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OF TURKU

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SYMPTOMS IN MATERNAL
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DURING PREGNANCY AND
INFANT ATTENTIONAL
PROCESSING OF EMOTIONAL
FACES AT THE AGE OF
EIGHT MONTHS

— the FinnBrain Birth Cohort Study

Eeva-Leena Kataja



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*If I have seen further it is by standing
on the shoulders of Giants*

- Sir Isaac Newton

To my Family, my Loved ones

ABSTRACT

Eeva-Leena Kataja

The Role of Maternal Depressive and Anxiety Symptoms in Maternal Cognitive Processing During Pregnancy and Infant Attentional Processing of Emotional Faces at the Age of Eight Months — the FinnBrain Birth Cohort Study

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Maternal pre- and postnatal depressive and anxiety symptoms are common. These symptoms of distress are known to adversely impact both maternal adaptations to motherhood as well as child development. Currently, little is known about the associations between maternal prenatal distress and cognitive functions, while maternal cognitive functions, especially executive functions are closely related to maternal parenting. Moreover, little is known about the role of maternal pre- and postnatal symptoms of distress in shaping the development of an infant's cognitive attention mechanisms, and more specifically, face processing. Finally, the moderating role of child sex on the pre- and early postnatal influences of maternal distress on infant attention development has been rarely explored.

The aims of this study were: 1) to compare maternal cognitive functioning during pregnancy between two different test methods using a traditional paper-and-pencil test and a computerized neuropsychological test battery (Study I), and further, to study the associations between maternal self-reported prenatal depressive and anxiety (i.e., both general anxiety and pregnancy-related anxiety) symptoms and cognitive functions (Study II); and 2) to explore the associations between maternal pre- and postnatal depressive and general anxiety symptoms and an 8-month-old infant's attention to social-emotional signals conveyed through faces (Studies III and IV). The participants for this study were mothers and infants and members of the FinnBrain Birth Cohort Study.

The results showed that the cognitive test methods correlated non-significantly or only modestly depending on the cognitive domain. Maternal prenatal symptoms of depression- and pregnancy-related anxiety, but not general anxiety, predicted the number of errors made in a visual maze task demanding planning and updating of visuo-spatial working memory. Both maternal decreasing and increasing depressive symptoms from the pre- to postnatal period versus consistently low symptoms were associated with enhanced infant processing of threat (i.e., fearful faces) in relation to other facial expressions, and this effect was similar for boys and girls. Maternal pre- and postnatal anxiety symptoms were differently associated with infant attention patterns, with sex-differences in the associations. Maternal prenatal anxiety, but not postnatal, associated with a heightened bias for threat for all infants. Maternal postnatal anxiety symptoms, in turn, associated with the overall disengagement probability from faces to distractors differently for boys and girls. Boys, in relation to maternal symptoms, disengaged their attention more often from faces to distractors and girls less often disengaged.

In conclusion, these findings suggest that maternal symptoms of depression and anxiety during the pre- and early postnatal periods, even if at sub-clinical level, relate to cognitive processing both in mothers themselves and in their infants. Some effects on infants may be sex-specific.

Keywords: prenatal depressive symptoms; postnatal depressive symptoms; prenatal anxiety symptoms; postnatal anxiety symptoms; pregnancy-related anxiety; symptoms of distress; cognitive functions; executive functions; parenting; face processing; threat processing; attention mechanisms; visuo-spatial working memory

TIIVISTELMÄ

Eeva-Leena Kataja

Äidin masennus- ja ahdistusoireiden yhteys hänen kognitiivisiin toimintoihinsa raskausaikana sekä 8-kuukauden ikäisen vauvan kasvojenilmeisiin suuntautuvaan tarkkaavaisuuteen – FinnBrain-syntymäkohorttitutkimus

Psykologian ja Logopedian laitos, Yhteiskuntatieteellinen tiedekunta, Turun yliopisto

Äidin raskausajan masennus- ja ahdistusoireet ovat yleisiä. Näiden stressioireiden on havaittu vaikuttavan haitallisesti sekä äidin valmistautumiseen vanhemmuuteen että lapsen kehitykseen. Vasta vähän tiedetään äidin raskausajan stressioireiden ja kognitiivisen suoriutumisen välisistä yhteyksistä, vaikka äidin kognitiivisilla toiminnoilla, erityisesti toiminnanohjauksella, tiedetään olevan keskeinen yhteys vanhempana toimimiseen. Vähän tiedetään myös siitä, miten äidin raskausajan ja synnytyksen jälkeiset oireet voivat muokata lapsen kognitiivisten tarkkaavaisuusmekanismien kehitystä, ja erityisesti kasvojenilmeisiin suuntautuva tarkkaavaisuutta. Lisäksi vauvan sukupuolen merkitystä äidin kokemien stressioireiden ja tarkkaavaisuuden kehityksen välillä ei ole juurikaan tutkittu.

Tämän väitöskirjan tavoitteena oli: 1) verrata äidin raskaudenaikaista kognitiivista suoriutumista kahden eri testimenetelmän välillä, perinteisessä kynä-paperi –testissä sekä tietokoneistetussa neuropsykologisessa testipatterissa (tutkimus I), ja lisäksi tarkastella äidin raskausaikana itseraportoitujen masennus- ja ahdistusoireiden (ml. yleinen ja raskausspesifi ahdistus) ja kognitiivisten toimintojen välisiä yhteyksiä (tutkimus II), sekä 2) tarkastella äidin raskausaikana sekä synnytyksen jälkeen raportoitujen masennus- ja ahdistusoireiden ja 8-kuukauden ikäisen vauvan kasvojenilmeisiin suuntautuvan tarkkaavaisuuden välisiä yhteyksiä (tutkimukset III ja IV). Tutkittavat olivat äitejä ja vauvoja, jotka ovat mukana FinnBrain-syntymäkohorttitutkimuksessa.

Kahden kognitiivisen testin eri osien välillä havaittiin ei-merkitseviä tai vain kohtalaisia yhteyksiä. Äidin masennusoireet ja raskausspesifi ahdistuneisuus, mutta ei yleinen ahdistuneisuus, ennustivat korkeampaa virheiden määrää näönvaraisessa sokkelotehtävässä, joka edellyttää suunnittelukykyä ja visuo-spatiaalisen työmuistin päivittämistä. Sekä äidin laskevat että nousevat masennusoireet alkuraskaudesta kuusi kuukautta synnytyksen jälkeen (vs. tasaisen matalat oireet) olivat yhteydessä vauvan voimakkaampaan tarkkaavaisuuden suuntautumiseen uhkaärsykkeisiin (pelokkaat kasvot) verrattuna muihin kasvojenilmeisiin, lapsen sukupuolesta riippumatta. Äidin raskausajan ja synnytyksen jälkeiset ahdistuneisuusoireet olivat eri tavoin yhteydessä vauvan tarkkaavaisuusprosesseihin, osin eri tavoin tyttö- ja poikavauvoilla. Äidin raskausajan ahdistusoireet olivat yhteydessä vauvan voimakkaampaan tarkkaavaisuuden suuntautumiseen uhkaärsykkeisiin sekä pojilla että tytöillä. Äidin synnytyksen jälkeiset ahdistusoireet olivat pojilla yhteydessä suurempaan todennäköisyyteen siirtää tarkkaavaisuus kasvoista häiriöärsykkeeseen ja tytöillä vähäisempään todennäköisyyteen siirtää katse pois kasvoista.

Yhteenvedon voidaan todeta, että äidin raskausajan ja synnytyksen jälkeisen ajan masennus- ja ahdistusoireet ovat yhteydessä hänen omaan sekä vauvan kognitiiviseen prosessointiin. Lapsen liittyviä vaikutuksia voi ohjata myös vauvan sukupuoli.

Avainsanat: raskausajan masennusoireet; synnytyksen jälkeiset masennusoireet; raskausajan ahdistusoireet; synnytyksen jälkeiset ahdistusoireet; raskausspesifi ahdistus; stressioireet; kognitiiviset toiminnot; toiminnanohjaus; vanhempana toimiminen; kasvojenilmeisiin suuntautuva tarkkaavaisuus; uhkaärsykkeiden prosessointi; tarkkaavaisuusmekanismi; visuo-spatiaalinen työmuisti

TABLE OF CONTENTS

ABSTRACT.....	4
TIIVISTELMÄ.....	5
ABBREVIATIONS.....	9
LIST OF ORIGINAL PUBLICATIONS.....	11
1 INTRODUCTION.....	13
2 REVIEW OF THE LITERATURE.....	15
2.1 Cognitive aspects of motherhood.....	15
2.1.1 General cognitive functioning, intelligence (IQ).....	16
2.1.2 Executive functions (EFs).....	17
2.2 Maternal depressive and anxiety symptoms during pre- and postnatal periods.....	18
2.2.1 Depressive symptoms.....	19
2.2.2 Anxiety symptoms.....	20
2.3 Maternal depressive and anxiety symptoms and their relation to cognitive functions.....	21
2.3.1 Depressive and anxiety symptoms and cognitive dysfunctions.....	22
2.3.2 Depressive and anxiety symptoms and cognitive functions during pregnancy.....	23
2.4 Maternal depressive and anxiety symptoms and their relation to child's neurocognitive development.....	24
2.4.1 Prenatal factors.....	24
2.4.2 Postnatal factors.....	26
2.4.3 Attention to socio-emotional signals during infancy.....	28
2.4.4 Maternal pre- and postnatal depressive and anxiety symptoms and their relation to infant attention to social-emotional signals.....	31
2.5 Summary of the current literature.....	34
3 AIMS OF THE STUDY.....	35
4 MATERIALS AND METHODS.....	37
4.1 Study design and participants.....	37
4.1.1 The FinnBrain Birth Cohort Study.....	37
4.2 Measures.....	42
4.2.1 Maternal self-reported pre- and postnatal depressive and anxiety symptoms.....	42
4.2.2 Maternal cognitive functions.....	43
4.2.3 Infant attention to faces and distractors.....	44
4.3 Statistical analysis.....	46
4.3.1 Study I.....	46
4.3.2 Study II.....	46
4.3.3 Study III.....	47
4.3.4 Study IV.....	51

4.4	Ethical considerations	53
5	RESULTS	54
5.1	Maternal cognitive functions during pregnancy or after delivery (Study I)	54
5.2	Maternal prenatal depressive and anxiety symptoms and cognitive functions (Study II)	58
5.3	Maternal pre- and postnatal depressive and anxiety symptoms and their relation to infant attention to emotional faces (Studies III and IV)	62
5.3.1	General results from the infant eye-tracking experiment	62
5.3.2	The associations between the trajectories of maternal pre- and postnatal depressive symptoms and infant attention to socio- emotional signals (Study III)	64
5.3.3	The associations between maternal anxiety symptoms during the pre- and postnatal periods and infant attention to socio- emotional signals (Study IV)	69
5.4	Summary of the results	73
6	DISCUSSION	74
6.1	Maternal prenatal depressive and anxiety symptoms and neuropsychological functions	74
6.1.1	Maternal neuropsychological functions assessed with two different cognitive test batteries	74
6.1.2	The associations between psychiatric symptoms and neuropsychological functions	75
6.2	Maternal pre- and postnatal depressive and anxiety symptoms and their relation to infant attention to emotional faces	80
6.2.1	General findings of the infant attention patterns	80
6.2.2	The trajectories of maternal depressive symptoms from the pre- to postnatal periods and infant attention disengagement from emotional faces	81
6.2.3	Maternal anxiety symptoms during the pre- and postnatal periods and infant attention disengagement from emotional faces	84
6.2.4	Concluding remarks about the associations between maternal pre- and postnatal psychiatric symptoms and infant attention to emotional faces	88
6.3	Strengths and limitations of the study	89
7	CONCLUSIONS	92
	ACKNOWLEDGEMENTS	95
	REFERENCES	97
	ORIGINAL PUBLICATIONS I-IV	117

ABBREVIATIONS

IQ	Intelligence Quotient
SES	Socioeconomic Status
EFs	Executive Functions
PFC	Prefrontal Cortex
HPA axis	Hypothalamic–Pituitary–Adrenal Axis
11 β -HSD2	11 β -Hydroxy Steroid Dehydrogenase Type 2
HPG axis	Hypothalamus-Pituitary-Gonadal Axis
ADHD	Attention Deficit Hyperactivity Disorder
ELS	Early Life Stress
PS	Prenatal Stress
gwk	gestational week
EPDS	Edinburgh Postnatal Depression Scale
SCL-90	Symptom Check List -90
PRAQ-R2	Pregnancy-Related Anxiety Questionnaire Revised 2
SSRIs	Selective Serotonin Reuptake Inhibitors
WAIS-IV	The Wechsler Adult Intelligence Scale, Fourth Edition
VCI	Verbal Comprehension Index
PRI	Perceptual Reasoning Index
WMI	Working Memory Index
PSI	Processing Speed Index
FSIQ	Full-Scale Intelligence Quotient
ISL	International Shopping List Task
ISLR	International Shopping List Task Recall
DET	Detection Task
IDN	Identification Task
OBK	One Back Task
OCL	One Card Learning Task
CPAL	Continuous Paired Associate Learning Task
GML	Groton Maze Learning Test
SECT	Social Emotional Cognition Task
LGMM	Latent Growth Mixture Modelling
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index

RMSEA	Root Mean Square of Error of Approximation
SRMR	Root Mean Square Residual
DP	Disengagement Probability
MELR	Mixed Effects Logistic Regression
BIC	Bayesian Information Criteria

LIST OF ORIGINAL PUBLICATIONS

This 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. Kataja, E-L., Karlsson, L., Tolvanen, M., Parsons, C., Schembri, A., Kiiski-Mäki, H. & Karlsson, H. (2016). Correlation between the Cogstate computerized measure and WAIS-IV among birth cohort mothers. *Archives of Clinical Neuropsychology*, 32(2): 252-258. <https://doi.org/10.1093/arcclin/acw099>
- II. Kataja, E-L., Karlsson, L., Huizink, A.C., Tolvanen, M., Parsons, C., Nolvi, S. & Karlsson, H. (2017). Pregnancy-anxiety and depressive symptoms associate with visuospatial working memory errors during pregnancy. *Journal of Affective Disorders*, 218:66-74. doi: 10.1016/j.jad.2017.04.033
- III. Kataja, E-L., Karlsson, L., Leppänen, J.M., Pelto, J., Häikiö, T., Nolvi, S., Pesonen, H., Parsons, C.E., Hyönä, J. & Karlsson, H. (2018). Maternal depressive symptoms during the pre- and postnatal periods and infant attention to emotional faces. *Child Development* [*Epub ahead of print*]. doi: [dx.doi.org/10.1111/cdev.13152](https://doi.org/10.1111/cdev.13152)
- IV. Kataja, E-L., Karlsson, L., Parsons, C.E., Pelto, J., Pesonen, H., Häikiö, T., Hyönä, J., Nolvi, S., Korja, R. & Karlsson, H. (2018). Maternal pre- and postnatal anxiety symptoms and infant attention disengagement from emotional faces. *Journal of Affective Disorders*, 243:280-289 [*Epub ahead of print*]. doi: doi.org/10.1016/j.jad.2018.09.064

1 INTRODUCTION

Stable parental care during early sensitive periods of development is essential for infant survival and lays a foundation for the neurobiological, cognitive, and social-emotional development of the child (Champagne et al., 2004; Tottenham, 2018). This care, in turn, is affected by the multiple psychological propensities of the mother, such as her executive functions and emotional state (Barrett & Fleming, 2011). Several maternal brain regions undergo remarkable structural and functional adaptations during pregnancy (Hoekzema et al., 2016; Workman, Barha, & Galea, 2011) with a continuum to postpartum period (Kim et al., 2010; Macbeth & Luine, 2010). As part of “maternal brain circuitry,” these brain areas regulate reward, emotion, learning, and executive functions, and ensure that the mother’s responding to her infant’s needs is motivated and temporally accurate, synchronous, and relevant (Moses-Kolko et al., 2014; Pereira & Ferreira, 2016). The neurocognitive changes of the mother, the “maternal programming,” starts from pregnancy and builds a foundation for child development and for the physiological, emotional, and cognitive adaptations of the mother (Agrati & Lonstein, 2016; Lewis & Galbally, 2018). According to this notion, parenting starts during pregnancy (Glover & Capron, 2017) and provides the first developmental environment for the child.

Due to the marked plasticity that the maternal brain undergoes during the perinatal period, this time has a high risk for maladaptation (Hillerer et al., 2014). Some women, especially if prone to experience depression or anxiety, are more vulnerable to the reproductive experience (Graignic-Philippe et al., 2014; Kammerer, Taylor, & Glover, 2006), and for these women, excessive mood change, such as depressive and anxiety symptoms, post-partum depression, and related cognitive disturbances may take place (Workman et al., 2011). Moreover, many women enter pregnancy with pre-existing psychiatric problems. Maternal cognitive functions play a significant role in parenting and in the development of the child. Therefore, their disturbance due to maternal symptoms of stress, depression, or anxiety may be of relevance for early-onset support and interventions targeted for pregnant women and their families (Goodman & Garber, 2017). First, these functions are closely related to the life-style factors and living conditions that the mother provides for her child from pregnancy (Lewis et al., 2014). Second, their role may be even more crucial for the actual caregiving and interaction behavior that lays a foundation for attachment and the development of the child’s self-regulation and mental health (Bridgett, Burt, Edwards, & Deater-Deckard, 2015). Finally, maternal cognitive functions interact with psychiatric symptoms and stress and are negatively impacted by maternal affective disorders (Barrett & Fleming, 2011; Moses-Kolko et al., 2014; Ouellette & Hampson, 2018; Young et al., 2017). Thus, how a

mother is able to adapt to the emotional and cognitive demands of motherhood from pregnancy may have far-reaching effects on her experience as a mother, the evolving mother-infant bond, and ultimately the development of the child (von Mohr, Mayes, & Rutherford, 2017). Therefore, a successful maternal adaptation process should be supported early.

“Fetal programming,” in turn, refers to the notion that the *in utero* environment can alter or organize the fetal biological systems with a long development or intrinsic plasticity to react and adapt during different critical or sensitive periods of development (Barker, 1990; O’Donnell & Meaney, 2017). According to this view, the fetus adapts its organs, brain, and behavior in order to better fit with the postnatal environment. The fetal period and early infancy are times of high plasticity, but also vulnerability, as the development of the child seeks to integrate information from the prevailing environment in order to prepare for the most adaptive direction for later development (Lewis & Galbally, 2018). The psychological well-being of the mother during pregnancy may have a fundamental influence on both maternal and fetal programming. If the mother faces difficulties in attaining a balance in her adaptation, pregnancy may become a period of heightened stress (Workman et al., 2012). This, in turn, may signal to the infant that the postnatal environment is threatening or otherwise adverse and thereby program the fetal and infant neurodevelopment to be prepared for adversity (Sandman et al., 2016). Thus, maternal prenatal mental health may have independent effects on child development through fetal programming increasing the risk for adverse neurodevelopment and behavioral and emotional problems in the child (Gentile, 2017; Van den Bergh et al., 2017). Moreover, it may set the ground for the maternal postnatal mood and her preparedness for the interaction and emotional bond with the infant. Given this, pregnancy has become an emerging area of interest in studies investigating the intergenerational transmission of mental health. Similarly, it has been acknowledged as a crucial target for prevention of neurodevelopmental and psychiatric disorders (Van den Bergh et al., 2018). However, a better understanding of the cognitive and affective processes that are part of normal pregnancy as well as markers of risk for maladaptation to motherhood might benefit the field working with early-onset mental health prevention and treatment among expecting mothers.

This study evaluated the associations between maternal symptoms of depression and anxiety and cognitive functions during pregnancy. Secondly, the associations between maternal symptoms of depression and anxiety during the pre- and postnatal periods and infant’s attention patterns to emotional faces were inspected. These studies were conducted as part of a wider FinnBrain Birth Cohort Study (Child Development and Parental Functioning Lab) aiming to investigate the development of child self-regulation in the context of maternal pre- and postnatal distress.

2 REVIEW OF THE LITERATURE

2.1 Cognitive aspects of motherhood

Parenting provides the first developmental environment for the child (Feldman, 2012). Therefore, parental cognitive functioning is important for child development. It affects how the parents cope with their environment, but also how they interact with their children, parent them, and facilitate their cognitive and emotional development (Bridgett et al., 2015; Young et al., 2017). Viewed this way, the assessment of parental cognition is of value in developmental studies, as it may inform us about the meaningful aspects of the child's developmental environment and moreover the interpersonal environment in which the development of the child's brain and behavior takes place (Meador et al., 2012; Walfisch et al., 2013; Walker et al., 2012).

Still, parental cognitive functions are often not assessed in larger-scale studies (Pechtel, & Pizzagalli, 2011). This may be due to the fact that many cognitive assessment methods require individual, relatively lengthy test sessions by an assessor trained for psychological evaluation and the specific test method, which challenge limited study resources (Frederickson et al., 2010). Moreover, many studies have used relatively narrow measures of cognitive abilities, such as SAT scores, school grades, or verbal tests as indicators of general cognitive abilities/educational attainment. However, more fluid cognitive measures, such as attentional set-shifting, spatial working memory, and other executive functions, might be more appropriate in light of parental cognition and parenting (reviews: Barrett, & Fleming, 2011; Bridgett et al., 2015; Crandall, Deater-Deckard, & Riley, 2015). Identifying easily administered test methods, in which the performance would rely less on IQ-related cognitive functions, might be beneficial for investigating individual differences in the cognitive correlates of parenthood and parenting behavior (Macbeth & Luine, 2010).

We are still limited in our understanding about the cognitive architecture of parenting (Rutherford et al., 2018), and it is likely that diverse cognitive characteristics of the parents (i.e., general cognitive abilities, executive functions) relate to their parenting on one hand and, on the other hand, onto their child's development. Therefore, it is valuable to try to enhance our knowledge about which specific cognitive factors seem to be the most important determinants of sensitive and responsive parental care, positive parenting practices, and healthy child development. Moreover, it is important to acknowledge which cognitive factors might be associated with less than optimal parenting (e.g., harsh discipline, over control), and how this knowledge could be used when planning interventions to enhance

positive parenting and better child adjustment (Huizink & De Rooij, 2018). Finally, due to the aforementioned reasons, the investigation of feasible test methods that might capture the most essential cognitive aspects of parenthood and parenting behaviors is important, as easily-administered and ecologically valid test methods would be of use in large-scale studies investigating the associations between parental factors and child neurocognitive, behavioral, and emotional development.

2.1.1 General cognitive functioning, intelligence (IQ)

Cognitive abilities refer to the overall cognitive functioning of the brain as indexed by the connectivity of multimodal association areas in widely distributed networks throughout the whole brain (Karama et al., 2009; Luders et al., 2009). Current knowledge about human intelligence views cognitive abilities as structural and hierarchical. General ability, *g*, is the broadest cognitive factor or ability, and under that are located a number of more narrow abilities (such as fluid reasoning/intelligence, comprehension-knowledge/crystallized intelligence, cognitive processing speed, short-term memory; Carroll, 1993). Broadly, cognitive functions may be defined as an ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly, and learn from experience (cf. Deary, 2013), and an intelligence quotient (IQ) can be used as an estimate (Karama et al., 2009). IQ is relatively easy to quantify and can be used cross-culturally (Sommerfelt, Ellertsen, & Markestad, 1995).

Of genetic cognitive traits, intelligence is highly heritable, and one of the important predictors of later life outcomes such as education and occupational career, mental and physical health and illness, and mortality (Plomin, & Deary, 2015; Whitley et al., 2013). Intelligence correlates positively with socioeconomic status (SES), which, in turn, is linked with/refers to health status, family income, housing conditions, education, and labor market access (Whitley et al., 2013; Krapohl, & Plomin, 2015). Parental IQ, in the form of academic attainment, has also been found to mediate the cross-generational linkage of positive parenting (Belsky, Conger, & Capaldi, 2009; Conger, Belsky, & Capaldi, 2009). So, in addition to the direct genetic impact on child cognitive development, parental IQ has also an indirect impact, such as on community and educational capital and on more positive parenting practices. Together, these demonstrate the interaction of both familial and environmental factors in child neurodevelopment (Galbally & Lewis, 2017; Marcus Jenkins, Woolley, Hooper, & De Bellis, 2013).

However, emerging evidence supports the contention that the effect of intelligence on later positive outcomes may be attributable to a more specific subset of cognitive abilities, such as executive functions (Duff, Mold, & Gidron, 2009; Hall et al.,

2009). Moreover, a growing corpus of research on parental executive functions suggest that these particular cognitive aspects of parenthood may be transmitted across generations and when dysfunctional, transfer the effects of negative parenting into adverse child development (Deater-Deckard, Sewell, Petrill, & Thompson, 2010; Deater-Deckard, Wang, Chen, & Bell, 2012).

