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TITLE Maternal Pre- and Postnatal Anxiety Symptoms and Infant Attention Disengagement from Emotional Faces

YEAR 2019

DOI https://doi.org/10.1016/j.jad.2018.09.064

VERSION Pre-print.

CITATION Eeva-Leena Kataja, Linnea Karlsson, Christine E. Parsons, Juho Pelto, Henri Pesonen, Tuomo Häikiö, Jukka Hyönä, Saara Nolvi, Riikka Korja, Hasse Karlsson,
Maternal pre- and postnatal anxiety symptoms and infant attention disengagement from emotional faces,
Journal of Affective Disorders, Volume 243,2019,Pages 280-289,ISSN 0165-0327,
https://doi.org/10.1016/j.jad.2018.09.064
(http://www.sciencedirect.com/science/article/pii/S0165032718312837)

Maternal Pre- and Postnatal Anxiety Symptoms and Infant Attention Disengagement from Emotional Faces

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Conflict of interest: None

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Key words: Maternal prenatal anxiety symptoms; Maternal postnatal anxiety symptoms; Infant attention to emotional faces; Attention disengagement; Attention bias to threat;

ABSTRACT

Background: Biases in socio-emotional attention may be early markers of risk for self-regulation difficulties and mental illness. We examined the associations between maternal pre- and postnatal anxiety symptoms and infant attention patterns to faces, with particular focus on attentional biases to threat, across male and female infants.

Methods: A general population, Caucasian sample of eight-month old infants (N=362) were tested using eye-tracking and an attention disengagement (overlap) paradigm, with happy, fearful, neutral, and phase-scrambled faces and distractors. Maternal self-reported anxiety symptoms were assessed with the Symptom Checklist-90/anxiety subscale at five time points between gestational week 14 and 6 months postpartum.

Results: Probability of disengagement was lowest for fearful faces in the whole sample. Maternal pre- but not postnatal anxiety symptoms associated with higher threat bias in infants, and the relation between maternal anxiety symptoms in early pregnancy remained significant after controlling for maternal postnatal symptoms. Maternal postnatal anxiety symptoms, in turn, associated with higher overall probability of disengagement from faces to distractors, but the effects varied by child sex.

Limitations: The small number of mothers suffering from very severe symptoms. No control for the comorbidity of depressive symptoms.

Conclusions: Maternal prenatal anxiety symptoms may enhance infant's attention bias for threat. Maternal postnatal anxiety symptoms, in turn, may associate with infant's overall disengagement probability differently for boys and girls. Boys may show enhanced vigilance for distractors, (except when viewing fearful faces), and girls enhanced vigilance for all socio-emotional stimuli. Long-term implications of these findings remain to be explored.

1 INTRODUCTION

Around 15-30% of women report symptoms of anxiety at some stages during pregnancy or early postpartum period (Fairbrother, Janssen, Antony, Tucker, & Young, 2016; Leach, Poyser, & Fairweather-Schmidt, 2017). Maternal prenatal anxiety, often conceptualized under the umbrella term "prenatal distress" referring to an adverse situation yielding emotional and/bodily responses in a pregnant mother, is a risk factor for adverse child neurodevelopment, increasing the probability of neurocognitive, behavioral and emotional problems later in life (Doyle & Cicchetti, 2018; Glover, 2014; Huizink & De Rooij, 2018; Van den Bergh et al., 2017; Van den Bergh, Dahnke, & Mennes, 2018). Prenatal distress, embedded in the framework of prenatal/fetal programming, may exert its influence through direct biological routes between mother and child (Sandman, Glynn, & Davis, 2016), such as an exposure to an adverse intrauterine environment (e.g. excessive cortisol exposure) and/or through epigenetic dysregulation (Daskalakis, Bagot, Parker, Vinkers, & De Kloet, 2013; O'Donnell et al., 2012; Van den Bergh, 2011), which may elicit long-term changes in the developmental trajectories of child brain structure and function, and increase the sensitivity to postnatal influences (Huizink & De Rooij, 2018; O'Donnell & Meaney, 2017).

Maternal postnatal mental health, in turn, may impact child development through negative changes to the child's environment, such as changes in daily interaction situations, problems in secure attachment formation and problematic parenting practices (Aktar & Bögels, 2017; Murray et al., 2008). Importantly, the postnatal environment has the potential to either attenuate or exacerbate the effects of maternal prenatal distress on child development (Kaplan, Evans, & Monk, 2008; Stein et al., 2014). The prenatal period is increasingly seen as a starting point for behavioral, cognitive and emotional development (Lickliter, 2018), and also considered as a key target for prevention of neurodevelopmental and psychiatric disorders in the offspring (Van den Bergh et al., 2018). While the lack of previous studies investigating maternal distress in each trimester and repeatedly during

early sensitive periods of child neurodevelopment hampers our understanding of the specific timing effects, it seems that the timing of exposure matters (Glover, O'Donnell, O'Connor, & Fisher, 2018; Van den Bergh et al., 2018).

