the effect sizes of breast milk cortisol on infant responses in each mask, but there was no indication that clear differences between the infant responses to different masks exist. However, our task was rather constructed to measure an overall fear reactivity than differentiating the effects of different stimuli, so we were not able to differentiate between dysregulated and normative fear. Differentiating between dysregulated and normative fear would be worth testing in future studies in regards to the effect of ELS on infant fear reactivity.

Finally, two conclusions on ELS and infant fear reactivity can be made. First, in our study, milk cortisol concentration at 2.5 months seems to measure a different stress than maternal anxiety and depressive symptoms. Second, both maternal self-reported prenatal stress and postnatal milk cortisol seem to be related to higher infant fear reactivity. However, at this stage, it is not possible to state whether high

fear reactivity at 8 months is predictive of risk for later anxiety or other internalizing disorders or some other developmental processes, such as earlier maturation of certain emotional functions. Consequently, more prospective research that follows maternal stress and breast milk cortisol level throughout the pre- and postnatal periods and fear reactivity as well as determination about the significance of fear reactivity in the samples of the current study is needed to address these questions.

6.3 Maternal pre- and postnatal stress and infant executive functioning

In Study IV, we used a measure of infant executive function (EF) as an indicator of infant top-down, effortful self-regulation. Maternal pre- and postnatal stress measured as self-reported overall anxiety were related to infant EF in a sex-specific manner. That is, even low to moderate levels of postnatal anxiety were related to slightly worse performance in girls, but there was no effect on boys' performance, respectively. In turn, there was a trend-level finding that high level of maternal prenatal anxiety predicted EF performance differently in girls and boys with girls performing better than boys in the presence of prenatal stress exposure. However, there was no evidence for an independent effect of prenatal stress effect on performance either in girls or boys.

To our knowledge, this is the first study to link postnatal stress with poorer EF skills as early as in infancy. The findings are in line with the studies showing that maternal postnatal self-reported stress is associated with poorer cognitive development and EF in early childhood (Grace et al., 2003; Hughes et al., 2013; Jensen et al., 2014; Kingston et al., 2015, 2012). However, the viability-vulnerability tradeoff theory of sex differences suggest that boys would be more vulnerable to ELS effects with regard to cognitive development (Sandman et al., 2013), whereas in the current study, girls were more susceptible to postnatal anxiety. This may result from the fact that EF is considered to measure at least partially distinct cognitive abilities than overall IQ or measures of neurodevelopment (Ardila, Pineda, & Rosselli, 2000; Friedman et al., 2006; Sun et al., 2009). Thus, as noted earlier, EF reflects top-down emotion regulation processes that can be developmentally distinct from other cognitive development (Bridgett et al., 2015; Zhou et al., 2012).

Although our hypothesis was that prenatal stress would be adversely associated with EF, we found a different pattern of results. After controlling for postnatal stress, there was no evidence for an independent effect of prenatal stress on EF performance in either sex. However, in the presence of high prenatal stress exposure, girls performed slightly better in contrast to boys. Some prior research has reported that prenatal stress would predict better cognitive performance (DiPietro

et al., 2006; Ellman et al., 2008; Keim et al., 2011). This has been suggested to result from moderate levels of stress and its beneficial effects for development (Daskalakis et al., 2013; DiPietro et al., 2006; Lyons et al., 2010). Interestingly, also in the study of Karam et al. (2016), it was showed that although prenatal stress predicted enhanced motor performance, postnatal parental stress was associated with poorer motor performance suggesting that at least in terms of motor development, the effects prenatal and early postnatal stress might be opposite to each other.