2.1.2 Executive functions (EFs)

Executive functions (EFs) refer to cognitive processes that control and regulate different brain functions and actions, for instance, by suppressing a habitual response or shifting between different tasks and situations. EFs are critical to adaptive functioning in the environment (Vohs & Baumeister, 2011), and important for both emotion and behavior regulation and successful parenting (for an extensive review see: Bridgett et al., 2015). The three core EFs: inhibition, working memory, and attentional set-shifting (Miyake & Friedman, 2012; Miyake et al., 2000), modulate reflexive behavior and high activation emotional responding (Hall, Fong, & Epp, 2014) by promoting regulation of thoughts, emotions, and actions (Barrett, Tugade, & Engel, 2004; Diamond, 2013; Rutherford, Wallace, Laurent, & Mayes, 2015). These higher order cognitive functions are carried out by the prefrontal cortex (PFC) that underpin social and cognitive abilities unique to humans (Arnsten, 2009; Saxe, 2006). The PFC has reciprocal connections with several different brain areas including the amygdala, which is implicated in emotional processing; the hippo-campus, which is implicated in memory functions; and temporal and parietal cortices which are higher-order sensory regions (Grossmann, 2013) and so is a key brain area in information processing, both emotional and unemotional, and self-regulation.

EFs are important correlates of general intelligence (Friedman et al., 2006). Both general intelligence and EFs share common genetic variance (Luciano et al., 2001) and correlate moderately and positively; people who get higher performance scores on one test perform better on other tests, also (Panizzon et al., 2014; Deary, 2013; Plomin & Deary, 2015). Not all EFs are related to intelligence, however. Effective EFs require partially distinct brain circuits from general intelligence, as indicated, for instance, by reports of frontal lobe damage perturbing EFs and leaving overall intelligence profile intact (Friedman et al., 2006). In addition to true correlations, these results may partly indicate the different capability of various cognitive measures to assess EFs and differentiate between crystallized and fluid intelligence, also (Ardila, Pineda, & Rosselli, 2000; Friedman et al., 2006; Roca et al. 2014). According to earlier studies, working memory and especially the capacity for updating the incoming information are most related to intelligence, whereas for

instance, inhibiting and shifting are less (Duan, Wei, Wang, & Shi, 2010; Friedman et al., 2006; Roca et al., 2014).

Working memory, inhibition, and flexibility in attention shifting are all crucial in appropriate social behavior, such as parenting (Bridgett et al., 2015; Deater-Deckard et al., 2010, 2012; Rutherford et al., 2015). Indeed, in parenthood, many coordinated actions involve the regulation of emotions, cognitions, and behavior, thus self-regulation, and here, parental EFs play a key role (Bridgett et al., 2015). Currently, there are many studies showing that maternal EFs, particularly working memory, are positively related to the mother's emotional responsiveness towards the child such as reflective functioning (i.e., the parent's ability to consider both their own and their child's thoughts, feelings, and behaviors; Rutherford et al., 2018) and sensitivity (Gonzales, Jenkins, Steiner, & Fleming, 2012). Problems in maternal working memory, in turn, have been found to associate with the actual parenting behavior. Poorer working memory may increase negative reactivity in the face of frustration (Deater-Deckard et al., 2010) and lead to an increased risk for harsh reactive parenting and child conduct problems (Deater-Deckard et al., 2012). One study showed that poorer maternal EFs were related to negative parenting experienced during childhood, and this, in turn, was reflected with the mother's interaction with their own infant as higher intrusiveness and negativity (Bridgett et al., 2017).

Importantly, recent studies have shown that the connections between maternal EFs and sensitivity are evident already during pregnancy (Rutherford et al., 2018) and so might be fruitful targets for interventions from the earliest stages of motherhood. Finally, parental EFs might be better targeted with interventions as contrast to interventions aimed to enhance general intelligence and educational achievement (cf. Tucker-Drob & Briley, 2014). For instance, they could be incorporated into how interventions are tailored to families, such as teaching the parent to recognize their own EFs, both strengths and difficulties, and in understanding the role that EFs play in self-regulation, parenting, and management of daily-life (Deater-Deckard, personal communication).

2.2 Maternal depressive and anxiety symptoms during pre- and postnatal periods

Not only is the integrity of cognitive functions important for motherhood and child development, but sensitive, responsive mothering also requires that the mother is affectively tuned to the cues and needs of her infant. Pregnancy prepares the mother for the upcoming motherhood. The feelings of bonding and attachment usually start to emerge and continue to grow during the postnatal period (Glover

& Capron, 2017). The functioning of the maternal stress systems shows adaptive changes, as the hypothalamus-pituitary-adrenal (HPA) axis (i.e., the major stress regulation system) and its secreted cortisol start to show blunted responses to physiological and psychological stressors, which protect both the mother and the fetus from excessive environmental stressors (Howland, Sandman, Glynn, Crippen, & Davis, 2016). However, maternal mental health problems, such as symptoms of depression and anxiety, are common during the pre- and postnatal periods, and even at sub-clinical level, are known to compromise the mother's ability for sensitivity, synchrony, and the parent-child interaction (Field, 2011). Moreover, maternal emotional distress during pregnancy potentially modifies the functioning of the maternal HPA axis and the activity of the placental barrier enzyme 11 β -hydroxy steroid de-hydrogenase Type II (11 β -HSD2) and may lead to greater transfer of stress-hormones to the fetus (Duthie & Reynolds, 2013; Huizink & De Rooij, 2018) and thus have direct biological influences on the unborn child. The emotional state of the mother during pregnancy often predicts her psychological well-being postnatally. Maternal symptoms of distress, as detectable and established markers of risk for both maternal functioning and child development, should be detected early and treated effectively (Glover, 2011, 2015; Korja et al., 2017).

2.2.1 Depressive symptoms

The incidence of depression, especially in girls, rises sharply after puberty, with the one-year prevalence estimate being 4–5% during mid- to late adolescence (Thapar, Collishaw, Pine, & Thapar, 2012) and remaining relatively constant across the life-span (Kessler & Bromet, 2013). While many women enter pregnancy with pre-existing histories of depression, still many have their first onset of depression during their reproductive age (Weissman, & Olfson, 1995). Maternal depression is one of the most common health problems of women during the perinatal period (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Evans, Heron, Francomb, Oke, & Golding, 2001) and also one of the most significant risk-factors for the neurocognitive and emotional development and later adjustment of the child (Galbally & Lewis, 2017; Gentile, 2017; Goodman & Garber, 2017; Field, 2011). The estimated prevalence for maternal depressive symptoms of varying severity ranges between 20–40% during the prenatal period and 5–15% for depressive disorder during the pre- and postpartum periods (Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2006; Gavin et al., 2005; Leight, Fitelson, Weston, & Wisner, 2010). Risk factors for developing depression include genes, early-life adversity including factors such as insecure attachment and lack of warmth (Heim, Plotsky, & Nemeroff, 2004), female gender, and stressful life events (Barrett & Fleming, 2011).

Prenatal depression is correlated with postnatal depression with an estimate of around 50% correlation (Gotlib, Whiffen, Mount, Milne, & Cordy, 1984; O'Hara & Swain, 1996). Depression is also correlated with other psychiatric symptoms, such as anxiety during the pre- and postnatal periods (Andersson et al., 2006), and a history of comorbid anxiety and depression appears to significantly increase the risk for postnatal depression (Agrati & Lonstein, 2016). Therefore, a shift in contemporary research has moved from investigating the significance of postnatal depression in shaping parenting and child development towards understanding the role that prenatal depressive symptoms play in predicting different adverse outcomes during motherhood and child development (Gentile, 2017). For many, the symptoms of depression start to emerge during mid-to-late pregnancy and peak at 1.5–3.0 months postpartum (Lonstein et al., 2015). This implicates that, in many cases, targeted interventions to alleviate maternal distress could be started well before child-birth. Currently, the screening of maternal depressive symptoms is recommended in maternal welfare clinics in many Western countries (Putnam et al., 2017), however, many women with depressive symptoms still remain unrecognized and untreated. In order to prevent a possibly negative trajectory of child development that originates from maternal prenatal psychological distress, more efficient screening of symptoms at different phases of the pre- and postnatal periods would be important. Moreover, early interventions targeted specifically to maternal depressive symptoms (i.e., the risk factor itself), and its diverse affective, cognitive, and behavioral features that ultimately lead to a risk for disrupted parenting and adverse child development would be crucial (Cicchetti & Toth, 2009; Galbally & Lewis, 2017; Goodman & Garber, 2017; Goodman & Gotlib, 1999).

2.2.2 Anxiety symptoms

Approximately 10–20% of women report suffering from symptoms of anxiety during pregnancy (Huizink et al., 2015; Leach, Poyser, & Fairweather-Schmidt, 2017) and around 15% may be classified as having an anxiety disorder during pregnancy and after child-birth (Fairbrother, Janssen, Antony, Tucker, & Young, 2016). It has been stated that the prevalence of anxiety disorders is higher among pregnant or postpartum women than among the general population, as for instance, obsessive-compulsive disorder and generalized anxiety disorder are twice as high among postpartum women as they are in the general population (3–4 vs. 1–2% and 4–8 vs. 3–4%, respectively) (Agrati & Lonstein, 2016; Ross & MacLean, 2006). This might be due to both the physiological strains of pregnancy (e.g., higher levels of circulating cortisol and inflammatory cytokines) as well as the emotional and psychosocial demands of pregnancy and motherhood (Raphael-Leff, 2005) that in-

crease the vulnerability for symptoms of anxiety. Although for most women feelings of anxiety and depression during pregnancy are transient and diminish, for some they persist. The discrepancy in maternal coping abilities and perceived demands of pregnancy and motherhood may set into motion diverse biological, cognitive, and behavioral consequences that disturb the early parenthood by, for instance, increasing parenting stress after child-birth (Huizink et al., 2017) and the several known adverse effects of maternal prenatal anxiety on fetal and child neurocognitive and emotional development (e.g., reviews: Dunkel Schetter & Tanner, 2012; Mulder et al., 2002; Van den Bergh et al., 2017, 2018).

Importantly, there seems to be a specific form of anxiety unique to the prenatal period. This form of anxiety is a distinct and definable syndrome that reflects the worries of the bodily changes caused by pregnancy, concerns of the health and well-being of the child to-be-born, and fear of delivery (Dunkel Schetter & Tanner, 2012). Pregnancy-related anxiety is more common among first-time mothers and may be regarded as a distinct clinical phenotype that predicts postnatal mood disturbances (Huizink et al., 2015, 2017). It has constantly been related to adverse effects on both the mother and the infant, such as spontaneous preterm birth (Rose, Pana, & Premji, 2016) as well as the child's attention dysregulation, cognitive problems, and higher reactivity to novelty and stress (Dunkel Schetter & Tanner, 2012; Nolvi et al., 2016). Despite the high prevalence of anxiety symptoms in child-bearing mothers, the screening of anxiety during the perinatal period is rare (Agrati & Lonstein, 2016; Lonstein, Lévy, & Fleming, 2015), although it indeed should be one screened aspect of maternal emotional adaptation due to its potentially negative impact on fetal development, maternal caregiving, attachment formation, and later child development (Huizink & De Rooij, 2018; Korja et al., 2017).

2.3 Maternal depressive and anxiety symptoms and their relation to cognitive functions

The PFC and the limbic system, including the hippocampus, are important brain areas for cognitive functions, such as attention, cognitive control, learning, and memory (Akirav & Maroun, 2006; Amat, Paul, Watkins, & Maier, 2008). These brain areas are sensitive to the fluctuation in reproductive hormones (Morrison, Brinton, Schmidt, & Gore, 2006; Smith et al., 2006) and also to symptoms of stress, depression, and anxiety due to their high receptor density for different neuroactive hormones (Arnsten, 2009; Langenecker et al., 2007; Pechtel & Pizzagalli, 2010; Workman et al., 2011). Thus far, only little attention has been paid to the

possibly interactive nature of maternal psychiatric symptoms and cognitive re-organization during pregnancy, while it is possible that the maternal programming and related neurocognitive changes may be disrupted by maternal mental health problems during pregnancy (Ouellette & Hampson, 2018; Stein et al., 2014; Von Mohr et al., 2017).

The reproductive system, including the hypothalamus-pituitary-gonadal (HPG) axis and its secreted reproductive hormones as well as the neuroendocrine stress-regulation system (HPA axis) and its secreted glucocorticoids, function in a complex relationship (Mulder et al., 2002). While this is a scarcely studied area as yet, it may be that maternal psychiatric symptoms and a heightened or dysregulated HPA axis and cortisol activity during pregnancy interact with reproductive hormones (e.g., estradiol and/or progesterone) and lead to cognitive problems, such as diminished memory (Glynn, 2010; Hampson et al., 2015; Ouellette & Hampson, 2018). Finally, as both anxiety and depressive symptoms are relatively common among pregnant women and are known to relate to both cognition and parenting, a better understanding about independent and combined effects of pregnancy and psychiatric symptoms on maternal cognitive functioning and later child outcomes would be of importance in planning maternal healthcare practices and developing interventions for parents and families (Crandall et al., 2015; Farrar et al., 2014).

2.3.1 Depressive and anxiety symptoms and cognitive dysfunctions

Cognitive deficits and specifically problems in memory and different aspects of EFs have been found to associate with depression and anxiety possibly contributing both to the onset and maintenance of symptoms (Gotlib & Joorman, 2010; LeMoult & Gotlib, 2018; McIntyre et al., 2013; Naismith et al., 2010; Vytal, Cornwell, Letkiewicz, Arkin, & Grillon, 2013). Depression is often characterized with executive dysfunctions, such as problems in working memory, set-shifting, and attention control, whereas the nature of cognitive dysfunction in anxiety is more unclear and may depend on the subtype of the disorder as well as the level of symptoms (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; McIntyre et al., 2013; Naismith et al., 2003). For instance, Salthouse (2012) noted that there might be an inverted U-relation between anxiety symptoms and cognitive functions at least on some cognitive domains. In studies measuring the direct brain responses in cognitive performance in relation to psychiatric symptoms, the cognitive deficits have been found to correspond, for instance, to altered prefrontal activity (Arnsten, 2009) as well as deviances in corticolimbic connectivity (Korgaonkar, Grieve, Etkin, Goslow, & Williams, 2013).

Overall, in depression, a negative, mood-congruent information processing style is prevalent leading to rumination of negative thoughts in the mind. It seems that individuals with dysfunctions in cognitive control (e.g., inhibitory and attention control) are more vulnerable to rumination and thus ultimately experience depressive episodes (Joorman, 2010; Joorman & Gotlib, 2010). Working memory, as a system for active maintenance and manipulation of information, plays an important role in directing our attentional resources. In depression, a person suffers from difficulties in inhibiting negative or unwanted ruminating thoughts from entering working memory, which then disturbs attention processes, goal-directed actions, and coherent stream of thoughts (Joorman 2010; LeMoult & Gotlib, 2018). Similar cognitive problems that are repetitive and distractive negative thoughts are also common in anxiety, such as pregnancy-related anxiety (Bayrampour et al., 2016). Thus, dysfunctions in cognitive control may be detectable markers of vulnerability for depressive or anxiety disorders on one hand and cognitive control training, on the other hand, may be one target for intervention in reducing psychiatric symptoms and preventing more severe forms of disorders (Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017). If depression and anxiety disturb cognition in non-pregnant subjects, then a question follows about how these symptoms and cognitive functions are associated during pregnancy.

2.3.2 Depressive and anxiety symptoms and cognitive functions during pregnancy

Many pregnant women report cognitive changes, such as memory deficits and problems in concentration and attention (Crawley, Grant, & Hinshaw, 2008; Logan, Hill, Jones, Holt-Lunstad, & Larson, 2014). One meta-analysis of the cognitive problems during pregnancy reported that the most consistent finding in studies among pregnant women was a deficit in memory measures that place a high demand on executive cognitive control (i.e., the executive component of working memory) (Henry, & Rendell, 2007). An update and an extension to this analysis reported different results, namely, deficits in general cognitive functions (e.g., reduced processing speed) but not in executive functions (Anderson and Rutherford, 2012; see also Christensen, Leach, & Mackinnon, 2010; Logan, Hill, Jones, Holt-Lunstad, & Larson, 2014). As the exact nature of cognitive re-organization during pregnancy seems unclear due to, for example, heterogeneous study samples, diverse cognitive test methods and other methodological problems, alternative explanations for cognitive deficits should be considered. One potential cause of cognitive problems might be maternal mood and anxiety (Hampson et al., 2015; Logan et al., 2014; Ouellette & Hampson, 2018), while only a few studies have investigated psychiatric symptoms when trying to understand the mechanisms underlying

variation in cognitive changes during pregnancy (Buckwalter et al., 1999; Farrar et al., 2014; Hampson et al., 2015; Ouellette & Hampson, 2018).

Recently, Hampson et al. (2015) reported a significant association between depression and working memory deficits among pregnant versus non-pregnant women. In this study, both lower estrogen and higher depressive symptoms predicted performance in a visuospatial working memory task. Still, other studies, assessing both pregnant women's psychiatric symptoms and cognitive functions, have failed to find significant interactions between the two (Buckwalter et al., 1999; Farrar et al., 2014; Logan et al., 2014). Consequently, more studies and possibly also more sensitive test methods are needed to investigate if women experiencing psychiatric symptoms during pregnancy are also prone to suffer from cognitive dysregulation. Further, different types of maternal distress (e.g., pregnancy-related anxiety) should be studied in pregnant populations to determine if these act as acute stressors rising cortisol levels impairing the functioning of the PFC and consequently cognitive functioning (Arnsten, 2009; Shields et al., 2016).

2.4 Maternal depressive and anxiety symptoms and their relation to child's neurocognitive development

2.4.1 Prenatal factors

Maternal prenatal distress, in the form of subjective stress, depressive, and/or anxiety symptoms, is one of the most common and widely observed factors programming the development of the child's brain, behavior, and later health (Frasch, Baier, Antonelli, & Metz, 2017; Galbally & Lewis, 2017; Korja et al., 2017; Sandman, Class, Glynn, & Davis, 2016; Van den Bergh et al., 2017, 2018). According to the fetal programming model, the intrauterine environment signals via maternal nutritional, vascular, immune, and endocrine functions, information about the quality of the external environment (Barker, 1990; Howland et al., 2016). In response, the fetus adapts its organs to better fit with the anticipated postnatal environment (Glover, 2015; Glover & Capron, 2017; O'Donnell & Meaney, 2017). If the postnatal environment matches the prenatal environment, then this adaptation may improve resilience and coping (Sandman, Davis, & Glynn, 2012). However, if there is a mismatch between the pre- and postnatal environments or the adaptation is inadequate, then an increased susceptibility to both somatic and mental illness may occur (Maniam, Antoniadis, & Morris, 2014; Sandman et al., 2012). The underlying biological mechanisms of the fetal programming are only beginning to

be revealed (Sandman et al., 2016a, 2016b) and possibly include exposure to inflammatory cytokines, catecholamines, and/or glucocorticoids in utero (Daskalakis et al., 2013; Glover & Capron, 2017; O'Donnell et al., 2012; Van den Bergh, 2011) that lead to altered fetal growth, epigenetic dysregulation, and changes in the developmental trajectories of the structure and function of the central nervous system (Cao-Lei et al., 2017; Charil, Laplante, Vaillancourt, & King, 2010; Frasch et al., 2017; Monk, Spicer, & Champagne, 2012). The placenta, and more specifically, the activity of the placental barrier enzyme 11 β -HSD2 that inactivates cortisol, may be one primary programming vector connecting the (dys)functioning of the maternal HPA axis to the development of child's (dys)functional HPA axis and hyper-reactivity to stress (Charil et al., 2010; Howland et al., 2016; O'Donnell et al., 2009). However, it seems that maternal psychosocial distress on one hand and the HPA axis/cortisol levels on the other hand may each, through different mechanisms, exert their influences on child neurodevelopment (Howland et al., 2016; Huizink & De Rooij, 2018; Zijlmans, Riksen-Walraven, & de Weerth, 2015) and so should not be considered as a uniform mechanism.

The evidence for an adverse effect of prenatal distress on child's cognitive, behavioral, and psychosocial development is substantial (O'Donnell et al., 2009) and includes aberrations in neurodevelopment, poorer neurocognitive functions, enhanced negative affectivity, and higher rates of psychiatric disorders (Tuovinen et al., 2018; Van den Bergh et al., 2017, 2018). A number of brain areas may be especially susceptible to exposure to prenatal distress, which include areas important for higher order cognitive functions, attention as well as emotional processing, such as the hippocampus, amygdala, corpus callosum, cerebellum, and the PFC (Charil et al., 2010; Van den Bergh et al., 2018). Exposure to prenatal distress may induce alterations in neurogenesis (i.e., the production of neurons) and corticogenesis (i.e., the development of the cortex) in the developing brain (cf. Marečková et al., 2018) and lead to susceptibility to psychiatric consequences. Until recently, the evidence for offspring brain correlates of exposure to prenatal distress stem from animal studies. However, in recent years, also human studies have shown a relation between prenatal exposure to maternal psychobiological distress and structural and functional development of the child's brain (see reviews: Franke et al., 2017; Van den Bergh et al., 2018). These include, for instance, reductions in grey matter density in brain areas involved in cortical processing (Buss et al., 2010); lower cortical thickness (Sandman, Buss, Head, & Davis, 2015) or overall cortical growth of the frontal lobes; more mood dysregulation in relation to cortical gray matter volume reduction during adolescence (Marečková et al., 2018); greater amygdala volume and affective problems in girls, but not in boys (Buss et al., 2012); and atypical amygdala-prefrontal connectivity (Posner et al., 2016). Some, but not all studies, have reported sex-specific associations between exposure to prenatal distress and child brain structure. However, more studies are warranted to

study both the effects of timing as well as the moderating role of child sex on the associations between exposure to prenatal distress and child development (Van den Bergh et al., 2018).

In conclusion, maternal prenatal distress may aberrantly program the development of the child's HPA axis (Apter-Levi et al., 2016; Howland et al., 2016; Van den Bergh et al., 2017) and structure and functioning of the brain areas important for inhibiting or dampening excessive stress responses (e.g., the hippocampus) as well as areas exciting the functioning of the HPA axis (i.e., the amygdala) (Frasch et al., 2017; Howland et al., 2016; Lewis et al., 2014; Loman & Gunnar, 2010; Maniam et al., 2014). This, then, may lead to exaggerated circulating glucocorticoid levels, enhanced vigilance and fearfulness, and hyper-responsiveness to stress (Posner et al., 2016) and a higher risk for self-regulation and mental health problems later in life. Similar brain mechanisms are found in both anxiety disorders and depression (Kim & Whalen, 2009; Ramasubbu et al., 2013), and these may also mediate the link between maternal prenatal distress and offspring neurodevelopmental as well as early emerging externalizing and internalizing problems (Van den Bergh et al., 2018).

2.4.2 Postnatal factors

The effects of prenatal distress on child development are diverse, and they are not inevitable. Instead, the timing and trajectory of maternal symptoms, the sex, genotype/phenotype of the child, and the physiological systems affected all contribute to the development of the child's self-regulation and mental health (Frasch et al., 2017). Moreover, the postnatal environment, including parental current symptom levels (Galbally & Lewis, 2017), sensitivity (Kaplan, Evans, & Monk, 2008), cognitive characteristics (Lin et al., 2017), and coping (Zhu et al., 2015), all significantly contribute to the development of the child in the context of early life distress (Frasch et al., 2017). While many of the adverse effects of prenatal distress have been noted to occur irrespective of postnatal influences (Galbally & Lewis, 2017; Glover & Capron, 2017), the plasticity of the central nervous system and the systems that regulate stress reactivity are high during early development and also during the postnatal period (Franke et al., 2017). Therefore, it is important to consider the postnatal period as a possibly compensative period for adverse prenatal environment (Huizink & Bögels, 2013). Indeed, O'Donnell and Meaney (2017) have suggested that prenatal adversity and compromised fetal development may establish a "meta-plastic" state in the individual that increases the sensitivity to the postnatal environment. In conjunction, the three-hit concept of resilience and vulnera-

bility to early-life adversity (Daskalakis et al., 2013) postulates that it is the accumulation of “hits” that determine the development of mental health and its disorders. Here, a genetic predisposition might be the first hit, early-life adversity (including both pre- and postnatal) the second, and adult-life stressors the third. Accumulation of adversity, or hits, then leads to psychopathology in a system afflicted by a dysfunctional HPA axis and atypical brain development (Frasch et al., 2017; Johnson, Jones, & Gliga, 2015). Currently, some large prospective longitudinal follow-up studies are ongoing that aim to investigate the child’s brain and behavior development from the prenatal period over an extended postnatal period. These studies will provide important information on mediating [e.g., (epi)genetics] and moderating factors (e.g., child sex, maternal and paternal postnatal distress, and the extended postnatal environment).