Cognitive mechanisms, and more specifically attentional biases for emotional stimuli (e.g. bias towards threat) have been proposed to 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). Difficulty disengaging from threat may be one potential early marker of vulnerability (Keehn et al., 2012; Nakagawa & Sukigara, 2012), and attentional control, referring to cognitive ability to regulate allocation of attention, one possible mediating mechanism (Cisler & Koster, 2010). The fetal brain, and the developing attention systems, may be sensitive to maternal anxiety symptoms already during pregnancy, through fetal programming (Glover, 2011; Newman et al., 2016). Maternal symptoms may program the development of child attention and stress-regulation systems in a more reactive and vigilant direction, for instance by altering functioning of the hypothalamus-pituitary-adrenal (HPA) axis towards hyper-responsiveness to stressors (e.g. Glover, O'Connor, & O'Donnell, 2010) as well as the structure and functioning of brain areas involved in emotional processing, threat detection and self-regulation (e.g. the amygdala, the prefrontal cortex; Buss et al., 2012; Charil, Laplante, Vaillancourt, & King, 2010; Rifkin-Graboi et al., 2015).

An evolutionary perspective on the plasticity of the developing brain, including the structural and functional changes occurring in relation to prenatal adversity, considers these changes as adaptations to anticipated adverse postnatal environment (Frasch et al, 2017; Glover & Hill, 2012; Loman & Gunnar, 2010). However, in safe environment, propensities such as enhanced vigilance and reactivity may be maladaptive and markers for risk for later self-regulation problems such as anxiety (Glover, 2011; Van den Bergh et al., 2018). In addition to prenatal period, the first postnatal year, rich in close face-to-face interactions with the caregiver, may sensitize the child's socio-emotional

attention systems through exposure to the parent's emotional expressions (Aktar & Bögels, 2017) and social modelling (Aktar, Nikolić, & Bögels, 2017). The development of experience-dependent emotional brain systems is rapid and malleable to environmental factors during early development (Leppänen & Nelson, 2009; Leppänen, 2011; Pollak & Kistler, 2002; Teicher & Samson, 2016), yet the prenatal origins of the development of early socio-emotional attention systems is only beginning to be explored. To understand both typical and atypical early development, integration of prenatal period in shaping perceptual, cognitive and emotional development is of value (Lickliter, 2018).

Infants of mothers with anxiety are a potentially informative group to study the development of affect-biased attention during its earliest emergence. Currently, however, research at this developmental stage is scarce. Several studies have found higher rates of attention deficit disorders/more distracted attention in general (e.g. problems in sustained attention, cognitive control and inhibitory control) among children exposed to maternal prenatal anxiety (Glover, 2011; Van den Bergh et al., 2017, 2018). These effects have been more pronounced in boys than in girls (reviewed in Van den Bergh et al., 2017). Furthermore, two studies have reported disruptions in socio-emotional information processing, such as 9-month-old infants' elevated responses to fearful (vs. happy) auditory stimuli in relation to exposure to maternal self-reported anxiety symptoms during the first trimester (Otte, Donkers, Braeken, & Van den Bergh, 2015) and four-year-old children's attention preference for neutral visual stimuli (possibly interpreted as ambiguous) over unpleasant stimuli in relation to exposure to maternal anxiety symptoms during the second trimester, independently of maternal postnatal symptoms (Van den Heuvel et al., 2017). Together the research evidence implicates that prenatal exposure to maternal anxiety symptoms may alter child attention systems by disturbing inhibitory processes, enhancing vigilance, and/or sensitizing the developing attention systems to threat-stimuli (see also a recent review: Van den Bergh et al., 2018). It is possible that the alterations in attention systems originating from the prenatal period disturb early postnatal socio-

emotional interactions and the development of more complex socio-emotional skills (Peltola, Yrttiaho, & Leppänen, 2018), while this awaits further examination.