However, this finding is inconsistent with that in our study that very high prenatal stress was related to a difference between girls and boys. There are still some possibilities that might explain this finding. First, when comparing the findings on infant EF to the findings on fear reactivity in girls in Study II, an interesting pattern of behavior emerges. There, prenatal stress predicted higher reactivity in girls, whilst postnatal stress was linked to lower fear reactivity in girls. Although not directly analyzed in this study, it can be hypothesized that infant girls exposed to prenatal stress might have been both more reactive and performed better than boys in an EF task. This lends support to the idea that infants with higher arousal or stress reactivity are more vigilant and also more rapid in their attention allocation (Colombo, Mitchell, Coldren, & Freeseman, 1991; Cuevas & Bell, 2014; de Barbaro, Clackson, & Wass, 2016, 2017), which might make them more efficient in an EF task requiring flexible attention shifting. However, the skills that make girls better EF performers early in life might also make them more susceptible to anxiety and other internalizing symptoms later, which is compatible with a higher prevalence of these disorders in females and a higher risk of females for these disorders after exposed to prenatal stress (Costello et al., 2003; Quarini et al., 2016; Sandman et al., 2013). Thus, the good performance in EF might not be purely beneficial but rather a side-effect of high arousal level.

Correspondingly, it may be that infant girls exposed to continuously increasing (postnatal) stress were both less fear reactive and fared worse in an EF task. Following the reasoning presented earlier, this might be related to the rigidity of attentional processes. By contrast, this rigidity might explain lower reactivity and also serve a self-regulatory purpose with infants exposed to current high levels of stress regulating their anxiety better with less reactivity and less attentional flexibility. Nevertheless, this explanation is not compatible with the idea proposed earlier that children with early life (postnatal) stress would be better top-down self-regulators (Gee et al., 2013; Humphreys et al., 2012). In our study, infant girls exposed to high postnatal stress had less efficient EF, whereas girls exposed prenatal stress showed better EF performance in contrast to boys. However, a clear conclusion about the significance of EF for broader self-regulation cannot be drawn for several reasons. First, we did not measure directly emotion regulation but rather cognitive self-regulation performance in a social setting. Second, the

predictive value of EF performance at the age of 8 months for future development is not well known. Thus, the relation of EF performance to emotional reactivity and the practical significance of EF for future development needs to be tested in future follow-up studies with the same sample.

In conclusion, based on our findings, maternal postnatal stress might have a modest adverse effect on girls' EF performance as early as during infancy. Second, prenatal stress exposure did not affect infant EF performance significantly in the current study, but our findings suggest that high prenatal stress may predict significant performance differences between girls and boys. However, the extent to which these differences are further moderated by infant bottom-up self-regulation tendencies (including fear reactivity) remains unclear and must be examined in future studies.

6.4 The moderating role of infant sex in early life programming

In the current study, we hypothesized that there would be sex differences in how ELS affects infant outcomes. Moreover, it was expected that girls would be more sensitive to the effects of pre- and postnatal stress exposure. In line with these hypotheses, sex-dependent associations between ELS exposure and infant outcome were found in all three studies where the moderating effect of sex was examined. In Studies II and III, higher prenatal stress and milk cortisol concentration were associated with higher fear reactivity in girls, whereas maternal prenatal stress predicted lower fear reactivity in boys. Similarly, in Study II, continuously increasing stress predicted lower fear reactivity in girls but not in boys. In Study IV, postnatal anxiety was related to worse performance only in girls, and prenatal anxiety predicted performance difference between girls and boys with girls performing better than boys in the presence of high prenatal anxiety. However, there was no stress by sex interaction in predicting maternal rating of fear reactivity in Studies I–III.

Overall, the findings suggest that infant girls might be more sensitive to ELS effects with regard to experimentally-induced fear responses and EF. This is in line with the viability-vulnerability tradeoff theory of sex differences in fetal programming (Sandman et al., 2013). Viability-vulnerability theory has an evolutionary background suggesting that females would have an additional advantage of high emotional reactivity and a general bias to threat than in males. Males instead may invest in growth with a simultaneous cost of neural plasticity and variation in emotionally adaptive strategies (Sandman et al., 2013). A number of recent studies about child sex and prenatal and postnatal stress influences propose that females are more prone to modify their emotional responses when facing environmental

stress (Braithwaite, Pickles, et al., 2017; Braithwaite, Murphy, et al., 2017; Buss et al., 2011; Ellman et al., 2008; Grey et al., 2013; Quarini et al., 2016; Zuloaga et al., 2011). Interestingly, other theories with evolutionary origin suggest that both females and males show sex-specific behavioral alterations. For example, girls would have the advantage of having a higher bias to threat, whereas boys would benefit from being less reactive and more impulsive (Glover & Hill, 2012). Indeed, we found some evidence supporting this hypothesis, as in Study II, boys seemed to show less than average fear reactivity after an exposure to prenatal stress.