Maternal depressive and anxiety symptoms often continue from the prenatal to the postnatal period. Whereas the prenatal environment may exert its influence on child development through shared biological routes between the mother and the fetus, the latter acts by shaping the psychosocial environment. Maternal postnatal distress has been connected to several different problems in maternal caregiving behavior such as difficulties in interpersonal contact, attachment formation, and sensitive and timely caregiving (Aktar, Majdandžic, de Vente, & Bögels, 2013; Aktar & Bögels, 2017; Grace, Evindar, & Stewart, 2003; Kingston, Tough, & Whitfield, 2012; Tronick & Reck, 2009). If the mother is unable to respond sensitively and consistently to a child’s needs during early, sensitive periods of development, and if there is some other disadvantage in the family life, this may increase the risk for disrupted psychosocial development in the child (Sohr-Preston & Scaramella, 2006; Sutter-Dallay et al., 2011). Moreover, dysfunctional parenting practices (Apter-Levi et al., 2016), the modelling of social-emotional interactions as well as verbal information of the environment given by the parent, may transmit the negative effects of maternal distress on child development (Aktar, Nikolić, & Bögels, 2017).

Thus, in an attempt to understand child development in the context of early life distress, it is imperative to consider the time-course as well as severity of symptoms when investigating the influence of maternal depression or anxiety on child developmental outcomes (Grace, Evindar, & Stewart, 2003; Madigan, Wade, Plamondon, & Jenkins, 2017; Matijasevich et al., 2015). For instance, it may be that chronic or especially severe maternal symptoms, in combination with other socio-demographic risk factors, are more predictive of adverse child outcomes compared to transient symptoms at some point in the child’s life (Campbell et al., 2004; Grace, Evindar, & Stewart, 2003; Madigan et al., 2018; Murray, Halligan, & Cooper, 2010; van der Waerden et al., 2015; Sandman, 2016a). Moreover, moder-

ating and mediating factors, such as genetic vulnerability, child sex, maternal cognitive functions and parenting practices, family functioning, and partner/social support all contribute to child development in the context of early-life adversity (Van den Bergh et al., 2017). Altogether, pregnant women and children at risk for adversity due to maternal psychological distress should be recognized early and should be protected from undue hardship and distress (Van den Bergh et al., 2017). The existing knowledge of the adverse consequences of early life distress on the mother, the child, and the family unit should be translated to families and health-care practitioners to avoid and alleviate excessive distress, and to treat early women and infants most vulnerable (Van den Bergh et al., 2017).

2.4.3 Attention to socio-emotional signals during infancy

Cognitive, attention-related mechanisms may play a key role in the development and maintenance of psychopathology (e.g., Armstrong & Olatunji, 2012; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburgh, & van IJzendoorn, 2007). Both problems in general control of attention as well as deviances in social-emotional information processing likely underlie the cognitive, emotional, and behavioral problems seen, for instance, in depressive and anxiety disorders (e.g., Cisler & Koster, 2010; Grahek, Everaert, Krebs, & Koster, 2018; Leppänen, 2011), but little is known about their developmental trajectories from early childhood. Already during infancy, attention mechanisms play an important role in self-regulation. The orienting component of attention, referring to the ability to engage to and disengage attention from environmental cues, is responsible for perceptual processing during the first year of life (Derryberry & Rothbart, 1988; Posner & Rothbart, 2007) and plays a key role in daily interaction and learning situations, social-emotional functioning, and self-regulation (Keehn, Müller, & Townsend, 2012; Posner & Rothbart, 2009; Scerif, 2010). Flexible orienting of attention enables the infant to engage to other people and objects as well as to disengage from them in order to regulate arousal and distress. Genetic factors are related to how child attention and self-regulation abilities develop (Leppänen et al., 2011; Papageorgiou & Ronald, 2017; Posner, Rothbart, & Sheese, 2007), but also environmental factors may moderate the association between the developing attention systems and self-regulation abilities (Aktar et al., 2018; Papageorgiou & Ronald, 2017; Zhang, Chen, Deng, & Lu, 2014). Thus, deviances in the orienting component of attention may reveal early vulnerabilities to social-emotional development and to later mental health (Nakagawa & Sukigara, 2012; Peltola, Forssman, Puura, van IJzendoorn, & Leppänen, 2015), although only a handful of studies to date have reported long-term associations between early attention orienting and later self-regulation.

Face perception is a specific form of attention (Haist & Anzures, 2016), and the human visual system is highly specialized in face processing (Johnson, 2005). Already newborn infants show preference for faces or face-like patterns (Johnson, 2005; Leppänen & Nelson, 2009; Leppänen et al., 2011). This orienting preference for faces, as a central factor to social engagement during early development, may build a basis for the acquisition of more complex social-emotional functions during childhood (Peltola, Yrttiaho, & Leppänen, 2018). Between 5 and 7 months of age, infants begin to reliably discriminate facial expressions, and soon after, exhibit enhanced orienting of attention to affectively salient facial expressions, especially signals of fear or threat (Leppänen & Nelson, 2013; Nelson & Dolgin, 1985). This well-documented attention bias for threat during infancy (see e.g., Ahtola et al., 2014; Forssman et al., 2014; Nakagawa & Sukigara, 2012; Peltola, Leppänen, Palokangas, & Hietanen, 2008) is manifested, for instance, in a slower or less frequent disengagement of attention from fearful or angry faces as compared to happy or neutral (Leppänen et al., 2010; Peltola, Leppänen, Palokangas, & Hietanen, 2008). The early emerging attention bias may represent an evolutionary conserved component of attention that functionally develops at this particular age and aids the infant to detect potentially harmful stimuli or social signals of danger when actively exploring the environment along with increased locomotion (Leppänen & Nelson, 2009). Neuroimaging work in adults shows the central role of the limbic system, namely the amygdala and the orbitofrontal cortex as well as cortical perceptual areas, in prioritization of threat-related stimuli (Leppänen & Nelson, 2013). During infancy, the processing of fear may depend more on the amygdala, whereas during adulthood also the hippocampus and frontal cortical areas all play a role (Gunnar, Hostinar, Sanchez, Tottenham, & Sullivan, 2015). The time-window for a developmental shift from hypo- to hypersensitivity of threat detection systems seems to be rather narrow during the middle of the first year of life. However, environmental and experiential factors may continue to shape the social-emotional attention systems and face perception well beyond early childhood (Nelson, 2013). Earlier studies have suggested that in healthy development, the normative threat-related attention biases may dissipate (Dudenev et al., 2015), but in psychopathological development may become overexpressed (Morales, Fu, & Pérez-Edgar, 2016; Schehner et al., 2012; Troller-Ronfree, Zeanah, Nelson, & Fox, 2017).

The emotional salience of faces, but also prior experiences, contribute to the perception of faces (Haist & Anzures, 2016; Leppänen & Nelson, 2009; Scerif, 2010). The evidence for an experience-dependent attention mechanism comes, for instance, from studies showing a strengthening of face preference during the second half of the first year (Frank, Vul, & Johnson, 2009; Peltola, Hietanen, Forssman, & Leppänen, 2013) and prioritization of faces that are more frequently encountered in the environment (Wheeler et al., 2011). Some recent studies propose that individual variation in face processing and more specifically, heightened processing

of fear/threat signals, may also arise from differences in early rearing environment, including moderate variations in maternal sensitivity (Zhang, Chen, Deng, & Lu, 2014) or symptoms of depression or anxiety (Forssman et al., 2014; Morales et al., 2017; but see Leppänen, Cataldo, Bosquet Enlow, & Nelson, 2018). The early preference of an infant to orient attention to faces conveying salient social-emotional information, and the potential role of early-life environment, and more specifically, maternal characteristics to modify this early attentional vigilance to biologically relevant stimuli, make face perception an interesting target for social-emotional developmental studies (Forssman et al., 2014). Identification of differences in this early emerging emotional trait, such as hypersensitivity to threat, may inform us about attention-related mechanisms of developmental psychopathology and also provide avenues for early interventions (Forssman & Wass, 2017).

With regard to face processing, difficulty disengaging from threat (e.g., fearful or angry faces) may be one potential early marker of vulnerability for anxiety and negative mood (Armstrong & Olatunji, 2012; Keehn et al., 2012; LeMoult & Gotlib, 2018; Leppänen, 2011). Attentional control, referring to cognitive ability to regulate allocation of attention, in turn, may be one possible mediating mechanism (Cisler & Koster, 2010). While only little is known about the long-term functional significance of the very early attention biases occurring during infancy and of the differences in early attention mechanisms and the development of later affective disorders, it may be that the first year of life is especially important for the emergence of exacerbated biases in emotional information processing (Leppänen & Nelson, 2013). Parental depressive and/or anxiety symptoms are found to be manifested in interaction situations with the infant, for instance, in reduced attention to infant cues as well as deviant expressivity of emotions towards the infant (Aktar, Colonnese, de Vente, Majdandžic, & Bögels, 2016). These difficulties in parental interaction may possibly reflect deviances in social-emotional processing on behalf of the parent experiencing depressive and/or anxiety symptoms and may be differently manifested in situations where the parent experiences primarily depressive versus anxiety symptoms (Aktar et al., 2016). According to Loman and Gunnar (2010), early exposure to negative parental emotional expressions, interaction, and caregiving may potentially alter infant social-emotional development, specifically threat processing (see also Aktar et al., 2018). Here, the inadequate, insensitive, or less-responsive parental care may shape, by neuroendocrine and neurobiological processes, a more reactive stress-response system in the infant and may contribute to the hyper-sensitivity of the developing threat-appraisal systems (e.g., high sensitivity to threat, high behavioral inhibition, and fearfulness), defiantly regulated by frontal cortical areas (seen e.g., in right frontal EEG asymmetry). This, then increases vulnerability to environmental stressors and increases the risk for internalizing and externalizing problems. High-quality parental care,

in turn, reportedly buffers the infant's stress biology and enhances healthy development (Gunnar et al., 2015). However, the nature of parental symptoms (i.e., anxiety vs. depression) may also cause different variance in infant social-emotional processing (cf. Leppänen et al., 2018). In recent years, research efforts have been directed to enhance our understanding about the significance of the early emerging threat bias in normative development as well as in the development of psychopathology.

2.4.4 Maternal pre- and postnatal depressive and anxiety symptoms and their relation to infant attention to social-emotional signals

Exposure to prenatal maternal distress has been found to associate with deficits in cortical processing and general attention control in the child, such that prenatal exposure may lead to deficits both in endogenous attention control as well as alterations in processing social-emotional information (Otte, Donkers, Braeken, & Van den Bergh, 2015; Van den Bergh et al., 2017, 2018; Van den Heuvel, Henrichs, Donkers, & Van den Bergh, 2017). With regard to general attention control, higher rates of attention deficit hyperactivity disorders (ADHD) have been reported among children exposed to prenatal adversity (Glover, 2011; 2015; Talge, Neal, & Glover, 2007; Van den Bergh et al., 2017; Wolford et al., 2017). Some of these general attention deficits have been found to be more pronounced in boys than girls (Van den Bergh et al., 2017) and thereby may reflect different strategies of evolutionary adaptation between sexes (DiPietro & Voegtline, 2017; Glover & Hill, 2012; Loman & Gunnar, 2010). To date, however, not many studies have investigated the moderating role of infant sex on the association between maternal prenatal distress and child attention developmental outcomes, while it is possible that there are sex-dependent differences in placental functions and/or epigenetic mechanisms (DiPietro & Voegtline, 2017; Lewis et al., 2014) leading to differences also in attention functions. This knowledge would be of importance for early targeted interventions, given that the psychiatric consequences of early life distress may differ for boys and girls (DiPietro & Voegtline, 2017; Van den Bergh et al., 2018). Furthermore, fetal neurophysiological alterations may be moderated by fetal sex, which, in turn, may increase sensitivity to postnatal factors differently for boys and girls (Glover & Hill, 2012; Glover et al., 2018). The prevalence of early emerging ADHD, cognitive problems, and/or externalizing behavior are significantly higher among boys, whereas internalizing symptoms, anxiety, and depression are significantly more prevalent among girls beginning from puberty (Glover & Hill, 2012; Stein et al., 2014; Van den Bergh et al., 2017). The prenatal origins of these disorders and sex-differences in their prevalence are only beginning to be revealed.

In terms of social-emotional information processing, already newborn infants of mothers with depression have been shown to exhibit cognitive and behavioral markers of risk for self-regulation difficulties (Field, 2010; Luby et al., 2003) with deviances in their general attention processes as well as interaction in social-emotional situations (Field, Diego, & Hernandez-Reif, 2009; Hernandez-Reif, Field, Diego, & Ruddock, 2006; Sohr-Preston & Scaramella, 2006; Sutter-Dallay, Murray, Glatigny-Dallay, & Verdoux, 2003). These infants have been found to be less responsive to faces and voices in general (Field et al., 2009; Field, 2011), and their overall presence has been characterized by higher arousal, lower attentiveness, and less “empathy” to social signals (Gentile, 2017; Salisbury et al., 2016). Moreover, these infants have been found to show patterns of atypical development, such as difficulties discriminating facial expressions and preference for social signals from strangers over their mother’s (Bornstein, Arterberry, Mash, & Manian, 2011; Pacheco & Figueiredo, 2012). Similarly, infants exposed to maternal prenatal anxiety have been found to show very early deviances from their non-exposed peers in how they habituate slower to standard sounds (Van den Heuvel, Johannes, Henrichs, & Van den Bergh, 2015); show increased attention or enhanced vigilance to fearful sounds (Otte et al., 2015); and prefer neutral stimuli, possibly interpreted as ambiguous, over an unpleasant (Van den Heuvel et al., 2017) or a stranger’s voice as compared to their own mother’s voice (Harvison et al., 2009). These behavioral and/or brain level markers may be indicators of delayed attention and cognitive development (e.g., inhibitory control) and/or slower or more thorough processing of social-emotional information due to exposure to maternal prenatal depression or anxiety (Field et al., 2009; Figueiredo, Pacheco, Costa, Conde, & Teixeira, 2010; Gentile, 2017; Van den Bergh et al. 2017, 2018). To date, little is known about how infants of mothers with prenatal anxiety or depression attend to emotional faces such as faces signaling threat. Given the deviances that the newborns of mothers with depression or anxiety show in their general attention processes and in processing social-emotional information other than faces, it may be expected that these infants show also deviances in face processing.

A handful of studies to date have investigated the associations between an infant’s attention bias to threat (e.g., fearful or angry faces) with an attention disengagement paradigm and maternal concurrent, thus postnatal, stressful life events and symptoms of depression or anxiety. Forssman et al. (2014), who investigated the interaction of genetic and experiential factors in shaping attention to social-emotional signals, found that 5–7 months old infants of mothers with heightened current versus low depressive symptoms showed relatively reduced disengagement of attention from fearful faces as compared to happy and neutral faces (i.e., an enhanced threat bias). Moreover, an increased number of life events currently affecting the mother were associated with a heightened bias for fearful faces in infants. This heightened threat bias was especially pronounced among T-carriers of the

TPH-2 gene, a factor that has, in other studies, been found to associate with enhanced cortical and amygdala responsiveness to emotional cues, reduced control of attention as well as susceptibility for depression (Forssman et al., 2014). Morales et al. (2017), using a similar attention disengagement paradigm with angry, happy and neutral faces, reported an association between maternal concurrent anxiety symptoms and 4–24 months old infant's heightened bias to threat. Finally, Leppänen et al. (2018) did not find moderate variations in maternal symptoms of depression or anxiety to associate with child's attention bias to threat, which was repeatedly assessed at 5, 7, 12, and 36 months of age. While the diversity in study set-ups [i.e., emotional expressions used (fearful versus angry), the number of models used in experimental paradigms as well as the number of presented trials] makes the comparison of the results among different studies difficult, it may be that the normative threat bias during infancy may be exacerbated by environmental factors. Further, it is possible that this hyper-sensitivity of the infant's developing threat-appraisal system may increase vulnerability to environmental stressors and mental health disorders, while more studies are needed to replicate previous findings and to investigate the long-term consequences of these findings.

In conclusion, in the different aspects of child development that may be affected by maternal distress, changes in attention and emotion regulation functions may be particularly consequential for the child's functional outcome. The pathways that regulate attention and stress responses overlap in the brain, and these developing systems are particularly plastic during pregnancy and during infancy (Loman & Gunnar, 2010). Attention to faces is one of the earliest emerging behavioral traits in infants and may reflect a specific form of attention (Haist & Anzures, 2016). While infants orient to faces at birth (Johnson, 2005), the development of this bias and associated specialization of cortical visual systems for face processing are also highly sensitive to postnatal experiences, particularly during the first years of life (Arcaro et al., 2017; Haist & Anzures, 2016; Leppänen & Nelson, 2009; Scerif, 2010). Individual differences in this developmental process and the emerging attentional biases for social signals (e.g., individual differences found in the context of maternal depression or anxiety) may have important long-term effects on the child's developmental outcomes given the allegedly central role of attention to faces in daily interaction, attachment formation, and interpersonal communication situations (Aktar & Bögels, 2017; Parsons, Young, Murray, Stein, & Kringelbach, 2010). Finally, the development of the child's brain and behavior occurs during interaction with the caregiver, where both members of the dyad contribute to each other (Pereira & Ferreira, 2016). Currently, however, little is known about whether exposure to prenatal distress has a potential to program the developing attention and threat-detection systems to social-emotional signals differently from early postnatal influences. Moreover, not much is known about whether these early emerging deviances in attention processes reflect difficulties in general attention

control or more specific deviances in processing social-emotional information. For the healthy development of the child's brain and behavior, it is important that the infant is able to form a positive interaction and secure attachment with the caregiver through well-functioning attention systems and endogenous attention control. By this, the infant will gradually be able to gain abilities for self-regulation. Investigating the differences in early attention regulation in social-emotional processing is of particular importance for our understanding about the development of self-regulation and mental health and the early markers of risk for this development.

2.5 Summary of the current literature

Different aspects of maternal cognitive functions, as part of maternal caregiving and parenting behavior, are important for child neurodevelopment and the development of self-regulation and mental health. We first compared two different cognitive test methods being a traditional IQ test and a computerized neuropsychological test battery in a smaller sample of pregnant or postpartum women. Ecologically valid, feasible test methods with low emphasis on IQ are needed to investigate the possibly meaningful differences in maternal cognitive functions and importantly their dysfunctions. We then investigated how maternal prenatal depressive, general anxiety, and pregnancy-related anxiety symptoms associate with the mother's cognitive processing. Psychiatric symptoms associate with cognitive dysfunctions in other than pregnant populations, but these associations have been minimally investigated among pregnant women. This knowledge is, however, important when trying to understand the differences in the adaptation to motherhood and parenting and when delivering information or planning interventions for pregnant women and their families. Finally, we investigated how maternal symptoms of depression and anxiety during the pre- and postnatal periods are associated with infant attention patterns to emotional faces. Both depression and anxiety are associated with deviances in social-emotional and face processing. Studying these cognitive mechanisms in a large sample of infants from mothers with depressive or anxiety symptoms may provide important information about the early emerging behavioral traits that may have long-term effects on the social-emotional and mental health development of the children. These studies have set a foundation in the larger FinnBrain Birth Cohort Study (Child Development and Parental Functioning Lab) for longitudinal assessments of: 1) maternal neurocognitive functions, and 2) the trajectories of child attention to emotional faces during early sensitive years of child development. Long-term, repeated follow-ups of the same individuals will inform us about the different aspects of maternal cognitive functions and child attention patterns in relation to child development in the long term.

3 AIMS OF THE STUDY

The aims of this study were: first, to evaluate the overlap between two cognitive test methods (i.e., a traditional IQ test and a computerized neuropsychological test method) between pregnant or early postpartum women and then to explore the associations between maternal prenatal depressive and anxiety, both general anxiety and pregnancy-related anxiety symptoms and cognitive functions during pregnancy; and second, to explore the associations between maternal pre- and postnatal depressive and general anxiety symptoms and an 8-month-old infant's attention to social-emotional signals conveyed through faces (Figure 1). Maternal pregnancy-related anxiety symptoms were left out on purpose, as one aim was to analyze longitudinal data on maternal pre- and postnatal symptoms and infant outcomes. The possible sex differences in the associations between maternal symptoms and infant attention patterns were also investigated. Maternal cognitive functions covered verbal and visuo-spatial working memory, speed of processing/reaction time, attention, and social cognition. An infant's social-emotional attention was assessed with eye-tracking and an attention disengagement paradigm with neutral, happy, fearful, and phase-scrambled faces and distractors.

Specifically, the aims were:

1. To study the associations between a traditional paper-and-pencil cognitive IQ test and a computerized neuropsychological test battery (Study I).
2. To study the associations among maternal self-reported depressive, pregnancy-related anxiety, and general anxiety symptoms during pregnancy (gwk 26–30) and different cognitive functions assessed with a computerized neuropsychological test battery (Study II).
3. To study the relationships among trajectories of maternal depressive symptoms from the prenatal to the early postnatal period and an infant's attention disengagement from emotional faces at 8 months. Moreover, sex-specific effects were explored (Study III).
4. To study the associations among maternal self-reported general anxiety symptoms during different stages of pregnancy and the early postnatal period and the 8-month-old infant's attention disengagement from emotional faces with specifically the difficulty to disengage from fearful faces. Sex-specific effects were also explored (Study IV).

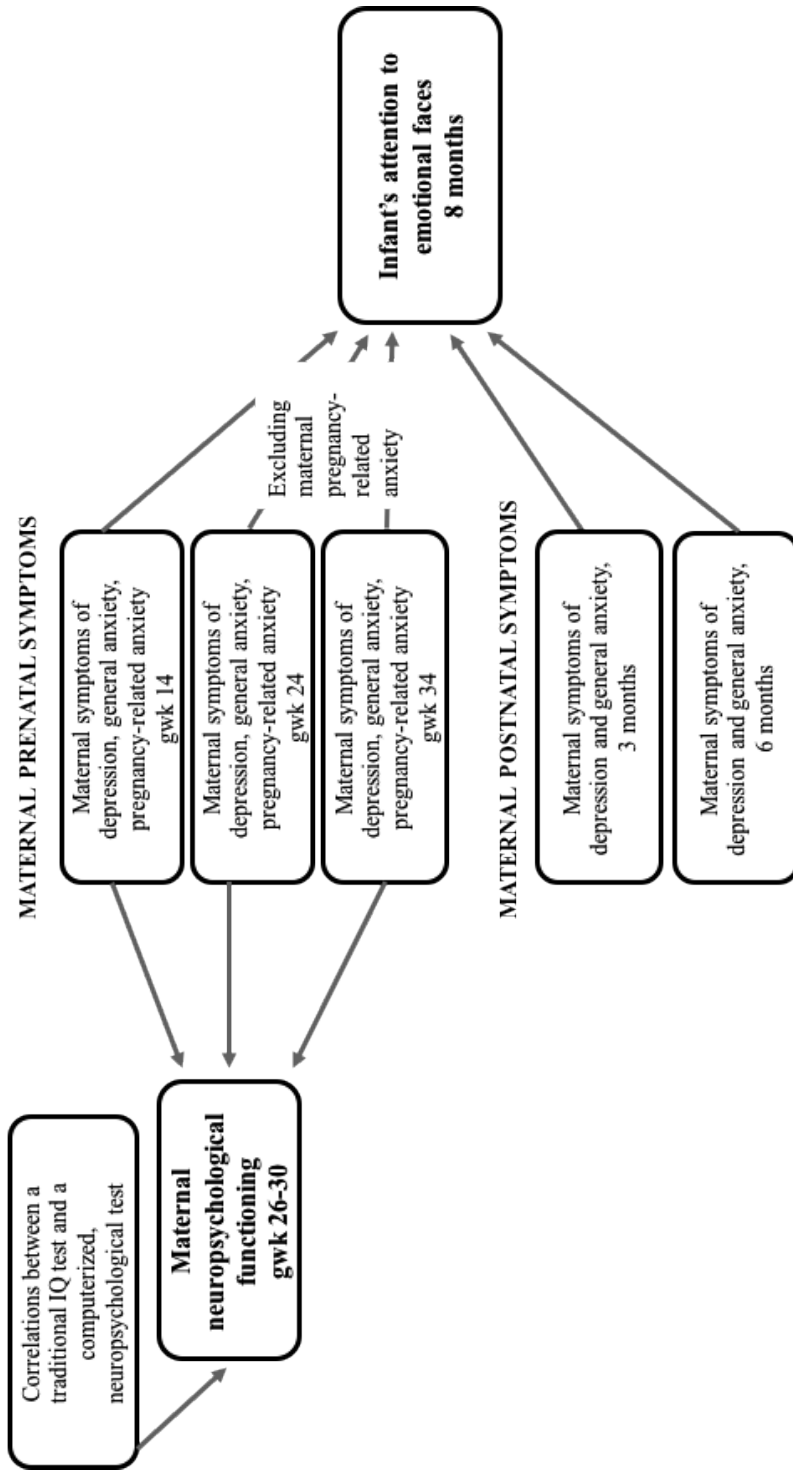


Figure 1. Flowchart of study aims

4 MATERIALS AND METHODS

4.1 Study design and participants

4.1.1 *The FinnBrain Birth Cohort Study*

The participants for this study were mothers and infants, mainly Caucasian, and members of an ongoing FinnBrain Birth Cohort Study (www.finnbrain.fi), a pregnancy cohort located in South-Western Finland. The aim of the ongoing FinnBrain Study is to prospectively study the effects of early life stress (ELS), including maternal prenatal stress (PS), in the form of depressive and/or anxiety symptoms or perceived current-life stress on child neurocognitive development and later mental and somatic health (Karlsson et al., 2018). Recruitment for the Cohort occurred at three maternal welfare clinics in the area of Southwest Finland Hospital District and the Åland Islands at the first ultrasound visit at the gestational week (gwk) 12 between December 2011 and April 2015 and relied on a personal contact by a research nurse. The inclusion criteria were: 1) an ultrasound-verified pregnancy and 2) sufficient knowledge of Finnish or Swedish to fill in the study questionnaires.