Studies examining the associations between maternal postnatal anxiety and child attention to faces have reported mixed findings. For example, Morales et al. (2017) found a positive association between maternal current general anxiety symptoms and infant (4─24 months) threat bias (angry vs. happy faces), whereas Leppänen, Cataldo, Bosquet Enlow, & Nelson (2018), assessing children repeatedly at 5, 7, 12, and 36 months using fearful, angry, happy, and phase-scrambled faces, did not find any associations between moderate levels of maternal self-reported anxiety or depressive symptoms and child threat bias. Studies, using clinical samples, such as Creswell et al. (2008) reported avoidance of fearful faces among 10-month-old infants of mothers with social phobia compared to infants of mothers with generalized anxiety or no anxiety. Mogg, Wilson, Hayward, Cunning, and Bradley (2012) reported an association between maternal panic disorder and attention bias to threat among daughters (9–14 years) of these mothers. Montagner et al. (2016) found that daughters (6–12 years) of mothers with an emotional disorder (mood, anxiety, or comorbid) demonstrated a threat bias, whereas sons only showed this effect if their mothers had a mood disorder. Finally, Ewing et al. (2016) did not find any cognitive biases among older children (5–9 years) of anxious versus non-anxious parents, as measured with an emotion recognition task and an ambiguous situations questionnaire.

While the diversity in paradigms and attention components measured, the age of the study participants as well as the use of clinical and sub-clinical populations complicate the interpretation of the findings, it seems that maternal pre- and postnatal anxiety symptoms may have an impact on the child's developing attention systems. Furthermore, the effects of prenatal maternal distress may be different for boys and girls (Sandman, Glynn, & Davis, 2013), while the origins of these differences are unclear (Van den Bergh et al., 2018). For instance, there may be sex-dependent differences in placental functions and/or epigenetic mechanisms (DiPietro & Voegtline, 2017; Van den Bergh et al.,

2018). Further, 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). Due to exposure to maternal psychobiological prenatal distress (e.g. self-reported anxiety or higher cortisol levels), girls may become more reactive and prone to anxiety, and boys less reactive and more externalizing/aggressive (Braithwaite et al., 2017; Sandman et al., 2013; Tibu, Hill, Sharp, Marshall, Glover, & Pickles, 2014). Furthermore, boys may show more problems in their general attentional control and top-down regulation (e.g. Van den Bergh et al., 2017) whereas girls may show deviances specifically in threat processing (Glover & Hill, 2012). However, results regarding the moderating role of child sex are mixed and more studies are needed to investigate these effects on different psychological phenotypes in infancy.

The present study

Moderate as well as clinical levels of maternal pre- and postnatal anxiety symptoms are associated with early risk for child self-regulation problems and later mental health disorders (O'Donnell, Glover, Barker, & O'Connor, 2014). Attention mechanisms may mediate this risk, and may be early markers of emotional vulnerability. Recent work suggests that in infancy self-regulation depends upon orienting attention systems, and early visual attention, in turn, associates with behavioral and emotional problems in childhood and adolescence (e.g. Papageorgiou & Ronald, 2017). To date, only a handful of studies have investigated the role of maternal prenatal anxiety symptoms on the development of infant socio-emotional attention processes. To our knowledge, no study has examined the possibly differential effects of maternal pre- and postnatal anxiety on infant attention to emotional faces, particularly to threat, although prenatal anxiety may set into motion both adaptive and maladaptive developmental trajectories in a sex-dependent manner. In the current study, we aimed to address this gap by investigating the associations between prospectively assessed maternal self-reported anxiety symptoms in each pregnancy trimester and 3 and 6 months after childbirth, and infant attention patterns to emotional faces. Due to a significant variability in anxiety symptom

trajectories during the pre- and postnatal periods (e.g. Bayrampour, Tomfohr, & Tough, 2016), the scarcity of studies reporting specific timing effects of exposure to maternal anxiety symptoms as well as the possible moderating effects of sex on child development (DiPietro & Voegtline, 2017; Lewis, Galbally, Gannon, & Symeonides, 2014), we chose to compare the associations between maternal anxiety symptoms assessed in multiple time-points during the perinatal period on infant attention patterns.

We assessed a large, community-based sample of 8-month-old infants. We used eye-tracking and an established attention disengagement paradigm (overlap) suitable for this age-range to study the impact of neutral, happy, and fearful faces and phase-scrambled faces on attention disengagement to distractors (e.g. Ahtola et al., 2014; Forssman et al., 2014; Nakagawa & Sukigara, 2012; Peltola, Leppänen, Palokangas, & Hietanen, 2008). Attentional biases towards threat have been observed across several different experimental tasks, and technically, if threatening (e.g. fearful or angry faces) and neutral stimuli are presented in the same task, anxious individuals likely show bias to threat/difficulty disengaging from threat (Cisler & Koster, 2010). However, infants also typically at the age of eight months, as part of normative development, show heightened threat bias (i.e. disengage less probably or more slowly from fearful faces vs happy and/or neutral) (Leppänen & Nelson, 2009; Leppänen, 2011). This evolutionary adaptive attention mechanism during the first year of life may be based on an automatic processing of threat that leads to orienting of attentional resources towards biologically prepared or high intense stimuli through increase in arousal systems (Cisler & Koster, 2010; Nakagawa & Sukigara, 2012). In later developmental stages, however, it may be modified by more effortful attention control systems (Nakagawa & Sukigara, 2012).