This is also in concordance with the higher fear reactivity and the higher prevalence of internalizing symptoms such as depressive and anxiety in females (Costello et al., 2003; Else-Quest, Hyde, Goldsmith, & Van Hulle, 2006; Salk et al., 2017) and even higher prevalence of these problems in girls after stress exposure (Buss et al., 2012; Kim et al., 2016). Accordingly, we found that infant girls not only initially scored higher for fear, but also were more susceptible to elevated fear reactivity in the presence of prenatal stress exposure. By contrast, in the presence of continuously increasing (postnatal) stress exposure, girls showed lower fear reactivity resembling the normative variation of fear reactivity in boys. Thus, it could be argued that prenatal exposure actually strengthens the originally existing sex differences in fear behavior, whereas chronic postnatal stress diminishes these differences. Notably, higher fear reactivity is proposed to predict later anxiety disorders (Buss & McDoniel, 2016; Clauss et al., 2015; Clauss & Blackford, 2012), but also lower than average fear reactivity is linked with more internalizing symptoms in girls in one study (Colder et al., 2002). However, we are not yet able to conclude whether alterations in fear behaviors of girls are risk factors for later mental health or functional and beneficial adaptations to environmental influences. This has to be addressed in future follow-ups of the current study sample.

We also found that postnatal stress affected EF performance of the girls in the first place, whilst prenatal stress predicted a slightly better performance of girls in contrast to boys. This fits the view that girls are not only more reactive but also more sensitive to modify their regulatory behavior as a response to stress. Earlier findings show that boys have poorer cognitive performance after prenatal stress exposure (Ellman et al., 2008). On the other hand, this finding is different from the finding of Buss et al. (2011) who reported a negative association between prenatal stress and lower inhibitory control in girls. However, the study of Buss et al. focused on school-aged children, whereas our study investigated infants. The differences in results are most probably due to the profound development in EF skills taking place between these two periods. Moreover, as discussed earlier, EF might reflect different cognitive abilities as overall cognitive development measures, and thus the sex by stress interactions in predicting EF might actually resemble those

of emotional responses. Based on this line of reasoning as well as the developmental course of EF, it is possible that the good performance of girls in infancy might turn out to reflect problems in emotion regulation and higher emotional reactivity later.

In conclusion, our study strengthens the hypothesis that males and females are differentially susceptible to ELS influences. Infant girls seem to be more prone to both maternal pre- and postnatal stress and postnatal milk cortisol influences with regard to emotional and self-regulatory behaviors, although we also found some evidence that girls and boys may use different strategies in adapting to stress. However, more studies are needed to determine the significance of these sex-specific patterns of behavioral alterations for future development.

6.5 Limitations and strengths

The major strength of the current study was the longitudinal prospective follow-up of ELS and infant self-regulatory behaviors. Due to the multiple time points of assessment, we were able to calculate robust measures of maternal pre- and postnatal stress and use latent growth mixture modeling in the assessment of maternal stress trajectories. Furthermore, given that the existing research has mostly focused on either pre- or postnatal programming of development, this study aimed at the simultaneous assessment of the independent effects of stress during both periods. Our focus was a general population of mothers with high and low prenatal stress, and our findings thus represent associations between ELS and infant self-regulation in a normative, non-clinical sample of mothers and infants.