N = 3808 (66%) of the invited mothers and N = 2623 fathers or partners agreed to participate. The total number of recruited children was N = 3837, including 29 twin pairs. This Cohort population represents the source population of Finland, except for the possibly lower prevalence of younger, multiparous, and smoking women as well as the prevalence of preterm births (see: Karlsson et al., 2018).

The subjects for the present study (except for Study I into which the participants were selected from the main Cohort, see below) belonged to a nested case-control population embedded in the main Cohort (i.e., the Focus Cohort) designed to investigate the effects of PS on child development (Karlsson et al., 2018). These mother-infant dyads were invited to take part in a more intensive follow-up during pregnancy and the postnatal period. The criteria for the FinnBrain Focus Cohort were determined by using the first 500 participating mothers' questionnaire data from gwks 14, 24, and 34 on depressive symptoms (Edinburgh Postnatal Depression Scale, EPDS), general anxiety (Symptom Check List -90/anxiety subscale, SCL-90), and pregnancy-related anxiety (Pregnancy-Related Anxiety Questionnaire Revised 2, PRAQ-R2) in exploratory analyses and establishing the cut-points for the highest and lowest 25th percentiles of maternal prenatal stress. The cut-points were ≥ 12 and ≤ 6 in depressive symptoms questionnaire (EPDS), ≥ 10 and ≤ 4 in general anxiety symptoms questionnaire (SCL-90), and ≥ 33 and ≤ 25 in pregnancy-related anxiety questionnaire (PRAQ-R2). If the mother scored above the selected threshold on two different questionnaires or twice on one instrument

during pregnancy or reported the use of serotonin reuptake inhibitors (SSRIs) during the pregnancy, she qualified as a “case,” thus a mother reporting high levels of PS. Qualifying as a control demanded scoring below the lower cut-point in all pregnancy assessments. This resulted in two groups: 27% (N = 710) of the whole Cohort members were controls with low PS, and 20% (N = 509) were “cases” with high PS. Furthermore, a small group of mothers (N = 97) participating in Study II were originally considered as being “cases,” thus reported high levels of PS in some questionnaires at an earlier pregnancy assessment point but did not finally qualify for neither case nor control after the third prenatal assessment. These mothers took part in the study between gwks 26–30, where the association between neuropsychological functions and psychiatric symptoms were assessed (Study II). Their infants were subsequently invited to take part to an infant developmental study (Studies III and IV) with the aim of combining the data from infants and their mothers. This group of mothers (and infants) was labeled as “the moderate symptom group.” Moreover, in Studies III and IV, some mother-infant dyads were invited to take part outside the previously mentioned groups in order to enrich the sample with infants, who had participated in the neonatal brain scan sub-study. See Figure 2 for flow chart of participants.

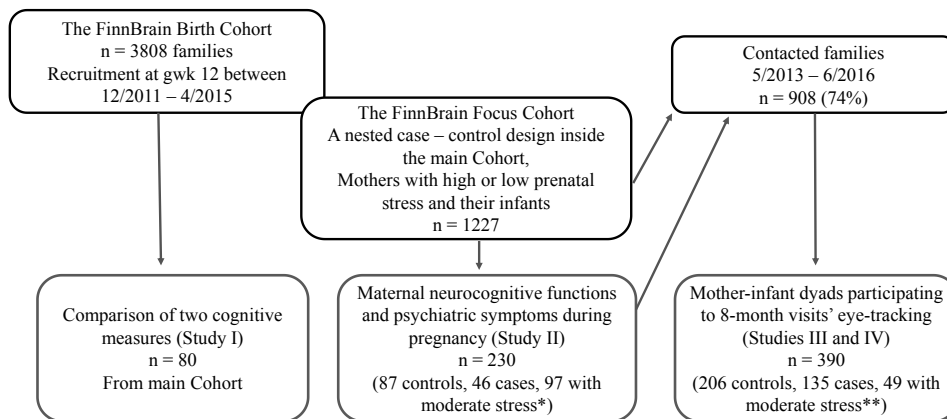


Figure 2. Flowchart of mothers (Studies I, II) and mother-infant dyads (Studies III, IV) participating in the current study.

* Mothers, originally considered as being cases, thus reported high levels of PS in some questionnaire at an earlier pregnancy assessment point, but did not eventually qualify for neither case nor control after the third prenatal assessment.

** Enriched sample of mother-infant dyads, of which the mother had participated to neuropsychological assessment during pregnancy and/or the infant had participated to brain scan at two months of age.

The characteristics of the participants in each study are displayed in Tables 1 and 2 and are described in more detail below.

4.1.1.1 Maternal neuropsychological functions during pregnancy or after delivery (Study I)

Of 240 eligible participants: (1) 109 (46%) wanted to participate, (2) 92 (38%) did not want to participate in this study, and (3) 39 (16%) were not reached. Those agreeing to participate did not differ from those not participating or reached in terms of age or years of formal education ($F_{2,236} = 0.41$, $p = 0.67$; $\chi^2[6] = 11.25$, $p = 0.08$, respectively). The exclusion criteria were based on self-report and included: (1) insufficient Finnish/Swedish language skills and (2) self-reported neurologic or psychiatric illness.

After 14 drop-outs, a total of 95 women completed the WAIS-IV during pregnancy (gestational weeks 22-35, mean = 28.1). Of these, 80 women completed also the Cogstate, 35 of them during pregnancy (mean age = 31.2; gestational weeks 21 – 34, mean = 28.5), and 45 after delivery (mean age = 30.4; 14-25 weeks, mean = 18.0). In this study, the study population comprised of those participating both in the WAIS-IV and Cogstate measurements ($N = 80$) during May 2012 – May 2013. The demographic characteristics of the study sample are presented in Table 1. Retrospective inspection of this sample revealed that of these women, 13 (16%) were later labeled as belonging to the case group, 27 (34%) were controls, and 40 (50%) were neither cases nor controls.

4.1.1.2 Maternal prenatal depressive and anxiety symptoms and cognitive functions (Study II)

Of 830 eligible Focus Cohort mothers, 596 (71%) were contacted due to limited study resources for this study. Of those contacted, 348 (58%) agreed to participate. Those agreeing to participate had a higher level of education than those not participating (38.2% had a university degree as compared to 28.2% in the declined group) ($\chi^2[2] = 8.83$, $p = 0.012$), but there were no age differences ($t[594] = -0.336$, $p = 0.74$).

Finally, a sample of 275 women attended the neuropsychological study visit, and 230 of them were pregnant between gwk 26 and 30 (45 women were excluded from the analysis, as they completed the test 4 months after delivery due to the delay in the test battery delivery) thus forming the current study population. An exception were women ($N = 97$), who did not belong to the Focus Cohort but were, at the time of recruitment (gwks 26 – 30), predicted to fulfil the criteria for being a “case” (thus scoring above the defined cut-point in some questionnaire at gwk 14), but who eventually, after the consideration of all three prenatal assessments,

did not qualify for neither case nor control. Consequently, in this sample, 46 (20%) mothers were “cases” and formed “the high symptom group,” 97 (42%) reported a moderate level of prenatal stress and formed “the moderate symptom group,” and 87 (38%) were controls and formed “the low symptom group.”

No significant demographic differences were found among the three symptom categories in terms of age ($F_{2,227} = 0.92, p = 0.40$), education ($\chi^2[4] = 1.98, p = 0.74$), parity ($\chi^2[2] = 0.49, p = 0.78$), child’s gender ($\chi^2[2] = 0.12, p = 0.94$), or smoking during early pregnancy ($\chi^2[2] = 3.02, p = 0.22$). The demographic characteristics of the study sample are presented in Table 1.

Table 1. Demographic characteristics of the samples in Studies I and II

Characteristic	Sample					
Study I	(n = 80)					
Age, Mean (SD)	30.76 (4.05)					
Monthly income (euros after taxes)						
< 1000	18.8%					
≥ 1000	81.2%					
Education ¹ (%)	low	26.3				
	middle	35.0				
	high	38.7				
Primiparous (%)	44.0					
Characteristic	Whole Sample (n = 230)	High symptom level group (n = 46)	Moderate symptom level group (n = 97)	Low symptom level group (n = 87)	p^2	
Study II						
Age Mean (SD)	31.4 (4.5)	30.6 (4.4)	31.7 (4.4)	31.5 (4.6)	0.40	
Education ¹ (%)						
	low	39.4	28.9	18.8	22.6	0.74
	middle	29.1	26.7	32.3	32.1	
	high	31.5	44.4	49.0	45.4	
Primiparous (%)	55.7	58.7	56.7	52.9	0.78	

¹ Education: low = High school/Vocational school or lower, middle = Polytechnics or Undergraduate Degree, high = University or higher

² p values based on t -test for age and χ^2 test for education and parity

4.1.1.3 Infant attention to emotional faces (Studies III and IV)

The sample for Studies III and IV consisted of mother-infant dyads ($N = 363$) participating in a child development study visit, when the infant age was 8 months, and corrected for prematurity as part of the FinnBrain Child Development and Parental Functioning sub-study between May 2013 and June 2016.

A total of 908 Focus Cohort families were contacted about participation in the current study. Of these, 694 (76%) were reached, and of those who were reached, 488 (70%) accepted the invitation. Finally, 437 (63% of were reached, 90% of initially agreed) families participated in the laboratory visit during, which, altogether, 421 eye-tracking; 427 infant temperament, with three temperament observations, and executive functioning assessments; and 197 mother-infant-interaction measurements were conducted. The recruited mothers had a higher level of education than the declined mothers (years of education: <12 years, 30.3% vs. 41.4%; 12-15 years, 32.1% vs. 31.6%; >15 years, 37.7% vs. 27.0%, respectively; $\chi^2[2] = 9.02$, $p = 0.01$). The declined mothers were more likely multiparous than those who participated (56.9% vs. 45.2%; $\chi^2[1] = 7.06$, $p < 0.01$).

Of the initial 421 infants assessed in the laboratory, 31 (7.4%) failed to either provide data (i.e., were fussy), or their data was invalid due to technical problems resulting in 390 eye-tracking assessments. Of these, 363 (93.1%) provided ≥ 3 valid trials per each stimulus condition and were included in the sample. Those mothers whose infants did not provide satisfactory data for final eye-tracking analyses did not differ from those whose infants provided data in terms of parity (primiparous versus multiparous, $p = 0.50$), education ($p = 0.39$), or maternal self-reported depressive ($p = 0.33 - 0.89$) or anxiety symptoms ($p = 0.39 - 0.85$) at different assessment points.

Of the sample of 363, 45.7% were girls and 54.3% were boys. 13 (3.6%) infants were born <37 weeks of gestational age (data from national birth registries, National Institute for Health and Welfare, www.thl.fi). All statistical analyses were conducted both with and without these infants. However, as this did not significantly alter the results, all infants were included in the final analyses. The mean length of gestation in this sample was 39.9 (range 34.4 – 42.3), and the mean age of infants at the time of study visit (from due date) was 8.1 months (range 7.2 – 9.1). The mean age of the participating mothers at the time of delivery was 30.8 years (SD = 4.3). In total, 58.3% were primiparous. Educational level, with missing information at 2.8%, was distributed as follows: 28.1% (< 12 years), 36.2% (12-15 years), and 33.7% (> 15 years). The demographic characteristics of the sample are presented in Table 2.

Table 2. Demographic characteristics of the sample of mother-infant dyads participating in Studies III and IV

Characteristic	Sample (n = 363)
Maternal age at the time of delivery	
Mean (range)	30.8 years (18 – 44)
Primiparous	58.3%
Length of gestation	
Mean (range)	39.9 weeks (34.4 – 42.3)
Education	
<12 years	28.1%
12 – 15 years	36.2%
>15 years	33.7%
Infant age at the time of testing	
Mean (range)	8.1 months (7.2 – 9.1)
Infant gender	Boys 54.3%, Girls 45.7%

4.2 Measures

4.2.1 *Maternal self-reported pre- and postnatal depressive and anxiety symptoms*

Maternal depressive symptoms were assessed using The Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden, & Sagovsky, 1987). The EPDS is a widely used questionnaire and has been validated in several countries and cultures for detection of both pre- and postnatal depression (Matijasevich et al., 2014). It consists of 10 questions scored on a 4-point Likert scale (from 0 to 3). The total scores range between 0 and 30. A continuous total sum score was used in Study II. In Study III, the course of maternal depressive symptoms during the pre- and postnatal periods was modeled using Latent Growth Mixture Modelling (LGMM; Muthén & Muthén, 2000).

Maternal general anxiety symptoms were assessed with the The Symptom Checklist-90 (SCL-90), anxiety subscale (Derogatis et al. 1973) validated also for use among Finnish population (Holi, Sammallahti, & Aalberg, 1998; Holi, 2003). This subscale consists of 10 items scored on a 5-point Likert scale (from 0 to 4), and the range of the total sum score is 0 – 40. A continuous sum score of prenatal (Study II) or both pre- and postnatal symptom scores (Study IV) was used.

Maternal pregnancy-related anxiety symptoms were assessed with The Pregnancy-Related Anxiety Questionnaire Revised 2 (PRAQ-R2) suitable for use in both primiparous and multiparous women (Huizink et al., 2015). Scores on each item range from 1 to 5, and the range of the total sum score is 10 – 50. The items of the PRAQ-R2 can be divided into three subscales; *Fear of Giving Birth*, *Worries about Bearing a Physically or Mentally Handicapped Child*, and *Concern about Own Appearance*. In Study II, the total and factor sum scores were used as continuous variables.

Maternal prenatal symptoms were assessed at gwk 14, 24, and 34 with the EPDS, the SCL-90, and the PRAQ-R2. Maternal postnatal symptoms were assessed with the EPDS and the SCL-90 at 3 and 6 months postpartum. In Study II, only prenatal questionnaires were used. In Studies III and IV, also postnatal questionnaires were used.

4.2.2 Maternal cognitive functions

Maternal cognitive functions were assessed by two different test methods (see below). The cognitive testing procedure was divided into two different sessions (random order), which took place at the University of Turku in quiet examination rooms.

4.2.2.1 General intelligence

The Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV, Wechsler, 2008; 2012), is one of the most widely used tests of general intelligence for adults. The test battery is comprised of 10 core subtests providing four index scores. These are Verbal Comprehension Index (VCI; derived from three subtests: Similarities, Information, and Vocabulary), Perceptual Reasoning Index (PRI; derived from three subtests: Block design, Matrix Reasoning, and Visual Puzzles), Working Memory Index (WMI; derived from two subtests: Digit Span, and Arithmetic), and Processing Speed Index (PSI; derived from two subtests: Symbol Search, and Coding). In addition, an overall Full Scale IQ Index score (FSIQ) is obtained from the 10 core subtests converted to a standard score ($M = 100$, $SD = 15$). The test is a traditional paper-and-pencil test.

The WAIS-IV assessments were administered by two graduate students trained and supervised by a senior researcher from the Department of Psychology, University of Turku. The test took approximately 90 minutes to complete.

4.2.2.2 Neuropsychological and executive functions

The Cogstate computerized test battery was used to measure different aspects of neuropsychological functioning and moreover executive functions. Nine different tasks were used to assess *verbal learning and memory* (International Shopping List Task + recall; ISL, ISLR, respectively, where number of correct responses was used as the unit of measurement), *processing speed/psychomotor function* (Detection Task; DET, speed of performance), *visual attention/vigilance* (Identification Task; IDN, speed of performance), *visual working memory/attention* (One Back Task; OBK, speed of performance), *visual recognition memory/attention* (One Card Learning Task; OCL, accuracy of performance), *spatial working memory* (Continuous Paired Associate Learning Task; CPAL, accuracy of performance), *reasoning and problem solving* (Groton Maze Learning Test; GML, number of total errors), and *social cognition* (Social Emotional Cognition Task; SECT, accuracy of performance). A Total Cognitive Score (a composite score) was also calculated from all the tasks.

The Cogstate assessments were administered by a trained doctoral student, according to guidelines and presented on a laptop computer, under supervision of the experimenter. The test session took 45 minutes to complete with a short practice before every task.

4.2.3 Infant attention to faces and distractors

Infant attention to faces was studied using eye tracking. The infant sat on his/her parent's lap during the experiment at the distance of 50–70 cm with the optimal camera-to-eye distance being 40–70 cm from the eye-tracker (EyeLink1000+, SR Research Ltd, Toronto, Ontario, Canada). Monocular data (right eye) was collected with a sampling frequency of 500 Hz. A five-point calibration procedure, with an audiovisual animation sequentially presented in five locations on the screen, was used before every measurement. The calibration could be repeated before actual testing and also during measurement when necessary. Small breaks were allowed during measurement, if necessary. The researcher sat in the same, dimly lit room as the infant and parent and used another independent computer to manage the measurement. A curtain was used in between the infant/parent and the researcher to avoid interference.

The overlap paradigm (Aslin & Salapatek, 1975; Peltola et al., 2008) was used to study infant attention to emotional faces. Specifically, attention disengagement from a centrally presented face or a scrambled face control stimulus to a lateral distractor was examined. Photographs of two different women portraying happy, fearful, and neutral faces together with scrambled non-face control pictures were shown (Peltola et al., 2008). A set of 48 trials was presented altogether, including

12 trials per condition, with each emotion and the control picture, and comprising 18 photographs of each woman and 12 non-face control pictures in a semi-random order.

First, the infant was shown a picture of a face or a non-face control stimulus in the center of the screen for 1000 ms (Figure 3). After that, a lateral distractor, black and white checkerboard or circles, appeared on either left or right side of the face at a visual angle of 13.6° , for 3000 ms simultaneously with the face. One trial lasted for 4000 ms. The sizes of the emotion-depicting pictures and distractor stimuli were $15.4^\circ \times 10.8^\circ$ and $15.4^\circ \times 4.3^\circ$, respectively. A brief animation was shown after each trial to capture the attention of the infant to the center of the screen. Once the infant's gaze was in the middle of the screen, the next trial was presented by the researcher. The order of the central stimuli was semi-randomized with a constraint that the same stimulus was not presented more than three times in a row. The lateral stimulus was selected and presented randomly for each trial.

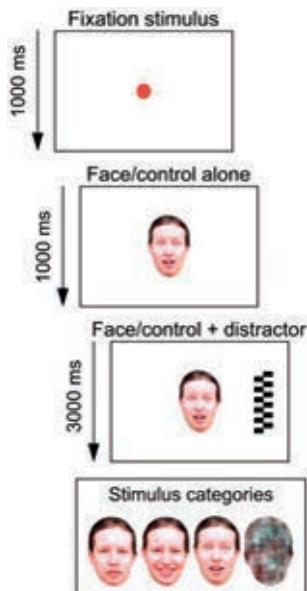


Figure 3. The overlap paradigm. A face or a control stimulus was presented in the center of the screen after the infant fixated on a fixation stimulus. A distractor appeared to the right or to the left side of the central stimulus after 1000 ms from face/control onset. The central stimulus was presented until the end of each trial (4000 ms) overlapping in time with the distractor. Figure reproduced from Yrttiaho et al., 2014, <https://doi.org/10.1371/journal.pone.0100811.g001> under the terms of the Creative Commons Attribute license.

4.3 Statistical analysis

4.3.1 Study I

Study I was a methodological study assessing the overlap between a traditional IQ test (WAIS-IV) and a computerized neuropsychological test battery (Cogstate). Due to the non-normal distribution of Cogstate scores after logarithmic and arcsine transformations, nonparametric Spearman correlations were used to analyze the relationships between the WAIS-IV subtests and indices and the Cogstate measures.

All women performed the WAIS-IV during pregnancy. However, due to the delay in test battery delivery from the test provider, the Cogstate measures were conducted either during pregnancy (prenatal test group, $N = 35$ women) or four months after delivery (postnatal test group, $N = 45$ women). Therefore, before correlation analyses, we first calculated the parameters for Cogstate tasks separately for both groups and compared the scores between the groups with Mann-Whitney U test. The performance was similar between the two groups (p values > 0.05) except in one task (ISLR) ($p < 0.05$). Hence, we decided to treat these groups as one, except for the ISLR task, where partial correlation was used to control for the effects of timing of the test. An *alpha* level of ($p < 0.01$) was applied to account for multiple comparisons. The analyses were run by SPSS software (International Business Machines Corp., Armonk, NY, USA), version 22.

4.3.2 Study II

The relations between different sources of maternal PS and cognitive functions were first evaluated by comparing the cognitive performance of the groups of mothers with low, moderate, or high self-reported PS in different cognitive tasks. A non-parametric Kruskal-Wallis test was first used to test the potential differences among the three groups in cognitive test performance. Then, a Mann-Whitney U Test was used for paired comparisons. A pooled effect size estimator, r , was calculated for the estimate of effect size.

Second, as one cognitive task (GML) differentiated the performance among the three groups, Spearman's Rank Order Correlations (2-tailed) were used to analyze the relationships between different self-reported psychiatric symptoms scores (i.e., depressive, general anxiety, pregnancy-related anxiety) and cognitive task performance. Correlations < 0.30 were considered to represent weak correlations, $0.30 - 0.50$ moderate and > 0.50 strong correlations (Pallant, 2010) with an *alpha* level of $p < 0.05$.

Third, hierarchical multiple regression was used to evaluate predictors of cognitive functioning in the GML task. Analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity (Pallant, 2010). Maternal age and parity were controlled for in the regression model (due to their potential effects on cognitive functioning during pregnancy; Workman et al., 2011). Also, one model was run with maternal self-reported sleep problems (Basic Nordic Sleep Questionnaire, BNSQ, Partinen & Gislason, 1995) as a predictor of cognitive performance. However, sleep did not predict maternal cognitive performance (*Insomnia*, $p = 0.33$; *Day-time Sleepiness*, $p = 0.13$) in cognitive task, and so we decided not to include sleep in our final regression model. All analyses were performed using SPSS 22.0.

4.3.3 Study III

The associations between the trajectories of maternal depressive symptoms from early pregnancy until six months postpartum and infants' attention disengagement from emotional faces to distractors were studied. We hypothesized that: 1) infants of mothers with predominantly prenatal symptoms might disengage from all central facial stimuli to distractors in the attention-distraction task (as compared to infants with no exposure to maternal depressive symptoms) and that 2) maternal depressive symptoms would be associated with heightened bias to threat (i.e., fearful faces) in infants.

The trajectories of maternal pre- and postnatal depressive symptoms were modeled with Latent Growth Mixture Modelling (LGMM) in Mplus, version 8.0 (Muthén & Muthén, 2000). In this approach, growth curves of depressive symptoms are estimated for each individual, and then prototypic growth curves are identified for the whole sample. The aim is to select the latent curves (i.e., the developmental patterns in symptoms) that most optimally describe the data. Moreover, the interpretability of the latent curves is also used to determine the optimal model. Participants with missing data on depressive symptoms were incorporated in the analyses to minimize bias (Nagin, 2005) by using maximum likelihood under the missing-at-random assumption (Graham, 2009).

First, the factor structure of maternal self-reported depressive symptoms (EPDS) during the pre- and postnatal period was examined using structural equation modeling. The longitudinal Confirmatory Factor Analysis of EPDS showed good fit with the data [$\chi^2 [1050] = 1620.152$, $p < 0.001$, CFI = 0.92 (CFI values close to 0.90 indicating a suitable model), RMSEA = 0.039 (values lower than .05 indicating close fit), SRMR = 0.066 (values below 0.08 reflecting good fit); see e.g. Hu & Bentler, 1999; Steiger, 1990]. Consecutive items 1 and 2, 4 and 5, 8 and 9 were allowed to correlate to improve model fit. Second, measurement invariance in

EPDS was tested by investigating χ^2 difference between the first and second model with the constrained factor loadings of CFA. The difference in χ^2 between the first and second model was significant, $\chi^2_{\text{diff}}[36] = 0.01$, but the difference between CFI (ΔCFI) was 0.003 demonstrating adequate invariance in measures across the measurement points (Cheung & Rensvold, 2002).