The aims of this study were to investigate the associations between both maternal pre- and postnatal anxiety symptoms and infant attention patterns to faces in the overlap paradigm.

Based on previous literature we predicted that 1a) maternal postnatal anxiety symptoms would associate with higher 'threat bias' (i.e. higher disengagement probability from fearful faces to

distractors as compared to happy and neutral faces). 1b) We were also interested whether already prenatal symptoms would associate with higher threat bias, as this is an unexplored area as yet. 1c) Further, we explored if infant sex would moderate this association.

Our second hypothesis was formed on basis of the following fact: high threat bias in the overlap paradigm may be either a result of higher general disengagement probability from centrally presented faces/non-face stimuli to distractors except when highly salient fearful faces are presented, and possibly be an indicator of weak attention control (as infants typically at this age show robust bias to faces vs non-face control stimuli; e.g. Leppänen et al., 2018; Peltola et al., 2018). Alternatively, high threat bias may be a result of an especially strong influence of fearful faces in reducing attention disengagement as compared to other faces. Based on literature of the associations between maternal prenatal anxiety and child's general attention control problems we hypothesized that 2a) maternal anxiety symptoms would positively associate with overall probability of disengagement from faces to distractors. 2b) Due to the possibly differential effects of maternal anxiety symptoms on the developmental outcomes of boys and girls, we investigated whether infant sex would moderate this association.

2 METHODS

2.1. Participants

The participants (n=362 mother-infant dyads) are part of an ongoing pregnancy cohort, the FinnBrain Birth Cohort Study (N=3808 families) and were recruited at the first ultra-sound visit at gestational week (gwk) 12. They belong to a nested case-control population (the Focus Cohort) embedded in the main Cohort, that has been designed to investigate the effects of maternal prenatal stress (PS) on child development. Inclusion in the Focus Cohort required scoring in the highest or lowest ~25th percentiles on depression, anxiety, and/or pregnancy-related anxiety symptom questionnaires across pregnancy (see Karlsson et al. 2018). All participating mothers provided informed consent, also on behalf of their infants for this particular study. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol. The study was conducted in full compliance with the Helsinki Declaration.

2.2 Infant neurodevelopmental study

437 (63.0% of reached, 89.5% of initially agreed) Focus Cohort mother-infant dyads participated in the laboratory visit, where altogether 421 eye-tracking, 427 temperament and 197 mother-infant-interaction measurements were conducted when the infant was eight months (corrected for gestational age). The recruited mothers tended to have higher education level (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; $\chi^2[2] = 9.02$, $p = .01$, effect size $\eta_p^2 = 0.12$) and were more likely primiparous than declined mothers (56.9% vs. 45.2%; $\chi^2[1] = 7.06$, $p < .01$, $\eta_p^2 = .10$).

Infants' attention to emotional faces was assessed with eye-tracking, along with a laboratory assessment of temperament and mother-child interaction. Psychologists or advanced psychology students conducted the study visits of 1 to 1.5 hours in the FinnBrain laboratories at the University of

Turku. Parents were informed about the study procedures and their option to withdraw from testing at any time without providing a specific reason.

Of the initial 421 infants, 31 (7.4%) failed to either provide data (i.e. were too fussy) or their data was invalid due to technical problems. For the remaining participants, 363 (93.1%) provided ≥3 valid trials per each stimulus condition and were included in the sample. Of these, 362 had information on maternal anxiety symptoms during pregnancy and after birth, and formed the final sample of our analyses. Those mothers whose infants did not provide satisfactory data for final analyses, did not differ from those whose infants provided data in terms of parity (primi vs multiparity, p = .50), education (p = .39), or maternal self-reported anxiety symptoms at different assessment points (p = .39 – .85).

Of the final sample, 45.7% were girls (data from national birth registries, National Institute for Health and Welfare, www.thl.fi). The mean length of gestation in this sample was 39.92 weeks, 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). 58.3% were primiparous. Educational level was distributed as follows: 28.1% (< 12 years), 36.2 % (12-15 years), and 33.7% (> 15 years).

2.3 Measures of maternal pre- and postnatal anxiety

Symptom Checklist-90/anxiety subscale (SCL-90; Derogatis et al. 1973; Holi et al., 1998), with good psychometric properties (Prinz et al., 2013), was used to assess maternal general anxiety symptoms at gwk 14, 24, and 34, and 3 and 6 months postpartum. This subscale consists of 10 items scored on a 5-point Likert scale (from 0 to 4). The range of the total sum score is 0-40. In this study, a sum score was used. The questionnaires were either mailed to the participants or filled out on-line. The SCL-90 showed good internal consistency in each assessment point (α = 0.85–0.90).