Another strength was the multi-methodological approach to the assessment of infant fear reactivity. Parent report measures are considered as valid measures that tap a larger range of everyday behaviors of the infant in comparison to laboratory-based assessments (Gartstein & Marmion, 2008; Rothbart, 1981). Many studies have also reported anticipated relations between laboratory- and parent report measures (Gartstein & Marmion, 2008; Goldsmith & Campos, 1990; Vroman, Lo, & Durbin, 2014). However, in our study, correlations between mother-reported fear and observed fear were modest. The issue of possible biases of the parent reports have been pointed out in earlier literature (Rothbart & Bates, 1998; Rothbart & Goldsmith, 1985). Interestingly, in Study II, the ratings of mothers with prenatal stress were in line with their infants' actual reactivity, thus, infant girls of these mothers had higher observed fear, and mothers also rated them higher in fear. In contrast, mothers with continuously increasing stress did not differ from other mothers in their ratings of infant fear, although their infants had lower fear reactions. Earlier studies have noted that current maternal emotional distress might

result in lower correspondence between observed reactivity and mother's ratings of infant reactivity (Gartstein & Marmion, 2008; Leerkes & Crockenberg, 2003) underscoring the importance of several methodologies in assessing infant reactivity.

However, the current study also has limitations. First of all, our study lacks the prenatal stress assessment with cortisol or other biomarkers of stress, which is a common approach to study fetal programming (Zijlmans et al., 2015). Therefore, the transmission of the effects of maternal prenatal stress via GCs or other biomarkers remains unclear in this study. Another limitation in this study is that maternal stress was only measured as self-reported psychiatric symptoms, and stressful live events or daily hassles as a source of stress were not considered in the analyses. This was based on the initial criteria of the FinnBrain Focus Cohort, which was identified based on maternal psychiatric symptoms and also the aim to consider continuous measures of stress instead of categorical measures of presence of stressful live events. However, it is possible that the inclusion of life-event stress could have had an effect on the results, and future analyses could be conducted to compare the difference of life events/daily hassles and psychiatric symptoms related to infant fear reactivity and executive functioning. Our study also lacks the consideration of gestational hypertension, which has been recently shown to affect child outcomes (Tuovinen, Aalto-Viljakainen, et al., 2014; Tuovinen, Eriksson, Kajantie, & Räikkönen, 2014), including EF (Wade & Jenkins, 2016). Future analyses should account for the maternal hypertensive disorder to ensure the specificity of the prenatal psychological distress in predicting child outcomes.

Similarly, the majority of the mothers were included in the sample based on their membership of either group of "high stress or "low stress", defined as at least two high scores in symptom questionnaires during pregnancy based on the first 500 mothers of the cohort. This could have led to a situation where mothers with heterogeneous symptom profiles were considered to have similar, high prenatal stress despite their different phenotypes, which could skew the characteristics of the sample. However, there was an endeavor to take this possibility into account by considering symptom scores as a continuous variables even within the focus cohort that differentiated between symptom types (e.g. depressive, anxiety and pregnancy-related anxiety symptoms) and including also a proportion of mothers with moderate stress in the sample. The demographic characteristics of the sample also resemble the larger birth cohort, although in observational visits, there was expectedly a smaller number of mothers with low education and monthly income than in source sample.

As a continuum for this discussion, based on the inspection of sociodemographic characteristics of the samples of this study, it is evident that mother-infant dyads

in this study represent a relatively urban, highly educated part of the Finnish population. Moreover, the attrition analyses of this study as well as the ones conducted in FinnBrain Birth Cohort more widely (Karlsson et al., 2017) suggest that parents with lower education and income tend to withdraw during the postnatal period diluting the possible associations between the early life stress and outcome variables. For instance, the results of the Study IV were not consistent with earlier work done on prenatal stress and child EF (Buss et al., 2011). However, based on the demographic information, the mothers in the sample of Buss et al. (2011) had remarkably higher levels of reported psychological distress than the mothers in our sample. Moreover, as can be seen from the cut-offs in Study IV, a small number of mothers in our sample reported clinical levels of depressive symptoms during the early postnatal period, which naturally affects the variance and study results. Hence, it is important to be cautious in generalizing about the findings in clinical or otherwise more socioeconomically disadvantaged populations.

Moreover, only a single parent report and observation of fear was gathered in the current study. In order to identify whether alterations in fear reactivity are indicators of risk, more frequent follow-ups would have been needed. Furthermore, in Study III, we only gathered one milk cortisol sample per participating mother, and no report of fear at the time of sample collection was available, which might account for the differences between the present study and earlier study on milk cortisol and fear. Thus, we were only able to study the association between 3-month milk cortisol and 6- and 8-month fear, and neither changes in milk cortisol nor fear between these assessments could not be detected. Thus, given the novelty of the field of lactocrine programming, our study only provides suggestive evidence about the relation between milk cortisol and infant behavior.