After the establishment of three latent groups (see Results section), we investigated the possible differences in infant disengagement probability (DPs) in an eye-tracking task. The infants of mothers with consistently low symptoms were used as a reference group. As there were large individual differences in the infants' overall DPs in our sample (see Results, Figure 4), we decided to model the DPs using mixed effects logistic regression (MELR) models with random intercept for each infant.

The DPs were dependent on the trial number (Figure 4 in Results), so trial number was included in our MELR models. Furthermore, due to the possibility that the trial number dependency would vary by condition, we modeled the trial number dependency by fitting a natural cubic spline with one cut-point between trials 24 and 25 separately for each condition. That is, we included main effects of trial number spline and condition with their interaction in our first model (Model 1). We also compared Model 1 to a model without the interaction terms (Model 0) using a likelihood ratio test, as in all the following model comparisons, to find out if the trial number by condition-interaction was significant. Table 3 below describes all models used in the analyses.

Next, we constructed Model 1.1 by adding the latent EPDS growth curve group (EPDS group) main effect to Model 1 and Model 2 by adding the EPDS group main effect and its interaction with condition to Model 1. Model 1.1 was then compared to Model 1 to test the main effect of EPDS group, i.e., to test if the overall DPs are different in different EPDS groups. Furthermore, Model 2 was compared to Model 1.1 to test the interaction of the condition and EPDS group. We also constructed Model 3 by adding all possible interactions with the trial number spline to Model 2 (see Table 3 for the details). By comparing Model 3 to Model 2, we were then able to test if the trial number dependency was different for different EPDS groups. Finally, we constructed Model 4 by adding child gender main effect and all interactions among gender, condition, and EPDS group to Model 2, and then compared it to Model 2 to find out if the effect of EPDS group on the DPs was different for boys and girls.

We also carried out comparable analyses to previous studies (e.g., Forssman et al., 2014; Peltola et al., 2015), where the trial number dependency had not been taken into account. We constructed Models 1b, 1.1b, and 2b, which were similar to Models 1, 1.1, and 2, respectively but without the trial number terms. Models 2b and

1.1b were then compared to Model 1b to find out if the EPDS group was associated with the DPs, when the trial number effect was not taken into account.

Post hoc tests were performed with Models 1.1b and 2b to analyze our hypotheses 1 and 2. We contrasted overall DPs and fear bias among the EPDS groups of Increasing/Decreasing, Increasing/Low, Decreasing/Low and Increasing and Decreasing/Low. The Holm-Bonferroni method (Holm, 1979) was used to control the family-wise error rate when assessing the statistical significance of the *post hoc* tests.

The fear bias was defined here as the difference between infants' tendency to disengage from a fearful condition and their tendency to disengage from a neutral/happy condition [i.e., infants who had (much) higher probability to disengage from a happy/neutral condition than from fearful condition had high fear bias]. Technically, the fear bias was defined as the ratio of the odds to disengage from the happy/neutral condition to the odds to disengage from fearful condition. The analyses were run using R (R Core Team, 2017) with package lme4 (Bates et al, 2015). Figures 3 – 4 were made using R package ggplot2 (Wikham, 2009).

Table 3. Fixed effects in the mixed effects logistic regression models

All the mixed effects logistic regression models used to analyze the DPs included a random intercept for each infant as the only random effect.

The fixed effects used in each model are given below:

Model 0: Condition + TNS

Model 1: Condition + TNS + Condition×TNS

Model 1.1: Condition + TNS + EPDSG

Model 2: Condition + TNS + Condition×TNS + EPDSG + Condition×EPDSG

Model 3: Condition + TNS + Condition×TNS + EPDSG + Condition×EPDSG + TNS×EPDSG + Condition×TNS×EPDSG

Model 4: Condition + TNS + Condition×TNS + EPDSG + Condition×EPDSG + Sex + Condition×Sex + EPDSG×Sex + Condition×EPDSG×Sex

Model 1b: Condition

Model 1.1b: Condition + EPDSG

Model 2b: Condition + EPDSG + Condition×EPDSG

Explanations:

Condition = Categorical variable with four levels (Control, Happy, Neutral and Fearful)

TNS = Trial number spline terms, i.e., *sum of two* natural cubic spline terms.

EPDSG = EPDS growth curve group; categorical variable with three levels (Decreasing, Increasing and Low)

Sex = Categorical variable with two levels (Boy and Girl)

4.3.4 Study IV

The associations between maternal anxiety symptoms (i.e., a continuous sum score for each assessment point) during the pre- and postnatal periods and the disengagement probabilities of the infant in the attention-distraction task were investigated with mixed effects (binary) logistic regression (MELR) with random intercept for each infant. We predicted that: 1 a) maternal postnatal anxiety symptoms would associate with a higher “threat bias” (i.e., higher disengagement probability from fearful faces to distractors as compared to happy and neutral faces); 1 b) already prenatal symptoms would associate with a higher threat bias, 1c) infant sex would moderate this association. We also predicted that: 2 a) maternal anxiety symptoms would positively associate with overall probability of disengagement from faces to distractors and 2 b) infant sex would moderate this association.

First, missing anxiety scores (see Table 11 for the number of missing scores) were imputed using MissForest (Stekhoven & Bühlmann, 2012), an iterative imputation method based on a Random Forest method, with anxiety scores from the other time points used as the predictors for the missing scores. However, only the participants, who had at least one (non-imputed) postnatal anxiety score available ($N = 341$), were included in the analyses concerning the postnatal symptoms. All participants had at least one prenatal score and were therefore included in the analyses concerning the prenatal anxiety.

An infant’s disengagement probability (DP) was defined as the infant’s probability to disengage his/her attention from the central (e.g., fearful, happy, neutral face, or a non-face) to the lateral stimulus (i.e., a geometric shape). A binary disengagement variable, indicating whether there was an attention disengagement or not, was used in our statistical models as the response variable when the DPs were estimated. There was no significant difference between the average number of scorable trials in the eye-tracking tests (8.9–9.3/condition) for boys and girls ($p > 0.05$).

In this study, the term threat bias was used instead of fear bias (used in Study III), as it is more often used in anxiety literature (e.g., Cisler & Koster, 2010). Threat bias was defined similarly to the fear bias variable (i.e., the ratio of the average odds to disengage from the happy and neutral conditions to the odds to disengage from fearful condition).

The DPs were modeled using mixed effects logistic regression (MELR) models with the binary disengagement variable. All our MELR models had a one-child specific effect (random effect) for each condition, i.e., four random effects per infant were included. Furthermore, as the DPs depended strongly on trial number (Figure 4 in Results, p. 63), we controlled for its effect in all our models. The trial

number dependency was modeled by a natural cubic spline with one cut-point between trials 24 and 25, similarly to Study III.

Our first hypotheses, 1 a) and 1 b), i.e., if threat bias was associated with maternal anxiety, were tested using a model having the fixed effects:

$$Condition + SCL + Condition \times SCL + TNS$$

where *Condition* is a categorical variable with four values: neutral, happy, fearful and control, *SCL* is the SCL-90 total score at gwk 14/24/34 or 3/6 months postpartum, and *TNS* means the two trial number spline terms. For *Condition*, we used such contrast coding that we were able to compare the average of the happy and neutral conditions against the fearful condition, i.e., to test the threat bias. Our hypotheses were then tested by testing the significance of the product of the threat bias contrast and *SCL*. To test the association between prenatal anxiety and threat bias, while controlling for 6 months' postpartum anxiety, a model with the fixed effects was used:

$$Condition + (SCL_{pre1/2/3} + SCL_{post6}) + Condition \times (SCL_{pre1/2/3} + SCL_{post6}) + TNS$$

Hypothesis 1 c), i.e., if infant sex moderates the association between maternal anxiety and threat bias, was tested using a model with the fixed effects:

$$Condition + SCL + Sex + Condition \times SCL + Condition \times Sex + SCL \times Sex + Condition \times SCL \times Sex + TNS$$

using the same coding for *Condition* as above. The tested term was the product of threat bias contrast, *SCL* and *Sex* (the predicted DPs shown in Figure 2 were also predicted using this model, but without the TNS term, to get trial number independent DPs).

Hypothesis 2 a), if maternal anxiety is associated with the overall DPs, was tested by testing the effect of *SCL* in the model with the fixed effects:

$$Condition + SCL + TNS$$

and hypothesis 2 b), if this association is moderated by sex, was tested by testing the product $SCL \times Sex$ in the model with the fixed effects:

$$Condition + SCL + Sex + SCL \times Sex + TNS.$$

Here, the standard treatment coding for *Condition* was used.

All the statistical analyses were made using R (R Core Team, 2018) with the packages lme4 (Bates et al, 2015) for running the MELR models and missForest (Stekhoven, 2013) for the imputation.

4.4 Ethical considerations

The FinnBrain Birth Cohort Study and all the individual studies presented here have been approved by the Ethics Committee of the Hospital District of Southwest Finland. All attending mothers gave informed consent, also on behalf of their child, during the study visits. For the data drawn from national birth registries (from the National Institute for Health and Welfare, www.thl.fi), the register-keeping organization gave their permission to use the data (according to the Finnish data protection legislation). With regard to computerized cognitive data (collected for Studies I and II), the participants gave separate informed consent on storing the data on Cogstate server.

5 RESULTS

5.1 Maternal cognitive functions during pregnancy or after delivery (Study I)

Means and standard deviations for the whole sample (i.e., WAIS-IV and Cogstate measures) and separately for pre- and postnatal groups, for Cogstate measures that were conducted either on gwk 26 – 30 or four months after delivery, are presented in Table 4. The distributions of key background characteristics (i.e., age, formal education, parity) were equal between the pre- and postnatal assessment groups (p values > 0.05) and so were not controlled for in further analysis.

With regard to WAIS-IV, the performance of the whole sample represented relatively well the average cognitive performance level of the general Finnish population. In five WAIS-IV subtests (i.e., Block Design, Digit Span, Arithmetic, Visual Puzzles, and Information) and three indices (i.e., VCI, PRI, and WMI), there was a normally distributed WAIS-IV distribution (i.e., subtests, normative $M = 10$, $SD = 3$, indices normative $M = 100$, $SD = 15$). In the Vocabulary subtest, the mean level of performance was slightly below average, and in the Similarities, Matrix Reasoning, Symbol Search, and Coding subtests as well as in the PSI index, the performance was slightly above average (Table 4). The Full Scale IQ of the sample was 102.69 ($SD = 14.55$) corresponding well with the cognitive level of general population.

In terms of Cogstate performance, the completion pass rate was 100% in every Cogstate task, and the integrity pass rate exceeded 97.6% in every task, hence the battery was well-tolerated by the participants. The performance was highly similar across different Cogstate tasks during the pre- and postnatal periods (U tests, p values = 0.199 – 0.965) with the exception of the ISLR ($U = 579.00$, $p = 0.036$, $d = 0.50$). Hence, these groups were treated as one, except for the ISLR task, where partial correlation was used in correlation analyses to control for the effects of timing of the test.

Table 4. Means of cognitive measures (WAIS-IV and Cogstate). WAIS-IV performance during pregnancy was compared to the Finnish normative population. CogState performance was compared between the pre- and postnatal group.

Cognitive subtest	Whole group (N = 80)	Prenatal group (N = 35)	Postnatal group (N = 45)
WAIS-IV Subtests			
Block design	10.5 (3.0)	-	-
Similarities	10.7 (2.8) *	-	-
Digit Span	9.9 (2.6)	-	-
Matrix Reasoning	10.9 (2.3) **	-	-
Vocabulary	9.3 (3.2) *	-	-
Arithmetic	10.0 (2.7)	-	-
Symbol Search	10.9 (3.2) *	-	-
Visual Puzzles	9.7 (2.6)	-	-
Information	9.7 (3.7)	-	-
Coding	12.1 (3.1) ***	-	-
WAIS-IV Indices			
VCI	99.1 (16.38)	-	-
PRI	101.9 (12.90)	-	-
WMI	99.86 (14.05)	-	-
PSI	108.52 (14.70) ***	-	-
FSIQ	102.69 (14.55)	-	-
CogState measures			
CPAL ^a	8.19 (10.62)	8.03 (12.38)	8.31 (9.25)
DET ^a	2.50 (0.06)	2.49 (0.06)	2.50 (0.07)
GML ^a	40.18 (10.68)	39.03 (11.45)	41.07 (10.09)
OBK ^a	2.88 (0.08)	2.88 (0.08)	2.89 (0.09)
IDN ^a	2.68 (0.05)	2.68 (0.04)	2.68 (0.05)
ISL ^b	28.30 (2.91)	28.51 (2.71)	28.13 (3.08)
ISLR ^b	10.52 (1.21)	10.86 (1.06)	10.27 (1.27)*
OCL ^b	1.10 (0.10)	1.11 (0.10)	1.10 (0.10)
SECT ^b	1.19 (0.09)	1.20 (0.09)	1.18 (0.10)
Total cognitive score ^b	0.02 (0.46)	0.10 (0.42)	-0.04 (0.49)

Note: ^a lower score = better performance, ^b higher score = better performance

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

Intercorrelations of the Cogstate tasks and WAIS-IV are presented in Table 5. The strength of the correlations varied between the Cogstate measures and the WAIS-IV sub-tests and indices from nonexistent to moderate:

WAIS-IV, Verbal Comprehension Index (VCI). Overall, the individual Cogstate measures had only low correlations with the three subtests of the VCI. None of the Cogstate measures were significantly related to the whole VCI as such.

WAIS-IV, Perceptual Reasoning Index (PRI). Three of the Cogstate measures (i.e., OBK, CPAL, and IDN) had positive, low to moderate correlations with the three subtests of the PRI. There was a moderate correlation between the Cogstate Total Cognitive Score and the PRI ($r = 0.31$, $p = 0.006$).

WAIS-IV, Working Memory Index (WMI). A wide range of Cogstate measures (i.e., CPAL, GML, OCL, OBK, and SECT) showed low to moderate correlations with the two subtests of the WMI. The Cogstate Total Cognitive Score and the WMI were moderately correlated ($r = 0.40$, $p < 0.0001$).

WAIS-IV, Processing Speed Index (PSI). Low to moderate correlations were also noted between the Cogstate measures (i.e., CPAL, DET, IDN, and OBK) and both subtests of the PSI. The Cogstate Total Cognitive Score and the PSI correlated moderately ($r = 0.31$, $p = 0.005$).

WAIS-IV, Full Scale IQ (FSIQ). One Cogstate measure (i.e., OBK) was observed to correlate with the FSIQ derived from all ten WAIS-IV core subtests. Finally, the Cogstate Total Cognitive Score correlated moderately with the FSIQ ($r = 0.39$, $p < 0.001$).

Table 5. Correlation matrix of the WAIS-IV subtests and indices and Cogstate tasks

WAIS-IV Subtests Indices	Cogstate Tests										
	CPAL err ^b	DET lmn ^b	GML ter ^b	IDN lmn ^b	ISL cor ^c	ISLR cor ^{a,c}	OCL acc ^c	OBK lmn ^b	SECT acc ^c	COGN score ^c	
Block Design	-0.07	-0.06	-0.10	-0.01	0.05	-0.04	0.10	-0.28*	0.22	0.17	
Similarities	-0.12	-0.07	-0.04	-0.02	0.03	0.25*	0.13	-0.01	-0.03	0.14	
Digit Span	-0.25*	-0.18	-0.32**	-0.21	-0.03	0.24*	0.22*	-0.21	0.24*	0.41**	
Matrix Reasoning	-0.33**	-0.10	-0.02	-0.26*	0.10	0.33**	0.10	-0.27*	0.04	0.36**	
Vocabulary	-0.08	-0.15	-0.14	-0.04	0.06	0.24*	0.19	0.00	0.12	0.21	
Arithmetic	-0.15	-0.13	-0.28*	0.02	0.15	0.22*	0.20	-0.18	0.24*	0.34**	
Symbol Search	-0.06	0.09	0.06	-0.16	0.08	-0.01	-0.14	-0.26*	0.02	0.09	
Visual Puzzles	-0.20	0.01	-0.07	-0.02	0.10	0.12	0.03	-0.19	0.13	0.23*	
Information	-0.04	-0.01	-0.12	-0.06	0.02	0.14	0.12	-0.19	0.19	0.17	
Coding	-0.24*	-0.25*	-0.18	-0.35**	0.10	0.12	-0.05	-0.32**	-0.01	0.35**	
VCI	-0.09	-0.08	-0.12	-0.05	0.04	0.24*	0.13	-0.11	0.13	0.19	
PRI	-0.25*	-0.05	-0.08	-0.12	0.13	0.13	0.10	-0.31**	0.16	0.31**	
WMI	-0.18	-0.20	-0.32**	-0.12	0.02	0.25*	0.23*	-0.21	0.30**	0.40**	
PSI	-0.16	-0.16	-0.08	-0.36**	0.10	0.12	-0.12	-0.38**	0.01	0.31**	
FSIQ	-0.21	-0.12	-0.17	-0.21	0.08	0.25*	0.12	-0.30**	0.19	0.39**	

Spearman correlations (2-tailed) were performed

Note. ^a Partial correlation was used, ^b lower score = better performance, ^c higher score = better performance

* $p < 0.05$ ** $p < 0.01$

CPAL= Continuous Paired Associate Learning Task, DET= Detection Task, GML= Groton Maze Learning Test, IDN= Identification Task, ISL= International Shopping List Task, ISLR= International Shopping List Task-Recall, OCL= One Card Learning Task, OBK= One Back Memory Task, SECT= Social Emotional Cognition Task, COGN_score= Total Cognitive Score, VCI= Verbal Comprehension Index, PRI= Perceptual Reasoning Index, WMI= Working Memory Index, PSI= Processing Speed Index, FSIQ= Full-Scale Intelligence Quotient

5.2 Maternal prenatal depressive and anxiety symptoms and cognitive functions (Study II)

Descriptive data on the EPDS, SCL-90, PRAQ-R2 questionnaires are presented in Table 6. In this sample, the levels of maternal symptoms of depression and anxiety were generally low. Finally, the mean symptom levels were significantly different among the three experimental groups with all p values < 0.05 .

The means and standard deviations of the Cogstate task scores are presented in Table 6. The three groups did not show significantly different task performance (p values = 0.11 – 0.99) with the exception of the Groton Maze Learning test (GML, total errors, $p = 0.004$), a task of visuospatial learning/executive functioning. There was a significant difference between high and low symptom groups ($U = 1343.00$, $z = -3.11$, $p = 0.002$, $r = 0.27$) and between moderate and low symptom groups ($U = 3449.00$, $z = -2.14$, $p = 0.033$, $r = 0.16$) with the number of total errors being the lowest for low symptom group. The test results between high and moderate symptom groups also approached significance ($U = 1848.00$, $z = -1.66$, $p = 0.098$, $r = 0.14$).

Next, the contributions of different symptom dimensions (i.e., depression, anxiety, pregnancy-related anxiety) to the GML test errors were investigated with correlation analyses between the symptom counts and the GML test errors over the whole study population. The GML task errors correlated positively and significantly with the EPDS symptom count at all three assessments points (r ranging between 0.147 and 0.161, p values 0.009 – 0.013). Moreover, the GML errors correlated significantly with concurrent total score of pregnancy-related anxiety ($r = 0.151$, $p = 0.012$) and its factor 2 (“Worries about Bearing a Physically or Mentally Handicapped Child”) ($r = 0.216$, $p = 0.001$). No correlation was found between the GML performance and general anxiety symptoms (SCL-90).

Lastly, the regression analysis for different psychiatric symptom categories and the GML errors, adjusted for maternal age and parity, showed that higher scores in PRAQ-R2, factor 2 ($\beta = 0.237$, $p = 0.001$), a higher EPDS score ($\beta = 0.193$, $p = 0.004$), and a higher maternal age ($\beta = 0.135$, $p = 0.049$) all predicted positively the amount of GML task errors. The regression model is presented in Table 7.

Table 6. Means (and standard deviations) and ranges of psychiatric symptoms in low, moderate, and high symptom groups

Measure	Whole Sample (n = 230) Mean (SD)	High symptom level group (n = 46) Mean (SD), Range	Moderate symptom level group (n = 97) Mean (SD), Range	Low symptom level group (n = 87) Mean (SD), Range	<i>p</i> values*
EPDS					
(theoretical range 0-30)					
Gwk 14	4.18 (3.99)	8.91(4.98), 0-20	3.58 (3.05), 0-12	2.34 (1.79), 0-12	< 0.001
Gwk 24	4.00 (3.46)	7.18 (4.57), 0-20	4.15 (2.97), 0-10	2.22 (1.69), 0-10	< 0.001
Gwk 34	4.10 (3.67)	7.05 (4.68), 0-17	4.41 (3.45), 0-16	2.32 (1.84), 0-16	< 0.001
SCL-90					
(theoretical range 0-40)					
Gwk 14	3.13 (5.57)	6.85 (5.50), 0-19	3.18 (6.95), 0-40	1.10 (1.14), 0-40	< 0.001
Gwk 24	3.65 (6.46)	8.77 (9.80), 0-40	3.57 (6.01), 0-40	1.14 (1.30), 0-40	< 0.001
Gwk 34	2.65 (4.70)	5.77 (6.92), 0-37	2.65 (4.75), 0-40	1.08 (1.29), 0-40	< 0.001
PRAQ-R2					
(theoretical range 10-50)					
Gwk 14†	21.19 (6.00)	25.56 (5.20), 18-35	23.01 (5.87), 14-38	17.73 (4.50), 14-38	< 0.001
Factor 1†	6.21 (2.49)	6.67 (2.35), 3-10	6.97 (2.80), 3-12	5.20 (1.77), 3-12	0.020
Factor 2†	8.42 (3.04)	9.89 (3.44), 5-14	9.47 (2.86), 4-16	6.80 (2.38), 4-16	0.001
Factor 3†	6.56 (2.59)	9.00 (4.12), 3-15	6.65 (1.87), 3-11	5.73 (2.33), 3-11	0.031

Gwk 24	22.80 (6.32)	27.16 (7.37), 10-42	24.39 (5.50), 12-34	18.87 (4.00), 12-34	< 0.001
Factor 1	6.61 (2.42)	7.23 (2.44), 3-12	7.30 (2.57), 3-15	5.55 (1.80), 3-15	< 0.001
Factor 2	8.61 (3.30)	10.59 (4.03), 4-20	9.21 (2.94), 4-17	6.97 (2.38), 4-17	< 0.001
Factor 3	7.58 (2.86)	9.34 (3.58), 3-15	7.88 (2.52), 3-13	6.36 (2.21), 3-13	< 0.001
Gwk 34	22.81 (5.99)	26.66 (6.46), 12-42	24.54 (5.66), 10-41	19.22 (3.75), 10-41	< 0.001
Factor 1	6.86 (2.34)	7.82 (2.48), 3-15	7.43 (2.36), 3-15	5.84 (1.82), 3-15	< 0.001
Factor 2	8.71 (3.21)	9.86 (3.76), 4-19	9.51 (3.13), 4-19	7.39 (2.46), 4-19	< 0.001
Factor 3	7.23 (2.72)	8.98 (3.39), 3-15	7.61 (2.31), 3-13	5.99 (2.07), 3-13	< 0.001

Note. EPDS = Edinburgh Postnatal Depression Scale; SCL = Symptom Check List-90/anxiety subscale;

PRAQ-R2 = Pregnancy-Related Anxiety Questionnaire, revised.

* tested columns 2-4

† PRAQ-R2 was added into the protocol of first assessment in a later phase of the study. Hence, a smaller number, N = 73.

Table 7. Means (SD) of cognitive measures

Cogstate Measure	Whole Sample (n = 230) Mean (SD)	High Symptom Level Group (n = 46) Mean (SD)	Moderate Symptom Level Group (n = 97) Mean (SD)	Low Symptom Level Group (n = 87) Mean (SD)	<i>p</i>
CPAL ^a	10.91 (12.43)	10.04 (11.75)	11.05 (12.60)	11.21 (12.70)	0.710
DET ^a	2.51 (0.09)	2.50 (0.07)	2.51 (0.09)	2.51 (0.09)	0.987
GML ^a	40.38 (12.76)	44.83 (14.33)	41.28 (13.23)	37.03 (10.37)	0.004
OBK ^a	2.88 (0.09)	2.88 (0.08)	2.88 (0.09)	2.86 (0.09)	0.244
IDN ^a	2.68 (0.06)	2.68 (0.06)	2.69 (0.06)	2.67 (0.05)	0.358
ISL ^b	28.58 (3.14)	28.54 (2.96)	28.31 (3.15)	28.91 (3.22)	0.223
ISLR ^b	10.78 (1.15)	10.78 (0.96)	10.64 (1.24)	10.93 (1.14)	0.168
OCL ^b	1.09 (0.11)	1.08 (0.10)	1.09 (0.10)	1.11 (0.12)	0.112
SECT ^b	1.19 (0.09)	1.17 (0.11)	1.19 (0.09)	1.20 (0.08)	0.722

Note: ^a lower score = better performance, ^b higher score = better performance

Table 8. Hierarchical multiple regression for Groton Maze Learning Task total errors

	<i>R</i> ²	ΔR^2	β	Partial <i>R</i>
Step 1	0.011	0.011		
Maternal age			0.105	0.097
Parity			-0.005	-0.004
Step 2	0.075**	0.064**		
	*	*		
Maternal age			0.124	0.118
Parity			-0.023	-0.022
EPDS mean across pregnancy			0.255**	0.255***
			*	
Step 3	0.124**	0.050**		
Maternal age			0.135*	0.132
Parity			0.026	0.025
EPDS mean across pregnancy			0.193**	0.195**
PRAQ-R2, factor 2, gwk 24			0.237**	0.231**

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

5.3 Maternal pre- and postnatal depressive and anxiety symptoms and their relation to infant attention to emotional faces (Studies III and IV)

5.3.1 General results from the infant eye-tracking experiment

Studies III and IV utilized the same sample of mother-infant dyads. The associations between infant eye-tracking data and maternal self-reported psychiatric symptoms data separately for depressive and general anxiety symptoms (Studies III and IV, respectively) from the pre- and postnatal periods were studied. Before conducting analyses for our main research questions, the general features of the infant eye-tracking data were explored.