2.4. Eye-tracking of infant attention to facial expressions

2.4.1 Procedure

During eye-tracking, the infant sat on the parent's lap at a 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). The researcher used another independent computer to manage the measurement. (See e.g. Forssman et al., 2017, for an illustration of the similar study setting)

2.4.2. Gaze acquisition and raw data processing

The overlap paradigm (Aslin & Salapatek, 1975; e.g. Peltola et al., 2009) was used. It assesses disengagement of attention from a centrally presented face (neutral, happy, fearful) or a non-face control stimulus to a lateral distractor. Photographs of two different women portraying different emotions together with scrambled non-face control pictures (Peltola et al., 2009) were used. Altogether, a set of 48 trials was presented, including 12 trials per condition (each emotion and the control picture), in a semi-random order. Figure 1 illustrates the overlap paradigm.

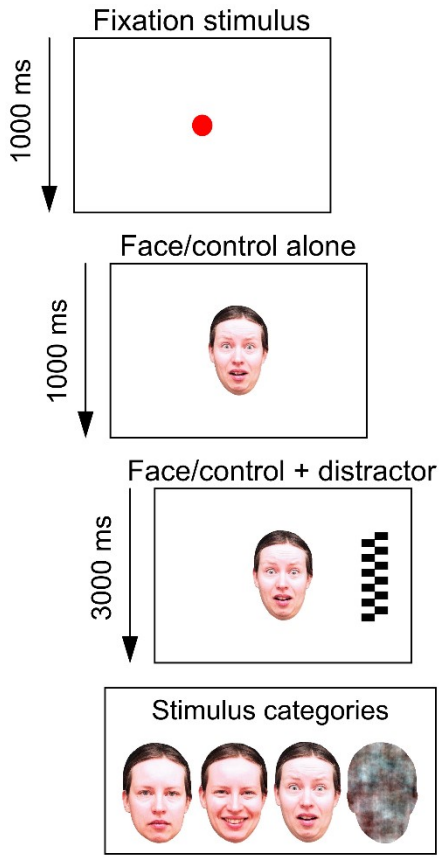

Figure 1 The overlap paradigm. A face or a control stimulus was presented in the center of the screen after the infant fixated on a fixation stimulus at the screen center. A distractor appeared to the right or to the left side of the central stimulus after 1000ms from face/control onset. The central stimulus was presented until the end of each trial (4000ms), overlapping in time with the distractor. The bottom picture presents the four stimulus categories used. (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.)

The trial data, comprising of timestamps for the onset times of central and lateral pictures and the xy coordinates of the participants' gaze position (500 samples/second) were stored as text files, and analyzed using automated MATLAB (Mathworks, Natick, MA) scripts and identical criteria to prior studies (e.g. Leppänen, Forssman, Kaatiala, Yrttiaho, & Wass, 2015). The following quality control criteria, based on prior studies (Leppänen et al., 2015) to retain trials for the analysis, were used: 1) Trials had to have sufficiently long fixation on the central stimulus (i.e., >70 % of the time) during the time preceding gaze disengagement or the end of the analysis period (i.e., 1000ms from the appearance of the lateral distractor), 2) Trials had to have a sufficient number of valid samples in the

gaze data (i.e., no gaps >200 ms), 3) Trials had to have valid information about the eye movement from the central to the lateral stimulus (i.e., the eye movement did not occur during a period of missing gaze data).

2.4.3. Eye-tracking variables

Disengagement probability, DP

An infant's disengagement probability (DP) was defined as the infant's probability to disengage his/her attention from the central (fearful, happy, neutral face, or a non-face) to the lateral stimulus (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 ($p > 0.05$).

Threat bias

The threat bias was defined as the difference between infants' tendency to disengage from neutral/happy faces and their tendency to disengage from fearful faces. Technically, the threat bias was defined as the ratio of the average odds to disengage from the happy and neutral conditions to the odds to disengage from fearful condition.

2.4.4. Statistical analyses

First, missing anxiety scores (see Table 1 for the number of missing scores) were imputed using MissForest (Stekhoven & Bühlmann, 2012), an iterative imputation method based on a random forest, 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 (N=362) had at least one prenatal score and were therefore included in the analyses concerning the prenatal anxiety.

The DPs were modeled using mixed effects logistic regression (MELR) models with the binary disengagement variable. All our MELR models had 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 (see Appendix, Figure S1b), 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. (See Kataja et al., (accepted for publication) for more detailed discussion on the trial number dependency as well as the general features of the attention patterns in this sample of infants.) Our first hypotheses, 1a) and 1b), 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

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

was used.