Moreover, despite the challenges in conducting complex EF tasks in infancy, we were able to test more than 200 eight-month-old infants with a relatively large variation in performance. However, the task was relatively difficult for infants at this age, and a proportion of infants showed fussiness or a difficulty in concentrating on the task. Earlier studies have shown that child emotionality might have effects on EF (Henderson & Wachs, 2007; Ursache et al., 2013; Wolfe & Bell, 2007). In the future, the analyses on emotional reactivity and EF shall be conducted in the current study sample to reveal to possible interplay between reactivity and regulatory tendencies of the infant.

Finally, a major limitation of this study is the lack of parent-infant interaction measures in the analyses. As already discussed, it is well known that parent-infant interaction quality has profound effects on child emotionality and behavior. However, in the current study, the sample sizes would have been notably smaller if

parent-infant interactions would have been included in the analyses. Future analyses in the smaller samples should consider the parent-infant interactions as a mediator or moderator between ELS and child fear reactivity/EF.

6.6 Clinical implications

First of all, the present study strengthens the current view that ELS has an effect on child emotional reactivity already in infancy. Thus, infants exposed to ELS showed altered fear reactivity and problems in EF and recovery from negative emotions, which can be regarded as risk factors for later self-regulation and mental health. Our findings have several clinical implications. First, though the effect found was clear and consistent, the effect sizes of ELS were modest. Given that many mothers are concerned about the possible harmful effects that their stress may cause for the fetus or the infant, observations in this current study, the overwhelming worry of the parents can be reassured by clinicians.

On the other hand, our study showed that even moderate levels of maternal anxiety in a community sample may have a small effect on infant self-regulation, and many earlier studies have emphasized that ELS clearly has clinically significant effects on infant development (Glover, 2014). Consequently, prenatal anxiety, depressive and pregnancy-related anxiety symptoms have an effect on infant emotional development, and they are thus feasible targets for prevention and interventions. For instance, promising results from using mindfulness and cognitive-behavioral therapy (CBT) in relieving prenatal anxiety have been reported (Green, Haber, Frey, & McCabe, 2015; Hall, Beattie, Lau, East, & Anne Biro, 2015; van den Heuvel, Johannes, Henrichs, & Van den Bergh, 2015; Vieten & Astin, 2008).

Moreover, as most of the research has focused on maternal postpartum depression as a risk factor for child development, our findings underline the significance of allocating equal attention to the screening and treatment of maternal pre- and postnatal anxiety. Specifically, in line with the current views in the field (O'Donnell & Meaney, 2017), the current study provided evidence that pregnancy-specific anxiety might have independent effects on parental ratings of child behavior and development. However, further research is needed to elucidate the differences between the forms of maternal distress in predicting different child outcomes as well as genetic factors underlying both maternal and offspring phenotypes.

Third, higher infant reactivity resulting from stressful early life conditions might further adversely affect parenting and the parent-infant relationship. This is especially concerning as parents with high stress usually show more insensitive and negative parenting (Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Nicol-Harper,

Harvey, & Stein, 2007; Zelkowitz, Papageorgiou, Bardin, & Wang, 2009). Consequently, educating prospective and recent parents about infant reactivity and temperament differences and promoting flexible parenting practices should be a part of child health center check-up protocols (Melvin, 1995). For instance, there is evidence that parents may strengthen the inhibited behavior shown in fearful children, and that on the other hand, negative parenting increases and maintains high fear reactivity (Kiel & Buss, 2011; Kiel et al., 2016; Kiff, Lengua, & Zalewski, 2011; Lengua & Kovacs, 2005). Similarly, infant emotional characteristics affect parent-infant relationship (Calkins & Fox, 1992; Nolvi et al., 2016; Parfitt, Ayers, Pike, Jessop, & Ford, 2014) and may presage later problematic interactions of parenting and child behavior underscoring the advantages of early enough intervention.