In the whole sample, there were large individual differences in the infants' overall disengagement probabilities (DPs) from the centrally presented face (or scrambled face) to a lateral distractor (Figure 4, Left). Moreover, the DPs were dependent on the trial number (Figure 4, Right). That is, the proportion of "no gaze shift" trials increased in all conditions over the course of the experiment. This trial number dependency varied by stimulus condition. The DPs were highest for the control stimulus and lowest for the fearful condition. The DPs for the happy and neutral conditions were between those and approximately equal to each other. However, with the exception of a difference between the control condition and face conditions, this "trial effect" did not vary for the three facial expressions. This indicated that the differential trial effect did not explain the bias for face or the biases for specific emotional expressions (i.e., these biases are fairly consistent throughout the course of the experiment). Consequently, it justified the calculation of attention bias scores (i.e., fear or threat bias, see below) in infant emotion processing in addition to inspecting differences in DPs between stimulus conditions.

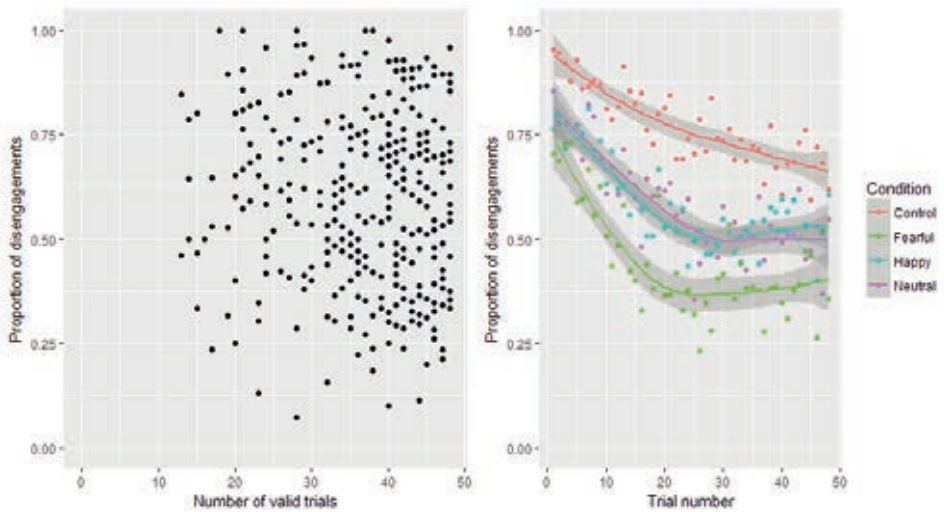


Figure 4. Left: Each infant’s observed disengagement proportions plotted against the number of valid trials illustrating the large individual differences in the infants’ overall DPs. Right: The observed proportions of disengagements (for the whole sample) are plotted as a function of trial number for each condition illustrating the dependence of the DPs on the trial number.

Using condition (i.e., 3 face conditions and a control condition) as the only predictor, we found that across the full sample, there were clear differences among disengagement probabilities (DPs) for the different face expressions ($\chi^2[3] = 946.9$, $p < 0.001$). Estimated DP was lowest for the fearful faces (DP = 0.44; 95% CI [0.41–0.48]) and highest for the control stimuli (DP = 0.83 [0.80–0.85]), DPs for neutral (DP = 0.62 CI [0.59–0.65]) and happy faces (DP = 0.61 CI [0.58–0.64]) being between them. All pairwise comparisons were also significant (adjusted p values < 0.001) except between neutral and happy faces ($z = -0.565$, adj. $p = 0.57$). Here, with this sample, we replicated the finding of the age-typical attention pattern for faces, and a robust bias for fearful faces in the overlap paradigm from several earlier infant studies (e.g., Morales et al., 2017; Nakagawa & Sukigara, 2012; Peltola, Forssman, Puura, van IJzendoorn, & Leppänen, 2015).

5.3.2 *The associations between the trajectories of maternal pre- and postnatal depressive symptoms and infant attention to socio-emotional signals (Study III)*

In Study III, maternal depressive symptoms trajectories were modeled using latent growth mixture modeling (LGMM). The number of latent growth curves was established by increasing the number of subgroups in the LGMM models and comparing fit indices of the outputs with an increasing number of subgroups. The decision about the optimal number of groups was based on the Bayesian Information Criteria (BIC, where a lower value indicates a better model fit; Nylund, Asparouhov, & Muthén, 2007), the posterior probability (i.e., the probability of an individual belonging to a group) for each trajectory group (i.e., a score of 0.80 or above is preferred; Nagin, 2005), and Entropy rate indexing classification accuracy (> 0.80 indicating excellent accuracy; Lubke, 2007).

The BIC scores continued to improve up to a 5-group model (8931.349 – 8806.672). However, the posterior probability scores as well as Entropy rate improved only up to the 3-group model (i.e., posterior probability scores for 3-group model 0.85/0.83/0.96; Entropy 0.85, indicating a good model; Muthén et al., 2002), so we adopted this solution. Moreover, with this solution, we were able to retain satisfactory latent group sizes. Thus, the following groups were formed: “Increasing symptoms” (N = 34, Estimate of intercept = 7.75, Estimate of slope = 1.50, $p = 0.008$), “Decreasing symptoms” (N = 48, Estimate of intercept = 12.19, Estimate of slope = -1.38, $p = 0.002$), “Consistently low symptoms” (N = 280, Estimate of intercept = 3.23, Estimate of slope = -0.11, $p = 0.22$).

The mean level of maternal depressive symptoms in the three latent groups based on the trajectories of EPDS symptoms

The mean level of maternal depressive symptoms in each depressive symptom group (Decreasing, N = 48, Increasing, N = 34, Consistently low, N = 280) at each assessment point is presented in Figure 5. The symptom levels differed across the three groups in all assessment points (Bonferroni corrected p values < 0.01), except at gwk 34, where the mean level of symptoms was equal between the decreasing and increasing symptoms groups ($p = 0.25$).

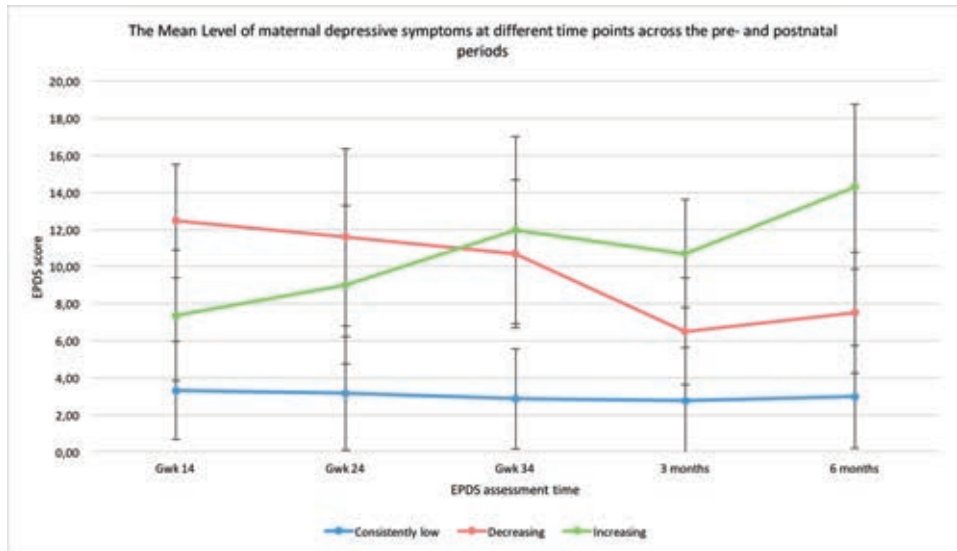


Figure 5. The mean level of maternal depressive symptoms (EPDS) for the three groups of infants classified according to the maternal depressive symptom trajectories. Error bars represent standard deviations. *Note:* The correlations (Spearman r_s) between maternal depressive symptoms at consecutive time points varied between 0.60 – 0.71 ($p < 0.001$).

The overall DPs in the whole infant sample and their dependence on trial number

The predicted values from Model 1 are shown in Figure 6a. The DPs were highest for the control stimulus and lowest for the fearful condition. The DPs for the happy and neutral conditions were in between and approximately equal to each other.

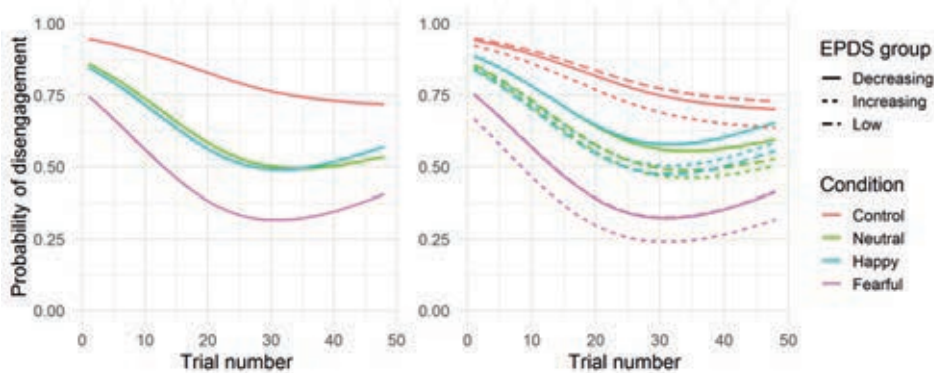
Similarly to Peltola et al. (2008), the reaction times [i.e., mean latency (ms) for gaze shift to the lateral distractor after its appearance excluding trials with no gaze shift] were longest for fearful ($M = 411.63$, $SD = 172.81$), following happy ($M = 382.02$, $SD = 158.36$) and neutral ($M = 388.48$, $SD = 159.83$) faces, and shortest for control stimuli ($M = 338.76$, $SD = 138.71$).

Figure 6a also shows the trial number dependency of the DPs (i.e., a clear decline in DP over the course of the experiment). Comparing Model 1 to Model 0 yielded a significant interaction between stimulus condition and trial number ($\chi^2_6 = 13.317$, $p = 0.038$) reflecting the fact that the DPs for non-face patterns continued to decrease even after the midpoint of the experiment, whereas the DPs of the three face conditions started to slightly increase towards the end of the experiment. The three face conditions did not differ in trial-number effects.

The overall DPs for the three different groups of infants

Comparison of Model 3 and Model 2 showed that there was no evidence of the association between EPDS group and trial number dependency of the DPs ($\chi^2_{16} = 12.42, p = 0.71$).

Figure 6b shows the predicted values for Model 2. We first tested our hypothesis 1. Comparing Model 1.1 to Model 1 showed that the overall DPs were not different for various EPDS groups, when trial number was controlled ($\chi^2_2 = 1.71, p = 0.43$). And similarly comparing Model 1.1b to Model 1b showed that the difference was not significant, when trial number was not included in the models ($\chi^2_2 = 1.67, p = 0.43$). Although the infants of mothers with increasing symptoms seemed to have overall lower DPs than the infants of mothers with decreasing symptoms (Figures 7a, 7b), *post hoc* comparisons between the groups showed that the difference was not significant (Table 9).



Figures 6a and 6b. The predicted DPs for the whole sample (Model 1; 3a) and for the three different groups of infants (Model 2; 3b), when trial number spline and condition main effects and their interaction are included in the model.

The DPs in different stimulus conditions and fear bias in the three different groups of infants

Comparing Model 2 to Model 1.1 and Model 2b to Model 1b showed that the interaction between the EPDS group and condition was significant, when trial number was controlled for ($\chi^2_6 = 19.32, p = 0.0037$) and when not ($\chi^2_6 = 18.08, p = 0.0060$), respectively. However, the significant interaction was not driven by any

of the individual conditions (see Table 10 for *post hoc* comparisons among the three groups of infants in different stimulus conditions and Figure 7a and 7b for illustration of the predicted DPs).

All predicted DPs from Model 2 are given in Figure 6b and predicted DPs for one selected trial [25] in the middle of the experiment are given in Figure 7a. Figure 7b shows the predicted DPs from Model 2b.

Then we tested our hypothesis 2 by comparing the fear bias among the EPDS groups. The infant groups of symptomatic mothers (i.e., the EPDS groups of “Decreasing” and “Increasing” symptoms) showed greater fear bias than the reference group ($p = 0.015$ and $p = 0.016$, respectively, and the results were significant after applying the Holm-Bonferroni method). All comparisons are presented in Table 9. Figure 7c illustrates the fear bias in three different groups of infants. Finally, we compared Model 4 to Model 2 but observed no sex difference in the DPs ($\chi^2_{12} = 3.98$, $p = 0.98$).

Table 9. The results (OR, p values) of the post hoc comparisons of the overall disengagement probabilities (DPs) and fear bias among the three different groups of infants (EPDS groups of Increasing, Decreasing, and Low symptom levels)

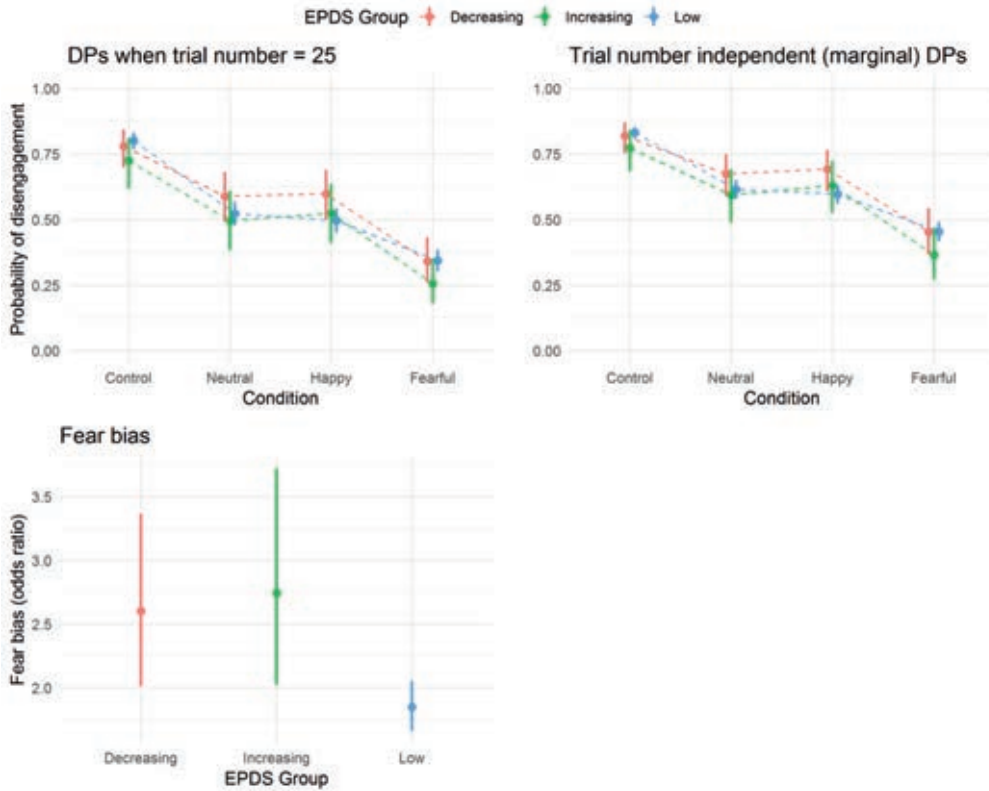
EPDS Group	Overall		Fear bias	
	OR ¹	<i>p</i> value ²	Ratio of ORs ³	<i>p</i> value ²
Increasing vs. Decreasing	0.73	0.20	1.05	0.80
Increasing vs. Low	0.85	0.42	1.49	0.016
Decreasing vs. Low	1.04	0.36	1.41	0.015
Increasing and Decreasing vs. Low	1.00	0.99	1.45	0.0013*

¹ Ratio between the overall disengagement odds in the first and the second group.

² All *p* values are uncorrected.

³ Ratio of fear bias (odds) between the first and the second group.

The *p* values of the tests where null hypothesis was rejected after applying the Holm-Bonferroni method are marked with asterisk (*)



Figures 7 a, b, c (*a and b*, upper panel) The predicted DPs (for infants for whom the random effect is zero) in three different groups of infants, when the trial number is 25 (Model 2; 4a) and trial number independent (marginal) DPs predicted by Model 2b (4b). The predicted probabilities are presented with 95% confidence intervals (uncorrected for multiple comparisons).

Note. We chose trial 25 in the middle of the experiment to illustrate the predicted DPs, when the trial number is taken into account, because the overall DPs were roughly at an average level in this trial making it easier to compare the predictions of the models with and without the trial number.

(*c*, lower panel) illustrates the fear bias in three different groups of infants.

Table 10. The results (OR, p values) of the *post hoc* comparisons of the disengagement probabilities (DPs) in different face conditions among the three different groups of infants (EPDS groups of Increasing, Decreasing, and Low symptom levels)

EPDS Group	Control		Neutral		Happy		Fearful	
	OR ¹	p^2	OR ¹	p^2	OR ¹	p^2	OR ¹	p^2
Increasing vs. Decreasing	0.75	0.35	0.71	0.23	0.75	0.33	0.69	0.20
Increasing vs. Low	0.69	0.13	0.91	0.70	1.15	0.55	0.69	0.11
Decreasing vs. Low	0.91	0.68	1.30	0.20	1.52	0.04	1.00	0.99
Increasing and Decreasing vs. Low	0.80	0.19	1.09	0.60	1.32	0.08	0.83	0.25

¹⁾ Ratio between the overall disengagement odds in the first and the second group.

²⁾ All p values are uncorrected for multiple comparisons.

5.3.3 *The associations between maternal anxiety symptoms during the pre- and postnatal periods and infant attention to socio-emotional signals (Study IV)*

Maternal anxiety symptoms during the pre- and postnatal periods

In the whole sample, the mean level of maternal anxiety symptoms was low. However, 7.6% – 16.9%, depending on the assessment point, of women reported elevated anxiety symptoms (SCL-90 cut-point ≥ 10 representing highest 25th percentile in the Cohort). Maternal anxiety symptoms reported at each assessment point are presented in Table 11.

Table 11. The mean level (SD; Range) of maternal self-reported anxiety symptoms (SCL-90) at each assessment point

SCL-90	Gwk 14	Gwk 24	Gwk 34	3 months	6 months
Mean (SD)	3.23 (4.1)	4.24 (5.17)	3.43 (4.85)	2.57 (3.80)*	2.91 (4.13)*
Range	0–24	0–28	0–33	0–23	0–23
N of missing values	8	4	10	41 (20/341)	56 (35/341)

Footnote. The theoretical range for SCL-90 is 0–40.

The percentages of women exceeding the cut-point ≥ 10 (representing highest 25th percentile in the Cohort) were 9.7%, 16.9%, 13.2%, 7.6% and 7.6%, respectively for each assessment point.

The correlations (Spearman r_s) among maternal anxiety symptoms at consecutive sample points varied between 0.62 – 0.77 (p values < 0.001).

*) N = 341

Maternal pre- and postnatal anxiety symptoms, infant sex, and threat bias

The associations between infant threat bias and maternal postnatal anxiety symptoms at 3 months ($p = 0.09$) or 6 months postpartum ($p = 0.18$) were not significant. However, there was a positive relation between infant threat bias and maternal prenatal anxiety symptoms at gwk 14 ($p = 0.02$) and gwk 34 ($p = 0.046$) but not at gwk 24 ($p = 0.42$). After controlling for maternal anxiety symptoms at 6 months postpartum, the association between maternal symptoms at gwk 14 ($p = 0.037$), but not at gwk 34 ($p = 0.074$), and infant threat bias remained significant. The effects did not differ between boys and girls (all p values > 0.50). Table 12 shows all the results of the association between maternal anxiety symptoms and infant attention patterns.

Maternal pre- and postnatal anxiety symptoms, infant sex, and the overall DPs

There was no significant relation between maternal anxiety symptoms at any assessment point and infant overall DPs (all p values > 0.21) in the whole sample. However, the relation between maternal anxiety symptoms and infant overall DPs differed between boys and girls at 3 months ($p = 0.044$) and 6 months ($p = 0.019$), but not at any prenatal assessment points (all p values > 0.15). Table 12 shows the results of the statistical comparisons, and Figure 8 illustrates the attention patterns of the boys and girls separately at each assessment point.

Table 12. The results of the association between maternal anxiety symptoms and infant attention patterns

Timepoint	Hypothesis 1 a		Hypothesis 1 b		Hypothesis 1 c		Hypothesis 2 a		Hypothesis 2 b	
	Effect size ¹	<i>p</i> value	Effect size ²	<i>p</i> value	Effect size ²	<i>p</i> value	Effect size ³	<i>p</i> value	Effect size ⁴	<i>p</i> value
gwk 14	1.030/1.032	0.021/0.037	1.010	0.69	1.012	0.44	1.026	0.40		
gwk 24	1.008/1.003	0.42/0.83	1.001	0.95	1.001	0.91	1.035	0.15		
gwk 34	1.022/1.028	0.046/0.074	0.989	0.63	1.003	0.80	1.027	0.30		
3 months	1.025	0.092	1.021	0.52	1.022	0.20	1.080	0.044		
6 months	1.018	0.18	0.998	0.94	0.998	0.91	1.078	0.019		

¹⁾ The effect of a one point increase in SCL to the overall disengagement odds.

²⁾ Ratio of the effect sizes in ¹⁾ between boys and girls.

³⁾ The effect of one-point increase in SCL to the overall disengagement odds.

⁴⁾ Ratio of the effect sizes in ³⁾ between boys and girls.

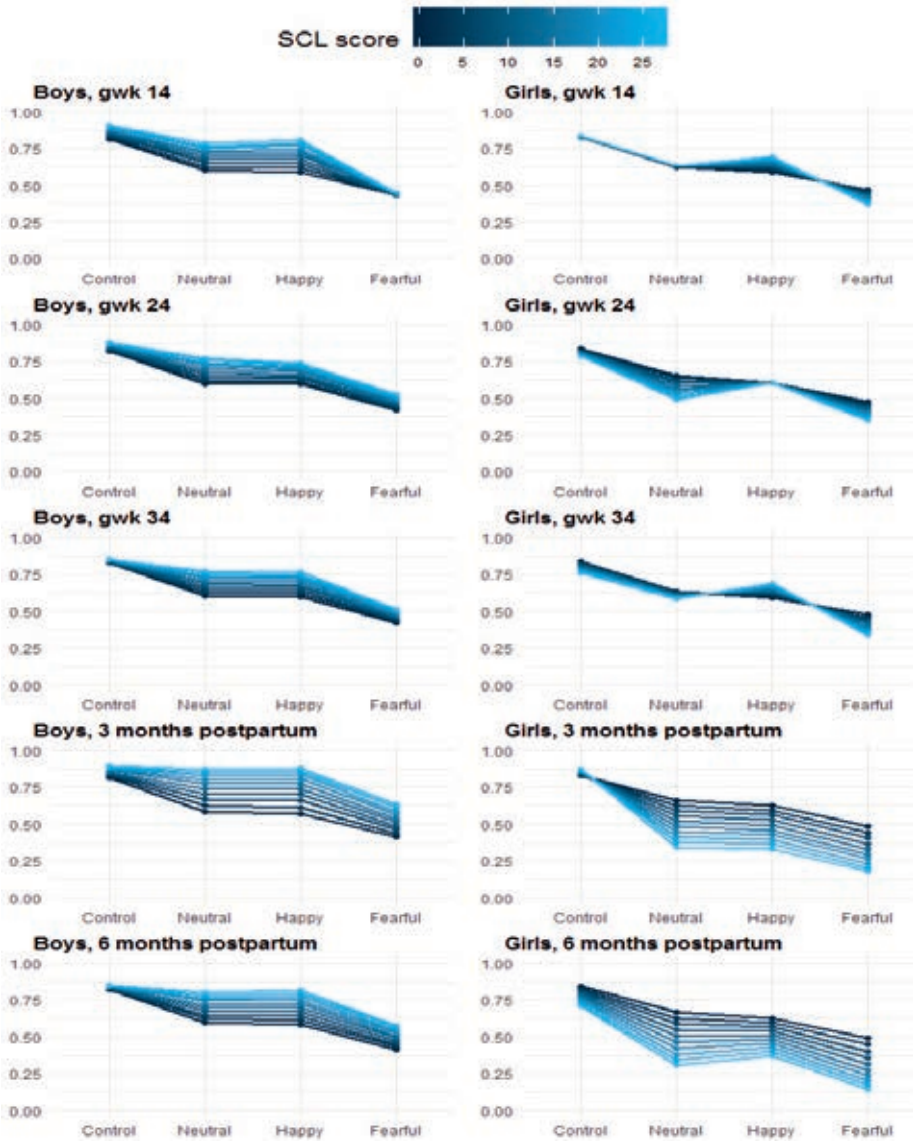


Figure 8. The predicted DPs for each condition (3 facial expressions, control stimulus) at the different levels of maternal anxiety symptoms (SCL-90) at different time points separately for male and female infants at eight months. This figure illustrates how maternal anxiety symptoms are associated with the infant attention patterns (e.g., overall DPs, threat bias).