Hypothesis 1c), 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 TNS term, to get trial number independent DPs.)

Hypothesis 2a), 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 2b), 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 analyses were carried out with the full sample (N=362/341) and with excluding infants born <37 gwk (N=13). As this did not impact the results, the final analyses were conducted with the full sample. 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. Figures S1a, S1b (Appendix) and Figure 2 were made using R package ggplot2 (Wikham, 2009).

3 RESULTS

3.1. 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 1.

Table 1 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 (4.10)	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 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) between maternal anxiety symptoms at consecutive sample points varied between .62–.77 (p values < .001).
) N=341

3.2. The overall probability of disengagement in the whole sample

Across the full sample, there were clear differences between disengagement probabilities (DPs) for the different face expressions. Estimated DP was lowest for the fearful faces, and highest for the control stimuli, DPs for neutral and happy faces being between them. See Kataja et al. (accepted for publication) for the reporting of these results. There was no difference between sexes neither in the overall nor condition-specific DPs. These results of lower probability of disengagement from fearful faces as compared to other face stimuli (happy, neutral), and from faces (fearful, happy, neutral) than non-face control stimuli in the whole-sample level replicate the finding from several earlier infant

studies (e.g. Morales et al., 2017; Nakagawa & Sukigara, 2012; Peltola, Forssman, Puura, van IJzendoorn, & Leppänen, 2015; Peltola et al., 2018).

Also, similarly to Peltola et al. (2008), the reaction times (i.e. 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).

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

Testing hypothesis 1a) showed that the associations between infant threat bias and maternal postnatal anxiety symptoms at 3 months (p = .092) or 6 months postpartum (p = .18) were not significant. However, with regard to hypothesis 1b), there was a positive relation between infant threat bias and maternal prenatal anxiety symptoms at gwk 14 (p = .021) and gwk 34 (p = .046), but not at gwk 24 (p = .42). After controlling for maternal anxiety symptoms at 6 months postpartum (the closest assessment point of maternal symptoms in relation to infant outcome) the association between maternal symptoms at gwk 14 (p = .037), but not at gwk 34 (p = .074), and infant threat bias remained significant. Testing hypothesis 1c) showed that the effects did not differ between boys and girls (all p values > .50). Table 2 shows all the results of the association between maternal anxiety symptoms and infant attention patterns.

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

With regard to our hypothesis 2a), we found that there was no significant relation between maternal anxiety symptoms in any assessment point and infant overall DPs (all p values > .21) in the whole sample. However, with regard to hypothesis 2b), the relation between maternal anxiety symptoms and infant overall DPs differed between boys and girls at 3 months (p = .044) and 6 months (p = .019), but not at any prenatal assessment points (all p values > .15). Table 2 shows the results of the

statistical comparisons and Figure 2 illustrates the attention patterns of the boys and girls separately for each assessment points.