Fourth, interestingly, the current study suggests that the stress experienced during pre- and postnatal periods might shape development independently, and pre- and postnatal stress might have different effects on infant fear reactivity and EF. However, postnatal interventions related to parenting and maternal care can be used to counteract or re-program the effects of prenatal stress (Kaplan et al., 2008; Lemaire et al., 2006; Sharp et al., 2015). Fifth, the significance of alterations of fear reactivity for future development in the context of the current study remains unclear, but it can be hypothesized that behavioral alterations are functional in an environment where the baby is currently living (Glover & Hill, 2012). Thus, in clinical settings, the judgement of an infant as “difficult” or “easy” should be avoided to not generate early and possibly false parental perceptions of what kind of child behavior is desirable.

Sixth, the current findings together with number of earlier studies suggest that girls might me more sensitive to ELS in terms of emotional, behavioral and self-regulatory development. Some emerging evidence also suggests that girls might be more sensitive to re-program after receiving positive environmental support after prenatal stress (Sharp et al., 2015). Consequently, health care personnel should be aware of possible gender differences in susceptibility to early environment and are sensitive in recognizing maternal stress and infant behavioral patterns that might require further support and intervention.

7 CONCLUSIONS

Stress limited to the prenatal period as well as to the forms of postnatal or more chronic stress had unique, although modest effects on infant fear reactivity and executive functioning. Even though the significance of behavioral alterations inspected remains unclear, these findings highlight the fact that several forms of ELS play a role in early stages of human infant development. Furthermore, there is some evidence that fear reactivity and poorer EF evidenced in the present study can be risk factors for later development (Buss & McDoniel, 2016; Clauss et al., 2015; Clauss & Blackford, 2012; Diamond, 2013; Putnam & Stifter, 2005), and thus, could represent a mediating link between ELS and later psychopathology (Capron et al., 2015; Quarini et al., 2016).

Consequently, it can be stated that the focus on maternal well-being during pre- and postnatal periods of life is crucial in terms of promoting child well-being and preventing later life emotional disorders. Although there is still limited evidence about the effectiveness of prenatal prevention, it is suggested to be most cost-effective intervention in comparison to treatments that are allotted later in childhood or adolescence after an onset of emotional problems (Doyle, Harmon, Heckman, & Tremblay, 2009). Thus, a shift from the treatment of psychopathology to supporting healthy family environments in early childhood would have the potential to "program" children's lives positively. This does not only refer to the screening of maternal psychological distress, including anxiety and worries related to pregnancy, but also to the socioeconomic and overall situation of the family and partner support that might profoundly affect ELS experienced by young children (Henrichs et al., 2011; Stapleton et al., 2012).

Interestingly, we found evidence for an association between breast milk cortisol concentration and infant fear reactivity. A more complete understanding about the mechanisms and potential of milk in steering infant development might have several future implications. For instance, an understanding about whether lactation always plays an important role in promoting positive child development would have implications for family health care. However, since the research on lactocrine programming is only emerging, our findings suggest that more research on not only milk GCs, but also on other components of milk (Fujita et al., 2012; Powe et al., 2010) and their interaction with infant and environmental characteristics are needed to reach this aim.

Moreover, the pattern of findings in our study communicates the complex nature of interactions between environmental and individual features in shaping behavioral phenotypes. For instance, although not analyzed in the current study, a bur-

geoning body of work suggests that early life negative affect, including fear reactivity, might reflect plasticity to environmental factors (Kopala-Sibley et al., 2016; Pluess & Belsky, 2010; Slagt et al., 2016). In the same vein, our findings support the idea that girls might be more susceptible to ELS with regard to emotional reactivity and regulatory functions (Glover & Hill, 2012; Sandman et al., 2013). Recent works have also suggested that ELS exposure can either heighten the risk or promote resilience depending on the intensity, timing and match between the environmental contexts during life course (Daskalakis et al., 2013). Finally, this functionality of behavioral patterns in the face of ELS is still not well understood and warrants more research preferably with longitudinal approaches starting from the prenatal period.

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