5.4 Summary of the results

- A traditional IQ test WAIS-IV and a computerized neuropsychological test battery Cogstate correlated only at low–moderate level in measures of visual/perceptual reasoning, working memory, and processing speed. Cogstate performance was relatively independent from crystallized, acquired abilities as can be seen from low correlations with WAIS-IV verbal tasks.
- Pregnant mothers with self-reported high, moderate, or low levels of prenatal stress, in the form of depressive, pregnancy-related anxiety, and/or general anxiety symptoms, differed in performance in a cognitive task measuring visuo-spatial working memory but not in other neuropsychological tasks assessing verbal learning/memory, processing speed/psychomotor function, visual attention/vigilance, visual recognition memory, and spatial working memory (without the updating component).
- Depressive symptoms throughout pregnancy and concurrent (gwk 24) pregnancy-related anxiety symptoms predicted visuo-spatial working memory task errors, whereas general anxiety symptoms were unrelated to the performance in this task.
- Maternal self-reported depressive symptoms across the pregnancy and the postpartum period were associated with infant attention patterns to emotional faces. The overall disengagement probability from faces to distractors was not related to maternal depressive symptoms, but fear bias was heightened in infants, whose mothers reported decreasing or increasing depressive symptoms (versus consistently low symptom levels).
- No sex differences were noted in relation to infant attention patterns and maternal depressive symptoms.
- Maternal self-reported prenatal but not postnatal anxiety symptoms associated with higher threat bias in infants, and the relation between maternal anxiety symptoms during early pregnancy remained significant after controlling for maternal postnatal anxiety symptoms.
- Maternal anxiety symptoms were not associated with the overall probability of disengagement from faces to distractors in the whole sample. However, boys and girls differed in their overall disengagement probabilities in relation to maternal postnatal anxiety symptoms.

6 DISCUSSION

The two main aims of the study were: first, it aimed to enhance our understanding about how maternal symptoms of depression and anxiety are associated with neuropsychological, especially executive functions during pregnancy. Second, it aimed to give insight into how maternal symptoms of depression or anxiety during pregnancy and early postpartum period are associated with infant attention patterns to salient facial expressions and distractors, and whether there would be sex-specific effects. The subjects comprised mother-infant dyads participating in an ongoing, general population-based FinnBrain Birth Cohort Study, the baseline of which was collected between years 2011 and 2015.

6.1 Maternal prenatal depressive and anxiety symptoms and neuropsychological functions

6.1.1 *Maternal neuropsychological functions assessed with two different cognitive test batteries*

In Study I, a test comparison related to our cognitive measures was conducted to assess the dependence of the computerized neuropsychological test on general IQ. This was done by comparing the computerized Cogstate against a traditional IQ test WAIS-IV in a small subsample of randomly selected pregnant women or women in their early postnatal periods. First, our general impression based on test sessions was that Cogstate was easily administered and well-tolerated by the participants, although this was not directly measured. The performance in the Cogstate battery was highly similar between the pre- and postnatal groups, as a significant group difference was found only in one task assessing verbal learning and memory. Here, the group of women taking the test during the prenatal period showed slightly better performance as compared to women taking the test during the early postnatal period. Hoekzema et al. (2017), in their prospective follow-up study, found a slight reduction in verbal word list learning from pre-pregnancy until postpartum but not in other cognitive tasks assessing working memory. The authors concluded that this effect might be related to fluctuating changes in hippocampal volume during the pre- and postnatal periods, which was also found in their MRI study of the same sample, but that these memory deficits might be subtle and transient by nature and not indicators of long-term memory deficits due to pregnancy and child-birth.

In general, the correlations between the computerized neuropsychological test and the IQ test were modest in the domains of visual/perceptual reasoning, working memory, and processing speed. The indices of overall performance showed more

consistent correlations than individual subtests. It is widely accepted that different cognitive tasks typically correlate with each other at least modestly due to their shared variance of the highest order cognitive factor, *g* (Panizzon et al., 2014; Deary, 2014; Plomin & Deary, 2015; Salthouse, 2012). Thus, as only modest correlations were noted in this study, these two tests appear to have somewhat distinct profiles in assessing underlying cognitive constructs, and therefore the decisions made on their individual or combined use should be based on the study design and guided by the research questions.

The assessment of crystallized, acquired abilities as well as verbal processing domains seem to be largely lacking from the Cogstate, as the individual Cogstate tasks correlated only weakly with WAIS-IV verbal tasks and did not correlate with WAIS-IV/verbal reasoning index. This may, however, be of benefit in studies comparing differences in more fluid cognitive functioning and self-regulation (Opitz, Lee, Gross, & Urry, 2014) as well as among participants from diverse cultural and educational backgrounds. Consequently, the performance in the above-mentioned domains has to be completed by other valid assessment methods, such as WAIS-IV verbal tasks, when needed.

Our sample was likely representative of the general FinnBrain cohort population, as the participating mothers did not differ from those not participating in terms of age or years of education. Moreover, their general cognitive level (The Full Scale IQ) corresponded well with the cognitive level of the Finnish general population (Finnish norms, Hogrefe Psychologien Kustannus, 2014), so the results might be generalizable to other samples of the same age of the general population as well.

6.1.2 *The associations between psychiatric symptoms and neuropsychological functions*

Pregnant women (Study II) reporting high or intermediate levels of prenatal psychological distress performed worse in a visual maze task (GML) demanding visuospatial learning, error monitoring, and executive functions as compared to women reporting low levels of symptoms. No differences were noted between the groups of mothers reporting high or intermediate levels of prenatal psychological distress and mothers with low levels of distress in other Cogstate cognitive tasks assessing verbal and visual learning and memory, speed of processing, and social cognition. A more thorough investigation of the associations among the performance in GML and different psychiatric symptom categories revealed that depressive symptoms throughout pregnancy and concurrent pregnancy-related anxiety symptoms, and moreover concerns related to the well-being of the expected child (i.e. PRAQ-R2, factor 2, Worries about Bearing a Physically or Mentally Handicapped Child), predicted a higher amount of visuospatial working memory errors

in addition to maternal age. General anxiety symptoms did not predict performance in this task.

Few studies to date have investigated maternal psychiatric symptoms as the possible underlying mechanisms of cognitive dysfunction during pregnancy, despite the strong basic and clinical research showing that mood disturbances outside the pre- or postnatal periods impair working memory, attention, and cognitive control (Hampson & Ouellette, 2018; Joorman, 2010; Joorman & Gotlib, 2010). Studies assessing maternal psychiatric symptoms have not always found significant associations between maternal symptoms and cognitive deficits during pregnancy (see e.g., Buckwalter et al., 1999; Farrar et al., 2014; Logan et al., 2014). However, one recent study comparing pregnant women with and without elevated depressive symptom levels and non-pregnant women found maternal prenatal depressive symptoms — not pregnancy as such — to explain visuospatial working memory errors and executive dysfunctions (Hampson et al., 2015). Additionally, both lower serum estradiol levels and higher depressive symptom levels together predicted these prenatal dysfunctions of working memory. Interestingly, pregnant women with low depressive symptom levels outperformed non-pregnant control women reporting low levels of symptoms in working memory tasks (Hampson et al., 2015). It may also be that pregnancy, as a time of active cognitive re-organization and adaptation to motherhood and caregiving, enhances rather than reduces some cognitive functions (Macbeth & Luine, 2010; Anderson & Rutherford, 2012; Ouellette & Hampson, 2018). However, this time also possesses a risk for maladaptation, and for some women, excessive mood changes and cognitive disturbances may take place (Huizink & De Rooij, 2018; Workman et al., 2011).

To our knowledge, our study is the first one to report an association between pregnancy-related anxiety and impaired executive functioning during the prenatal period. This is an important finding as pregnancy-related anxiety seems to represent a specific form of maternal distress (Bayrampour et al., 2016; Huizink, Mulder, Robles De Medina, Visser, & Buitelaar, 2004) and has been found to differently relate to maternal as well as offspring outcomes as compared to depression and general anxiety during the pre- and postnatal periods (e.g., Dunkell Schetter & Tanner, 2012; Kane et al., 2014). Pregnancy-related anxiety, possibly related to the degree of adjustment to pregnancy, includes cognitive attributes characterized with excessive worries about different aspects of pregnancy, own appearance, and the well-being of the child (Bayrampour et al., 2016). These cognitive features, such as racing thoughts and excessive worries, may be connected with our findings of the problems in the updating component of working memory among women suffering from pregnancy-related anxiety. Together these findings highlight the importance of taking into account different types of psychiatric and/or (dis)stress symptoms, such as pregnancy-related anxiety, which is not a characteristic of any

specific psychiatric disorder when evaluating cognition and its possible dysfunctions among pregnant women (see also Ouellette & Hampson, 2018 for a discussion of the topic).

According to Pawluski, Lambert, & Kinsley (2016), the significance of visuospatial working memory in mothers may not be related to spatial abilities, *per se*, but instead reflect an ability to detect contextual patterns in the environment and thereby facilitate efficient and timely maternal responses. Indeed, some studies have found that this form of cognitive functioning is related to maternal sensitivity and self-regulation in emotionally arousing situations (Deater-Deckard et al. 2010, 2012; Gonzales et al., 2012; Rutherford et al., 2015). According to one view, better working memory may provide a larger working space for elaborate emotional experiences and select appropriate cognitions and actions to manage these experiences (Rutherford et al., 2015). Therefore, maternal maladaptive cognitive changes, such as working memory problems, should be acknowledged as one of the possible early emerging mechanisms that may later be related to problems in parental caregiving and adverse child developmental outcomes (see also Huizink & De Rooij, 2018). Currently, antenatal depression is a target for screening in the maternal welfare system but given the established maladaptive associations between pregnancy-related anxiety and birth outcomes and child development (e.g. Dunkel Schetter & Tanner, 2012), the future need to screen and consider interventions for both symptom categories should be considered.

Interestingly, maternal general anxiety symptoms were not related to the performance in the maze task, although people with anxiety often present working and spatial memory problems (Boldrini et al., 2005; Darke, 1988; Eysenck, 1998). However, findings from earlier studies have been somewhat contradictory and suggest that there is a lot of heterogeneity among different types of anxiety disorders and their associated cognitive dysfunctions (Castaneda et al., 2008; Vytal et al., 2013). Moreover, some studies have found an inverted U-relation between anxiety and cognitive functioning with an intermediate anxiety levels being beneficial for cognitive performance (De Visser et al., 2010; Salthouse, 2012). It should also be acknowledged that our cognitive test battery did not cover very broadly different components of EFs, and thereby restrict our conclusions of the associations between maternal general anxiety symptoms and executive dysfunctions.

Overall, our findings may be of practical importance and should be taken into consideration when delivering information or planning interventions for pregnant mothers. It is possible that maternal cognitive dysfunction is one mechanism bridging prenatal distress and problems in postnatal parenting and child development (Huizink & De Rooij, 2018), while follow-up studies are needed to adequately test

these associations. The therapists and health care professionals working with pregnant/postpartum mothers might benefit from a better understanding of the specific cognitive dysfunctions and their possibly associated daily-life problems (e.g., problems in an ability to commit to health-promoting activities, close relationships, relaxation, or performance at work) that the mothers with psychological distress may experience. Depression in adults is often successfully treated with psychotherapeutic interventions that target cognitive and/or behavioral components (Goodman & Garber, 2017). Among women with perinatal depression, different psychotherapeutic approaches (e.g., cognitive behavioral therapy, interpersonal psychotherapy) have proven to be effective in reducing symptom severity and recurrence of symptoms as well as having positive effects on children, parenting stress, and marital distress (Hollon, 2016; Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2014). However, the effectiveness of depression treatment reduces along with the recurrence of depressive episodes, and therefore, early-onset interventions targeting key underlying vulnerability factors are highly encouraged (Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017). Among women in their perinatal period, these therapeutic approaches could also target the cognitive dysfunctions of depression, including problems in working memory and attention control that possibly lead to a decreased ability to inhibit negative information entering into the mind and leading to rumination and ineffective emotion regulation (Joorman, 2010; Joorman & Vanderlind, 2014). In terms of pregnancy-related anxiety, antecedents of this specific source of distress include cognitive activity and excessive thinking of the uncertain outcome (e.g., child health, own physical health, and well-being) or an uncontrolled situation (e.g., delivery). Therefore, women suffering from high levels of pregnancy-related anxiety might benefit from increasing their self-perceived level of control of their current situation (Bayrampour et al., 2016) by, for instance, taking into consideration their actual concerns and taking them along to the preparation to child-birth. Generally, aiding women experiencing heightened levels of stress and anxiety to implement relaxation or mindfulness techniques as well as re-direction of attention to other aspects of daily-life might alleviate their symptoms of stress and anxiety and lead to a better functioning parent during the postnatal period (Bayrampour et al., 2016; Bögels, Lehtonen, & Restifo, 2010). Finally, the development of efficient psycho-social interventions, on side of or instead of medical treatment, to alleviate maternal (and familial) distress already during pregnancy is of paramount importance given the known impact of maternal distress, and untreated psychiatric symptoms/disorders on the fetus, the mother, and the family system (e.g., Gentile, 2017; Madigan et al., 2018). Many women do not want to consider medication as an option for treatment during pregnancy or breast feeding, and therefore may be left without treatment, if non-medical treatment options are unavailable.

In this study, we did not investigate the possible hormonal and neural mechanisms behind the cognitive differences. However, we may speculate that different mechanisms play a role in disturbing executive functions among women suffering from depressive and/or pregnancy-related anxiety symptoms, as depressive symptoms presented a more stable relationship with cognitive deficits across pregnancy, while only concurrent pregnancy-related anxiety was associated with the Cogstate performance. One view explaining our findings might be an altered functioning of the HPA and HPG axes and the following changes in hormonal (e.g., cortisol, estradiol, progesterone) balance (Glynn, 2010; Hampson et al., 2015; Ouellette & Hampson, 2018; Sundström-Poromaa & Gingnell, 2014). This might modify the functions of the cortical and limbic brain systems and biochemical processes in memory formation and retrieval in areas important for memory and EFs, such as the hippocampus and the PFC (Frodl et al., 2006; Tatomir et al., 2014). The hippocampus, as a central brain structure for learning and memory, but also for mental health, seems to show remarkable plasticity during the perinatal period (Pawluski et al., 2016), such as fluctuating trajectory of volume change across the pre- and postnatal periods (Hoekzema et al., 2017). The association between depressive symptoms and executive dysfunctions is well-established (e.g., Castaneda et al., 2008; Salthouse, 2012), a factor possibly mediated by differences in hippocampal volumes (Frodl et al., 2006; Levone et al., 2014). Also the performance in the GML task is sensitive to reduced hippocampal volume (Mielke et al., 2014; Lim et al., 2015). So, hippocampal plasticity is among the potential underlying mechanisms bridging prenatal psychiatric symptoms and compromised cognitive functioning, which should be studied further.

In terms of pregnancy-related anxiety, it may be that the acute stress of an expecting mother and the following rise in stress hormone levels (e.g., cortisol; see Hampson et al., 2015) impairs the functioning of the PFC and disturbs goal-directed EFs. Interestingly, though, in our study, general anxiety symptoms were not found to associate with visuospatial working memory deficits. Future studies could investigate whether the cognitive changes observed in our sample of women reporting high pregnancy-related anxiety reflect only transient differences in the cognitive reorganization during pregnancy rather than memory deficit (see Hampson et al., 2015), or whether they have long-term consequences. Some studies have found that the mother's own early-life adversity may be associated with higher pregnancy-related anxiety but also with a greater reduction of anxiety after childbirth (review: Agrati & Lonstein, 2016). There may be different courses of anxieties among pregnant women with some of them being only transient and more reflective of (i.e., current) adjustment to the prevailing circumstances or life changes. Longitudinal follow-ups investigating the later consequences of pregnancy-related anxiety on maternal and child outcomes will be important in understanding this specific source of distress in shaping the preparation to motherhood. Pregnancy-

related anxiety and general anxiety may both predict several forms of postnatal parenting stress (Huizink et al., 2017) and should be targeted with early prevention and intervention.

6.2 Maternal pre- and postnatal depressive and anxiety symptoms and their relation to infant attention to emotional faces

6.2.1 General findings of the infant attention patterns

The large sample of the infant eye-tracking data using the overlap paradigm in assessing individual differences in attention disengagement from emotional faces to distractors enabled us to investigate both the general attention patterns of the infants at this age as well as specific effects of pre- and postnatal exposures to maternal stress. We first found that among all infants, there were significant differences in disengagement probabilities depending on the different facial expressions. The disengagement probabilities were highest for the control stimuli and lowest for the fearful faces. For neutral and happy faces the disengagement probabilities were at an equal level. No differences in attention patterns were noted between girls and boys. Here, our sample replicated the finding of several earlier infant-based studies of the age-typical attention disengagement pattern for faces with a robust bias for fearful faces (e.g., Morales et al., 2017; Nakagawa & Sukigara, 2012; Peltola, Forssman, Puura, van IJzendoorn, & Leppänen, 2015).

Next, we noticed that the disengagement probabilities were highly dependent on the trial number. That is, as the experiment proceeded, infants started to suppress reflexive saccades from the faces to the distractors. A deeper inspection of this “no shift” effect over the course of the experiment revealed that the “trial effect” did not vary for the three facial expressions and differed only for the control condition in which the “no shift” effect was not prevalent. This gave us the knowledge that even though the disengagement probabilities are affected by the general time-related changes during the experiment, they are not emotion-specific, and so the task also captures attention biases to specific emotional faces (see also Ahtola et al., 2014). This background knowledge strengthens both our findings as well as the use of the overlap paradigm in infant samples in assessing the very early attention biases to or away from faces.

Finally, we investigated our study questions related to the associations between maternal depressive and anxiety symptoms during the pre- and postnatal periods and differences in infant attention patterns to faces. Here we found that the effects varied for different maternal symptom categories. We therefore chose to model these associations separately, despite the fact that maternal symptoms of depression and anxiety are often moderately correlated. As seen also in our sample, the

correlations between depressive and anxiety symptom varied between 0.64 - 0.70. Moreover, depression and anxiety are typically differently associated with attention biases to emotional faces. For instance, depressed individuals show modestly reduced orienting of attention to positive stimuli (e.g., happy faces) and/or extended maintenance of attention on dysphoric stimuli (e.g., sad faces), whereas anxiety is characterized with biased attention specifically for threat (Armstrong & Olatunji, 2012; Bar-Haim et al., 2007; Peckham, McHugh, & Otto, 2010). These factors gave us a further reason to investigate the possible effects of different maternal symptom categories separately.

6.2.2 The trajectories of maternal depressive symptoms from the pre- to postnatal periods and infant attention disengagement from emotional faces

We first identified three different trajectories of maternal depressive symptoms (“latent EPDS groups”) from early pregnancy up to six months postpartum. These were “decreasing symptoms” (13.3%), “increasing symptoms” (9.4%), and “consistently low symptoms” (77.3%) groups, which corresponded well for instance with the study by Christensen, Stuart, Perry, & Le (2011), who also identified three trajectory patterns of maternal depressive symptoms during the pre- and postnatal periods. Our first hypothesis was that infants exposed to maternal prenatal depressive symptoms would show more attention distractibility, thus disengaging from all central facial stimuli, in the attention-distraction task. Second, we hypothesized that maternal depressive symptoms would be associated with heightened bias to threat (i.e., fearful faces), but that this bias would be limited to infants of mothers with postnatal depressive symptoms.

Contrary to our first hypothesis, we did not find a main effect in the EPDS group on infant overall disengagement probabilities (DPs) from faces to distractors. Although the estimated DPs appeared to be higher for the infants of the decreasing symptoms group, thus exposed predominantly to prenatal symptoms (Figure 7b), this difference was not significant. However, our second hypothesis was supported by the current results. The infants of symptomatic mothers with increasing and decreasing symptoms groups showed heightened fear bias (i.e., the ratio of odds to disengage from the happy / neutral condition / the odds to disengage from fearful condition) as compared to the infants of mothers with consistently low symptom levels. This finding supports earlier studies showing that maternal depression may alter infant social-emotional processing by exacerbating threat processing. However, we extend previous research by showing that this heightened bias for threat may also be related to exposure to maternal prenatal symptoms. No interaction between infant sex and the EPDS group were found, so the effects seem to be similar for boys and girls. Finally, we investigated whether the detected differences in attention patterns would be due to a differential “trial effect” among the three

groups during the experiment (i.e., instead of an attentional bias towards fearful faces, reduced disengagement from fear might reflect differential changes in attention to faces over the course of the experiment) and thus in learning temporo-spatial contingencies. However, we did not find evidence for this as the effect of trial number was similar among the three infant groups.

In earlier studies, prenatal exposure to maternal psychobiological distress has been associated with adverse development of the child's stress regulation systems, higher order cognitive abilities, and general attention regulation (Sohr-Preston & Scaramella, 2006; van den Bergh et al., 2017). These infants have been characterized as "fussier" and less attentive in general, but also when processing social-emotional information or interacting with the parent or stranger (Field et al, 2006; Field, 2011). Higher stress reactivity, as indicated by autonomic nervous system arousal, seems to lead to a faster, more stimulus-driven attention profile during infancy (de Barbaro, Clackson, & Wass, 2016; Wass, de Barbaro, Clackson, & Leong, 2018) and/or problems in habituating to repeated visual stimuli (de Barbaro, Chiba, & Deak, 2011). Our hypothesis was that in the overlap paradigm, this might be manifested as a higher tendency to disengage attention from the central stimulus to a lateral distractor. This was not supported by the current results. So, therefore, it may be that face processing represents a specific form of attention during infancy and is not manifested as disruptions in attention control in the overlap paradigm with emotional faces and distractors. Alternatively, it may be that our sample was underpowered to detect small differences in the general DPs of the infant groups, due to relatively small groups of infants of mothers with heightened pre- or postnatal depressive symptoms. Further studies could test our hypothesis in larger infant samples and also in samples with more severe levels of maternal prenatal depression.

Our second hypothesis was that infants of mothers with postnatal depressive symptoms would show heightened threat bias, as some, but not all (Leppänen et al., 2018), earlier studies have found that postnatal maternal depressive symptoms exacerbate an infant's attention bias to threat (Forssman et al., 2014). Extending previous research, we found that the infants of the increasing symptoms group, who were exposed predominantly to postnatal maternal depressive symptoms and also the infants of the decreasing symptoms group, who were exposed to prenatal maternal depressive symptoms, showed higher bias for fearful faces as compared to the infants of the mothers with consistently low symptoms. Future studies should test whether underlying genetic factors explain maternal symptoms of depression, both pre- and postnatal, and infant attention for threat irrespective of the timing of exposure to maternal symptoms. Alternatively, there may be independent prenatal and postnatal effects but both lead to similar outcomes in the child, in this case,

heightened attention bias to threat. Disentangling the pre- and postnatal exposures remains an important aspect in future studies about infant attention development.

The early life environment, and especially in the caregiving received, significantly contributes to how the child's stress and attention regulation systems and their interconnections develop (Loman & Gunnar, 2010). One may speculate that maternal symptoms of depression at some stages of pregnancy and postnatal period are associated with changes in the mother's caregiving and emotional expressions and constitute a source of repeated stress to the infant. This may push the development of threat detection systems towards hypersensitivity to environmental threats (Feldman et al., 2009; Loman & Gunnar, 2010). For instance, the unpredictable, less positive interactive style found among mothers with depression, changing erratically from negative and intrusive to withdrawn, may enhance child vigilance towards social signals and threat (Aktar et al., 2016; McAndrew, 2017). Later, this bias in the attention systems, especially if combined with certain temperament styles or genetic predispositions (Aktar et al., 2018; Papageorgiou & Ronald, 2017), may predispose the child to a risk for later self-regulation problems and psychopathology. Evaluating parent-child-interaction patterns and also different parenting components that might be impaired by maternal depressive effects among these mother-infant pairs might shed more light on our findings.