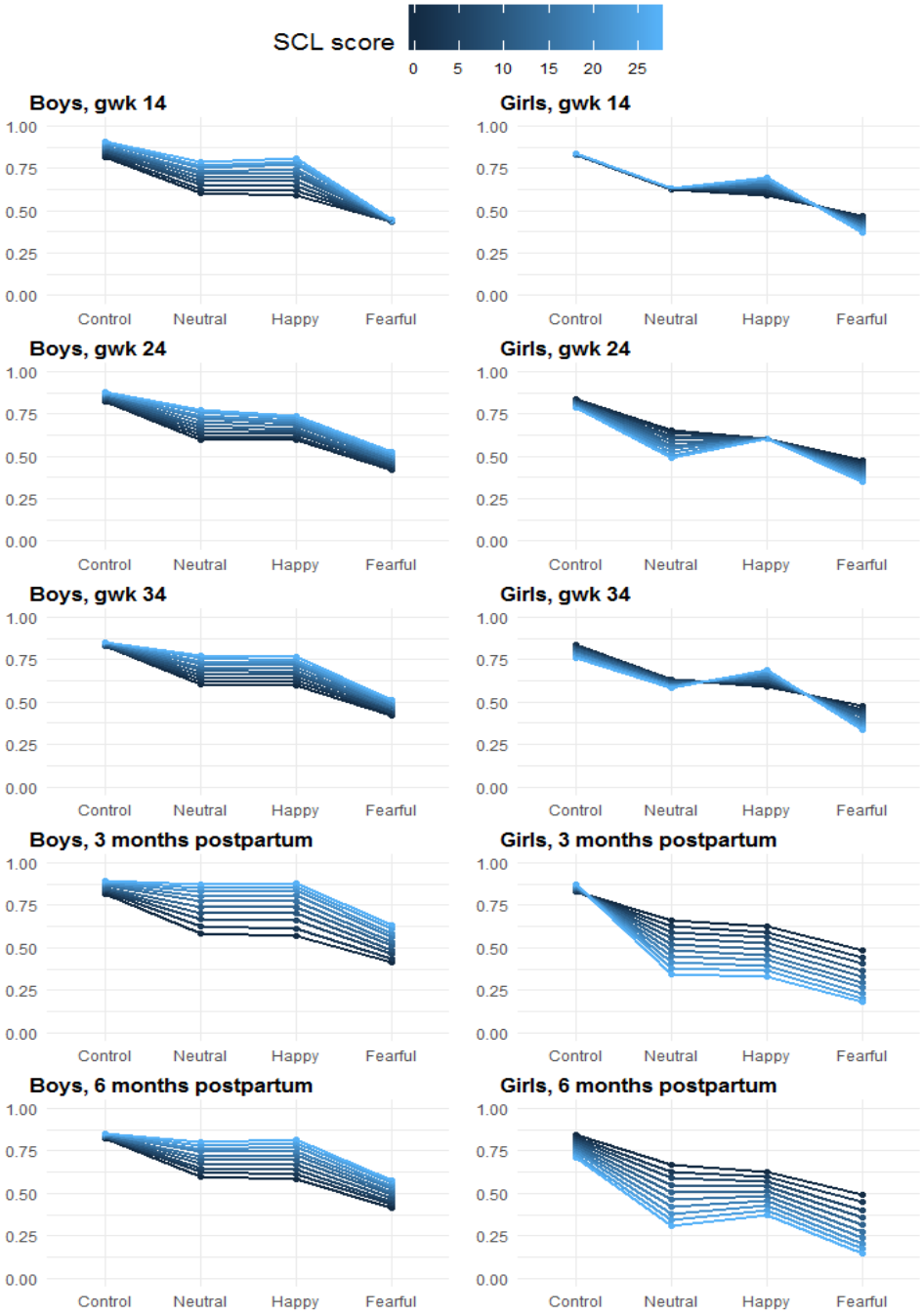

Figure 2 The predicted DPs for each condition (3 facial expressions, control stimulus) at the different levels of maternal anxiety symptoms (SCL-90) at different time points' separately for male and female infants at eight months. This figure illustrates how maternal anxiety symptoms are associated with the infant attention patterns (e.g. overall DPs, Threat bias).

Table 2 The results of the association between maternal anxiety symptoms and infant attention patterns

	Hypothesis 1a)	**1b)**	**Hypothesis 1c)**		**Hypothesis 2a)**		**Hypothesis 2b)**	
Timepoint	Effect size[1)]	p-value	Effect size[2)]	p-value	Effect size[3)]	p-value	Effect size[4)]	p-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 (multiplicative factor) of one point increase in SCL score to the threat bias odds ratio (when 6 months postpartum SCL is not/is controlled for).
[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.

4 DISCUSSION

This study examined the associations between repeatedly assessed maternal pre- and postnatal anxiety symptoms (gwk 14/24/34 and 3/6 months postpartum) and infant's processing of faces at the age of eight months. We used an attention disengagement paradigm (overlap), used in several previous infant studies (e.g. Forssman et al., 2014; Leppänen et al., 2018; Morales et al. 2017; Nakagawa, & Sukigara, 2012; Peltola, Hietanen, Forssman, & Leppänen, 2013), to investigate infant attention disengagement from neutral, happy, fearful faces, and non-face control stimuli to distractors and specifically the impact of fearful vs other faces on attention disengagement (i.e. a measure of fear/threat bias). We were interested whether the timing of maternal symptoms would be related to infant attention patterns (both threat bias as well as overall disengagement probabilities), and whether infant sex would moderate these associations.

Generally, the attention patterns in the whole sample corresponded with the finding of several previous studies of the age-typical attention bias to fearful faces (e.g. Morales et al., 2017; Nakagawa & Sukigara, 2012; Peltola et al. 2015, 2018; see also Kataja et al., accepted for publication, for more thorough description of this particular sample). With regard to our hypotheses, we first predicted that maternal postnatal anxiety symptoms would associate with higher threat bias (i.e. lower probability of disengagement to lateral distractors from fearful faces vs happy and neutral) in infants, as some (Morales et al., 2017), but not all (Leppänen et al., 2018) studies have found maternal current anxiety symptoms to predict higher threat bias in infants. However, as a novel approach, we were also interested in the possibility of the prenatal maternal symptoms to associate with infant attention patterns, and also the possibly distinct associations of maternal distress at different measurement points in relation to infant outcomes. 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 (our 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 symptoms, assessed at three and six months postpartum, did not associate with higher threat bias in infancy. Our results suggest, that the timing of maternal symptoms may matter, and the role of the prenatal period may be important when investigating the associations between maternal anxiety and child attention development.