Based on earlier studies, children at high familial risk for depression seem to show early patterns of a depressotypic information processing style with abnormal patterns of neural activation and brain structure development (Gotlib, Joormann, & Foland-Ross, 2014; Pagliaccio, Pine, Barch, Luby, & Leibenluft, 2018). These findings may be generalized to more general emotion perception in children at high risk for depression. Our results indicate that children at risk for self-regulation problems and mental health disorders based on their mothers' history of depressive symptoms may show very early deviances from their peers in how they attend to emotional faces. Long-term follow-up of the same infants is needed in order to understand the relevance of our findings and their implications for child social-emotional and mental health development.

Finally, consistent with prior studies (e.g., Ahtola et al., 2014; Leppänen et al., 2011), the current results showed that infants' probability of disengaging from the central to the lateral stimulus declined over the course of the experiment, possibly reflecting habituation or learning. These changes tended to be more pronounced in the three face conditions (as compared to the non-face, control condition). Given these effects, we investigated the possibility that the differences in attention patterns among the groups would be due to differential trial-related changes during the experiment (for example, instead of an attentional bias towards fearful faces, reduced disengagement from fear in infants of mothers with increasing symptoms

may reflect differential changes in attention to faces over the course of the experiment). However, we did not find evidence for this, as there was no difference across the infant groups between disengagement probability and trial number (Figure 6b). This suggests that the differential attention disengagement patterns among the three groups of infants reflect genuinely attentional phenomena not differential “trial effects” or changes in behavior during the experiment.

6.2.3 Maternal anxiety symptoms during the pre- and postnatal periods and infant attention disengagement from emotional faces

We investigated the associations between maternal general anxiety symptoms assessed at several time points during pregnancy and postnatal period and infant attention patterns to faces, and the possibly moderating role of infant sex. We found that maternal anxiety symptoms at the early and late pregnancy assessment points (gwk 14 and 34, respectively) associated with higher threat bias in infants at the age of eight months, and the association between maternal early pregnancy symptoms and infant threat bias remained significant after controlling for maternal symptoms at six months postpartum (the closest assessment point for maternal symptoms in relation to infant outcome). Contrary to our hypothesis and the study by Morales et al. (2017), but in line with the recent study by Leppänen et al. (2018), maternal postnatal anxiety symptoms assessed at three and six months postpartum did not associate with higher threat bias in infancy. These results suggest that maternal anxiety symptoms may enhance infant threat bias, but the timing of maternal symptoms may matter. The prenatal period may be an important factor to consider when investigating the associations between maternal anxiety and child attention development.

Secondly, we explored the associations between maternal pre- and postnatal anxiety symptoms and the overall disengagement probabilities of the infants. This was done due to the fact that technically, a high threat bias in the overlap task might be a result of either high probability of disengagement to lateral distractors from all other central stimuli (i.e., non-face, neutral, happy faces) but fearful faces or alternatively a result of especially low probability of disengagement specifically from fearful faces. We considered this study question of importance for our understanding of the possible individual and sex differences in attention functions in the context of prenatal exposure to maternal distress, and moreover, when trying to understand the early emerging deviances in attention biases during infancy. We found that in the whole-sample level, maternal anxiety symptoms were not associated with the overall probability of disengagement. However, infant sex moderated the associations between maternal postnatal anxiety symptoms and the infant’s overall disengagement probabilities. Thus, boys and girls differed in terms of overall disengagement probability in relation to maternal anxiety symptoms at three- and six-

months postpartum suggesting that the postnatal environment may shape child attention systems differently for boys and girls. In our sample, in relation to maternal postnatal anxiety symptoms, the probability of disengagement was nearly equal for non-face, control, and happy faces among the boys. The girls showed overall lower probability of disengagement from all face stimuli (see Figure 8 for illustration). This finding is novel in suggesting that the attention patterns of boys and girls may be differently related to maternal postnatal anxiety symptoms. Boys may be more “distractible” or vigilant to all suddenly appearing stimuli, except when viewing highly salient fearful faces, whereas girls may be more vigilant to all social signals (i.e., show difficulties in disengaging from faces). Future studies should consider these differences in attention patterns between boys and girls in infancy especially when using an attention distraction paradigm with emotional faces.

During infancy, self-regulation depends upon orienting attention systems, and so deviances in the early orienting systems may associate with behavioral and emotional problems during childhood and adolescence (e.g., Papageorgiou & Ronald, 2017). Currently, the significance of these early attention patterns to faces or orienting biases to threat for later child development is not established. During healthy development, the normative threat-related attention biases may dissipate (Dudeny et al., 2015), whereas in psychopathological development, they may become overexpressed (Morales et al., 2016; Schehner et al., 2012; Troller-Ronfree et al., 2017). These factors make the early emerging differences in attention orienting biases meaningful targets of developmental studies in the context of early-life adversity and the later risk for psychopathology.

It is well-established that maternal prenatal distress, in the form of anxiety symptoms along with other sources of stress, is related to cognitive, behavioral, and emotional problems in the child (e.g., Doyle & Cicchetti, 2018; Glover, 2014; Huizink & De Rooij, 2018). These problems may be mediated by early attention mechanisms. Previously, two studies reported deviances specifically in child emotional attention processes in relation to maternal prenatal anxiety. Otte et al. (2015) reported larger responses to fearful versus happy auditory stimuli in 9-month-old infants in relation to exposure to high maternal anxiety during the first pregnancy trimester indicating increased attention, or enhanced vigilance, to threat. At four years of age, these same children showed preference for neutral visual stimuli, possibly interpreted as ambiguous, over unpleasant stimuli in relation to exposure to maternal anxiety symptoms during the second trimester (Van den Heuvel et al., 2017). The authors concluded that a state of enhanced vigilance to threat or ambiguous stimuli may be a predictive marker for later anxiety, especially if the postnatal environment does not match with the prenatal (see also Van den Bergh et al., 2018). A longitudinal follow-up of the same infants is needed to understand if the

heightened bias for threat among infants of mothers reporting higher levels of prenatal anxiety in our sample is indicative of risk for later self-regulation difficulties, such as anxiety.

Two previous studies have investigated maternal concurrent (i.e., postnatal) anxiety symptoms and infant attention bias for threat using the overlap paradigm. Morales et al. (2017), with a smaller ($N = 97$) and more heterogeneous infant sample (age 4–24 months), reported heightened bias for threat (e.g., angry versus happy faces) among infants of mothers with anxiety symptoms. In this study, only 12 trials posed by 12 different models were used. In turn, a recent study by Leppänen et al. (2018), with a larger sample and with repeated measures of both infant attention and maternal symptoms (5-, 7-, 12 months, $N = 269$; and 36 months, $N = 191$), did not find associations between maternal postnatal anxiety symptoms and child threat bias at any assessment point. Here, 24 trials were shown, and each infant saw pictures of only one model out of two. While the diversity in study set-ups makes the comparison of the results among different studies difficult, it may be that maternal anxiety symptoms exacerbate infant threat processing. Our study, with a large, heterogeneous sample of infants, high number of presented trials (48), and repeated assessments of maternal anxiety symptoms add to the existing literature in suggesting that these effects may be more related to exposure to prenatal adversity and less to postnatal influences. More studies with comparable designs are clearly needed to investigate this issue further. In addition to early-life environment, genes are also known to significantly contribute to the development of attention (dys)regulation (Forssman et al., 2014; O'Donnell & Meaney, 2017). Thus, there may also be genetic influences in the relation between maternal anxiety symptoms and infant attention patterns. The inclusion of genetic information in longitudinal environmental risk studies will give important information about individual vulnerability to environmental factors, and moreover, guide targeted interventions, also in relation to developing attention mechanisms (Papageorgiou & Ronald, 2017).

Previous studies have connected maternal prenatal anxiety with higher rates of general attention problems (e.g., ADHD) in children, and these effects have been more pronounced in boys (e.g., Van den Bergh et al., 2017). In contrast, maternal postnatal anxiety symptoms/disorders have been found to associate with threat bias in children and more often in girls (e.g., Mogg et al., 2012; Montagner et al., 2016). It seems that the effects of pre- or early postnatal maternal distress may be different for boys and girls (Sandman, Glynn, & Davis, 2013), while the results regarding the moderating role of child sex have been mixed thus far (Van den Bergh et al., 2018). Socio-emotional attention has a strong evolutionary basis (Leppänen & Nelson, 2009), while environmental factors have the potential to shape it (Leppänen, 2011; Pollak & Kistler, 2002; Teicher & Samson, 2016). It has been

suggested that maternal prenatal anxiety might program the development of child attention and stress-regulation systems in a more reactive and vigilant direction, possibly by altering the structure and functions of the stress-regulation systems (Van den Bergh et al., 2018). Heightened threat bias, found in our sample of infants of mothers with prenatal anxiety symptoms, may reflect adaptations to the postnatal environment and its anticipated threats of which the mother's anxiety symptoms during pregnancy signal (Glover, 2011; Glover & Hill, 2012; Loman & Gunnar, 2010). Furthermore, some effects may differ for boys and girls and thereby reflect different strategies of evolutionary adaptation between genders (DiPietro & Voegtline, 2017; Glover & Hill, 2012; Loman & Gunnar, 2010). When exposed to maternal anxiety, boys often show more attention deficits, cognitive problems, and externalizing behavior, whereas girls tend to experience anxiety, depression, and internalizing symptoms (Glover & Hill, 2012; Stein et al., 2014). Aktar et al. (2017) reported a positive association between maternal life-time and prenatal anxiety and infant heightened attention towards their mother's face during face-to-face interactions. One may speculate that the attention pattern of heightened vigilance towards all faces serves an adaptive role for the girl infants also outside of face-to-face interaction situations with the parent. Experience-independent differences between sexes in socio-emotional processing are prevalent among human infants with girls showing more social sensitivity and interest (Simpson et al., 2015). So, if human female infants are naturally more drawn towards social signals in order to increase their own, and later their offspring's survival, this pattern of attention may be strengthened by early-life adversity. Moreover, hyperactivity/more distracted attention may be adaptive for boys but not for girls, as it has been found to lower maternal direction and praise, whereas the opposite is true for boys (cf. Glover, 2011). It remains to be seen how these patterns of attention are related to the development of boys and girls over the long-term.

The investigation of attentional biases during infancy in the context of maternal anxiety is important. It may shed light on the early emerging cognitive vulnerability factors and aid in understanding how these attention-related mechanisms may interfere with early interaction situations between the infant and the caregiver (Parsons, Young, Murray, Stein, & Kringelbach, 2010) and the development of mental health. According to Cisler & Koster (2010), a robust threat-related bias is well-established in anxious individuals from different populations and with a variety of experimental conditions, and so the next step is to understand how and why attention biases are manifested. Our study may add to the literature in showing how attention biases may be manifested already during infancy among population at-risk for anxiety or other self-regulation problems, and how these effects may be related already to the prenatal period. However, not all children are affected by maternal anxiety in the same way. The three-hit concept of resilience and vulnerability to early-life adversity proposes that risk or resilience for psychopathology

is determined by genetic susceptibility, early-life environment, and later-life environment (Daskalakis et al., 2013). The role that the postnatal environment and parental characteristics play in shaping child development is important (Huizink & Bögels, 2013) and should be studied also in relation to our findings.

6.2.4 Concluding remarks about the associations between maternal pre- and postnatal psychiatric symptoms and infant attention to emotional faces

In Studies III-IV, we inspected how early life distress in the form of exposure to maternal depressive and anxiety symptoms might be associated with differences in infant attention patterns to faces especially to threat. There are a number of studies suggesting that infants' attention regulation and social-emotional processing are influenced by maternal psychiatric symptoms, and that these influences may have their origins in prenatal effects. A conspicuous limitation of the existing studies has been, however, that the evidence for adverse effects has been mostly cross-sectional by examining symptoms at one time-point, and there have been no studies linking children's attention patterns with more long-term trajectories of maternal symptoms. This question is important given the data showing that the child's sensitivity to prenatal influences may be dependent on whether or not the symptoms are carried over to the postnatal phases (Stein et al., 2014). To our knowledge, the current study represents the first effort to relate infants' attention disengagement from emotional faces with longitudinal data on maternal pre- versus postnatal depressive and anxiety symptoms.

Here, we found that maternal symptoms of depression and anxiety associated with infant attention patterns. The timing of symptoms during the pre- and postnatal periods seem to associate differently with infant attention patterns, and some associations were moderated by the sex of the infant. However, in order to understand the development of the related psychopathology, a multilevel, longitudinal approach examining diverse pathways is needed (Aktar & Bögels, 2017; Apter, Bobin, Genet, Gratier, & Devouche, 2017). Thus, when evaluating the long-term trajectories of infant attention in the context of maternal psychiatric symptoms, it is important to consider the differences in infant attention patterns among our different infant groups and the adaptive, self-organizing nature of development (Cicchetti & Curtis, 2015). The predictive-adaptive-response model posits that an adverse early-life environment may confer an advantage for child development, if there is congruence between pre- and postnatal environments (see e.g., Sandman et al., 2012). Thus, in some circumstances, the behavior that deviates from "normalcy" may serve an adaptive role in the living environment of the individual. One example of this, reported in for instance in several studies by Tiffany Field et al., might be a tendency of the newborn infants of mothers with depression to mimic the biobehavioral characteristics (Field, 2011) as well as the attentive, interactive

behavior of their mothers (Apter et al., 2017). However, psychopathology may arise when adaptation becomes too difficult, for instance, due to the accumulation of dysfunction or negative individual characteristics and further adverse environmental factors (Apter et al., 2017). Therefore, also the idea that fetal exposure to environmental adversity may prepare the child for an adverse postnatal environment awaits further exploration. The attention development of the infants assessed in the current study will be followed by several repeated assessments during early childhood to achieve this goal. Finally, the inclusion of genetic information in longitudinal environmental risk studies will give important information about individual vulnerability to environmental factors, and moreover, guide targeted interventions also in relation to developing attention mechanisms (Papageorgiou & Ronald, 2017).

6.3 Strengths and limitations of the study

A major strength of the current study was a longitudinal, prospective study design, assessing diverse maternal psychiatric symptoms repeatedly during the pre- and postnatal periods. The repeated assessment of maternal symptoms enabled us to consider independently the effects of pre- versus postnatal distress on infant outcomes and also the more specific timing of these effects. Also, the relatively large sample sizes in Studies II–IV is a strength.

As a strength related to study methods, the use of objective psychological measures in assessing both maternal cognitive functions and infant attention should be mentioned. The use of a computerized cognitive test method provides a tool to collect temporally accurate data that contains less measurement error than the traditional paper-and-pencil tests are prone to contain. Moreover, the use of eye-tracking in assessing infant attention provides a temporally and spatially accurate method for studying attention and emotional processing in pre-verbal infants. Further, the use of an often-used attention distraction paradigm makes the interpretation of the results easier. However, a limitation can be considered the fact that, to date, no studies on infant attention patterns assessed with the overlap paradigm, where early differences in attention patterns have been connected to developmental outcomes, for instance, at school age, have been published yet. Some studies assessing longitudinal associations have been conducted. For instance, Peltola et al. (2015) found a lack of age-typical threat bias at seven months to predict insecure attachment at 14 months. Nakagawa & Sukigara (2012) found that attention bias to threat at 12 months positively associates with a negative affect during the first three years of life. Thus, no strong long-term conclusions may be made of the differences in attention patterns among infants without longitudinal follow-ups. As a significant contribution to the field, we investigated the more general infant attention patterns in the overlap paradigm. We illustrated how the disengagement probabilities of the

infants are affected by the general time-related changes during the experiment that are not emotion-specific. This shows that the task actually captures attention biases to specific emotional faces as been claimed.

As a limitation related to our measures, maternal symptoms of depression and anxiety were self-reported. Nevertheless, questionnaires, and moreover continuous measures of maternal symptoms of distress are consistently used in similar developmental studies and enable the evaluation of the severity of symptoms on different outcomes (Dunkel Schetter & Tanner, 2012; Stein et al., 2014). We used repeated assessment of the same symptoms, strengthening our measure of maternal mood during pre- and postnatal periods. Moreover, the number of mothers suffering from very severe symptoms and infants exposed to severe symptoms was relatively small due to the general population sample. However, there is some evidence of a dose-response effect of moderate to severe maternal psychiatric symptoms on child developmental outcomes (Glover, 2011). Therefore, studying the impact of subclinical symptom levels is also of interest. Finally, related to the analysis strategy with regard to maternal psychiatric symptoms in Studies III and IV, we deliberately did not control for the possible effects of the comorbidity of maternal symptoms. This was because there is some evidence of specific attention-related effects of maternal anxiety (Glover, 2011), and moreover, depression and anxiety seem to have different effects on the processing of socio-emotional information (e.g., Armstrong & Olatunji, 2012). Finally, the choice to inspect and model these symptom categories separately was made also in order to keep the analysis of the data simple and interpretable. Lastly, the associations between maternal symptoms of pregnancy-related anxiety and infant attention patterns were not investigated. The pregnancy-related anxiety questionnaire (PRAQ-R2) was added to the first pregnancy trimester questionnaire protocol at later stages of the data collection, and so the sample size of women reporting this specific source of distress at first pregnancy trimester was rather low in our sample. Future studies could investigate the role that pregnancy-related maternal anxiety plays in infant attention patterns to faces and also the role that comorbid symptoms play versus symptoms of only one category in shaping infant attention.

Finally, no brain structural, hormonal, or genetic mechanisms of either maternal cognitive deficits or altered infant attention patterns were investigated in the current study. For instance, there may be genetic influences in the relation between maternal psychiatric symptoms and infant attention patterns. Therefore, the inclusion of genetic information in longitudinal environmental risk studies is important, as it will give crucial information about individual vulnerability to environmental factors, and moreover, guide targeted interventions, also in relation to developing attention mechanism (Papageorgiou & Ronald, 2017). Moreover, the investigation

of hormonal effects (e.g., estrogen, cortisol) might aid in understanding how maternal psychiatric symptoms are transferred to cognitive dysfunctions, or how exposure to these symptoms during pregnancy might alter infant attention development. Also, functional and/or structural brain imaging would provide important information about the brain-level mechanisms behind our findings. Finally, investigation into mother-infant interactions would be useful in order to understand how the postnatal environment and maternal symptoms during this time exerts its influence on infant development. For many of these dimensions, data will be available within the Cohort, and the ability to combine these with the current datasets is among the many inspiring opportunities for the future research.

7 CONCLUSIONS

In studies presented here, we hypothesized that maternal symptoms of depression and anxiety during pregnancy would be related to her cognitive functions during pregnancy. Moreover, we expected to find a relation between maternal pre- and early postnatal symptoms of depression and anxiety and the development of child attention to emotional faces, a function also related to cognitive processing. These hypotheses were formed based on earlier research: 1) cognitive factors, such as problems in exerting cognitive control and executive functions, are closely related to both to the onset and maintenance of psychiatric symptoms or disorders, and 2) children of mothers with pre- and postnatal psychiatric symptoms reportedly show deficits in neurocognitive functioning and attention control.

In line with these hypotheses, we found that maternal symptoms of depression and pregnancy-related anxiety, but not general anxiety, were linearly associated with visuospatial working memory deficits during pregnancy (Study II). These symptoms, together with maternal age and parity, explained 12.4% of the variance in task performance. While it is difficult to estimate the functional relevance of this finding on, for instance, daily-functioning of these women, this question might be a meaningful target for future studies. In addition, as a clinical implication, health-care workers might consider the possible co-occurrence of working memory difficulties with psychiatric symptoms when working with expecting mothers. In Studies III and IV, we found that maternal symptoms of depression and anxiety were also related to infant attention patterns to emotional faces. Both maternal pre- and postnatal depressive symptoms seem to enhance infant threat processing in relation to other facial expressions, and this effect was similar for boys and girls. Maternal prenatal anxiety symptoms, but not postnatal, were also related to a higher threat bias in infants, even after the effects of maternal postnatal symptoms were controlled. Maternal postnatal anxiety symptoms, in turn, associated with the overall disengagement probabilities of the infants differently for boys and girls. Boys, in relation to maternal postnatal symptoms, disengaged more often from faces, whereas girls disengaged less often from all faces. The longitudinal approach in assessing maternal psychopathology before and after birth and infant emotional information processing is novel, and therefore no strong conclusions about the functional or clinical relevance of our findings can be made. In conclusion, our findings suggest that maternal symptoms of depression and anxiety, even if at sub-clinical level, relate to cognitive processing both in mothers themselves and in their infants. Some effects on infants may be sex-specific.

Together our findings highlight the need to properly screen and treat maternal psychiatric symptoms already during pregnancy and after child-birth. Different types

of symptoms should be acknowledged as cues for possibly harmful maternal distress during pregnancy or early postnatal period. This is important, because these symptoms of distress may disturb her cognitive processing and also her daily functioning. These symptoms should be assessed repeatedly, as it may be that the trajectories of symptoms are meaningful in understanding their possibly harmful effects on maternal caregiving and child development. Finally, sub-clinical symptom levels of distress should also be recognized as possibly influencing both maternal functioning and child development. In this study, dose-response associations of maternal depressive and anxiety symptoms were found with both maternal executive functioning and infant attention patterns to faces.

Several intervention methods exist supporting early motherhood and interaction between parent and child. These interventions should start already during pregnancy and aim at: 1) reducing maternal distress and symptom levels, and 2) reducing the problems that these mothers may face in their emotional bonding with their infants as well as in actual caregiving practices. Parenting starts already during pregnancy, and therefore it should be supported starting at pregnancy.

Mood and anxiety disorders are traditionally treated with medical and psychological therapeutic methods involving a differing amount of cognitive and behavioral techniques, depending on the therapeutic approach. Based on our results, mothers experiencing depressive symptoms during pregnancy show deficits in updating their working memory. This finding is well in line with the established feature of depression, where a negative, mood-congruent information processing style is prevalent leading to mental rumination of negative thoughts. It seems that individuals with dysfunctions in cognitive control (e.g., inhibitory and attention control) are more vulnerable to rumination and thus ultimately experience depressive episodes (Joorman, 2010; Joorman & Gotlib, 2010). Working memory, as a system for active maintenance and manipulation of information, plays an important role in directing our attentional resources. In depression, a person suffers from difficulties in inhibiting negative or unwanted ruminating thoughts from entering working memory that then disturbs attention processes and goal-directed actions and coherent stream of thoughts (LeMoult & Gotlib, 2018; Joorman 2010). Different processes of cognitive control may be detectable markers of vulnerability for depressive disorder on one hand and cognitive control training on the other hand one possible target for intervention in reducing depressive symptoms and preventing more severe forms of depression (Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017). Anxiety, including pregnancy-related anxiety, could be treated similarly, with an emphasis on empowering pregnant women by enhancing their self-perceived control of their own situation (i.e., the pregnancy, the well-being of the child to-be-born, and the delivery). Mothers experiencing heightened levels of symptoms of distress, depression, or anxiety would probably benefit from learning

techniques to re-direct their attentional resources to other aspects of their daily-lives than pregnancy and from relaxation and mindfulness techniques that could be easily implemented to ordinary days in life. For instance, mindfulness-based interventions (e.g., mindful parenting, see Bögels et al., 2010) aimed to improve parenting are thought to reduce parental stress partly through improvements in executive attention control. Interestingly, maternal mindfulness during pregnancy has also been found to be beneficial for the infant's social-emotional development (Van den Heuvel, 2015) and so might be a useful approach for interventions already during pregnancy.

Finally, a significant number of women suffer from symptoms of depression and anxiety also after delivery. As the development of the child's cognitive and emotional regulation takes place in a dyadic feedback process between the child and the parent, the interventions after delivery aimed to enhance a child's healthy development might be most effective, when the focus of the intervention would be on both child functioning and parenting behaviors (Tucker-Drop & Harden, 2012). Our study points to the direction that infant attention characteristics are also prone to differ individually, and some infants may, for instance, show higher distractibility in their attention patterns when processing emotional information, whereas some may be prone to engage to faces more intensively. Differences in infant characteristics should also be acknowledged as influencing factors in dyadic mother-infant interactions contributing to both maternal and infant brain and behavior (Pereira & Ferreira, 2016). Effective interventions should incorporate elements that enhance positive person-environment feedback loops (e.g., improving reciprocal interactions between the parent and the child instead of focusing solely on either parent or the child; Tucker-Drop & Harden, 2012), so that their positive effects would be maintained and possibly even amplified after the end of the intervention delivery (Huston et al., 2005). In recent years, attention training interventions have been developed to improve attention control and the following cognitive and emotional development of the infant during early childhood (Forssman & Wass, 2017). Interestingly, the training of basic attention control skills during infancy has been shown to transfer to social communication situations, in addition to more general attention processes (Forssman & Wass, 2017). However, more studies are needed to investigate the generalizability of this kind of intervention effect to real-life settings.

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