In infancy, self-regulation depends upon orienting attention systems and deviances in the early orienting systems may associate with behavioral and emotional problems in 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. Earlier studies have suggested that in healthy development, the normative threat-related attention biases may dissipate (Dudeney et al., 2015) but in psychopathological development, may become overexpressed (Kindt, Bögels, & Morren, 2003; Morales, Fu, & Pérez-Edgar, 2016; Schehner et al., 2012; Troller-Ronfree, Zeanah, Nelson, & Fox, 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 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 vs happy auditory stimuli in 9-month-old infants in relation to exposure to high maternal anxiety in 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 do 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 current (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 (angry vs 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 in 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 between 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 mechanism (Papageorgiou & Ronald, 2017).

Secondly, in this study we explored the associations between maternal pre- and postnatal anxiety symptoms and the overall disengagement probabilities of the infants. 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). Technically, a high threat bias in the overlap task may 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. This study question is of importance for our understanding of the possible individual and sex differences in attention biases in infancy. We found that maternal anxiety symptoms were not associated with the overall probability of disengagement in any assessment point in the whole sample. However, infant sex moderated the associations between maternal postnatal anxiety symptoms and 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 postnatal environment may shape child attention systems differently for boys and girls. In our sample, boys, in relation to maternal postnatal anxiety symptoms, disengaged nearly equally probably from non-face, control, and happy faces whereas girls showed overall lower probability of disengagement from all face stimuli. 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.

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). According to the predictive-adaptive-response model, exposure to early-life adversity confers an advantage for child development if there is congruence between pre- and postnatal environments (e.g. Sandman, Davis, & Glynn, 2012). Thus, in some circumstances, the observed behavior that deviates from 'normalcy' serves an adaptive role in the environment of the individual, whereas in other environments it may become maladaptive and lead to later pathology. Heightened threat bias, found in our sample of infants of mothers with prenatal anxiety symptoms may reflect adaptations to postnatal environment and its anticipated threats (of which the mother's anxiety symptoms during pregnancy have been signals of; 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, Colonnesi, De Vente, Majdandžić, & Bögels (2017) reported a positive association between maternal life-time and prenatal anxiety and infant heightened attention towards mother's face in face-to-face interaction.

One may speculate that the attention pattern of heightened vigilance towards all faces serves an adaptive role for the girl infants also outside face-to-face interaction situations with the parent. Experience-independent differences between genders 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) 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). Moreover, the prevalence of anxiety disorders is twice as high in women as in men (Bandelow & Michaelis, 2015). It remains to be seen whether the pattern of enhanced attention to all faces is related to higher risk for later affective disorders.

In conclusion, our study illustrates that maternal anxiety symptoms during the pre- and postnatal periods may be associated with infant attention patterns to socio-emotional signals. Maternal prenatal anxiety may increase threat bias in infants, whereas maternal postnatal anxiety may associate with infant attention patterns differently for boys and girls. The investigation of attentional biases in 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 in infancy among population at-risk for anxiety or other self-regulation problems and how these effects may be related already to prenatal period. However, not all children are affected by maternal anxiety, or 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).

Strengths and limitations

There are several strengths to our study. We used a prospective design with a large sample of mother-infant pairs and repeated measures of maternal anxiety symptoms from early pregnancy until six months postpartum. Our sample enabled us to use regression method at several sensitive time points with regard to infant development, to better account for the graded differences in exposure to maternal anxiety symptoms. It also enabled us to compare the effects between boys and girls.

There are also some limitations. The number of mothers suffering from very severe symptoms (and infants exposed to severe symptoms) was relatively small. However, there is some evidence of a dose-response effect of moderate to severe maternal anxiety symptoms on child developmental outcomes (Glover, 2011). Therefore, studying the impact of subclinical anxiety symptoms is also of interest. Moreover, we did not control for the possible effects of maternal depressive symptoms or the comorbidity of 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, paternal anxiety symptoms were not investigated in this study, confounding our understanding of early differences in infant attention processes.

Acknowledgements: The authors wish to thank the FinnBrain study participants for their contribution, and the staff and assisting personnel for their invaluable work for the logistics of the project. We also wish to thank PhD Jukka M. Leppänen for sharing his expertise in infant eye-tracking data analysis.

This work was supported by: State Grant for Clinical Research (EVO), Academy of Finland (253270, 134950, 308176), Jane and Aatos Erkko Foundation, Signe and Ane Gyllenberg Foundation, Yrjö Jahnsson Foundation, Turku University Foundation, Finnish Cultural Foundation, Suomen Aivosäätiö

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APPENDIX

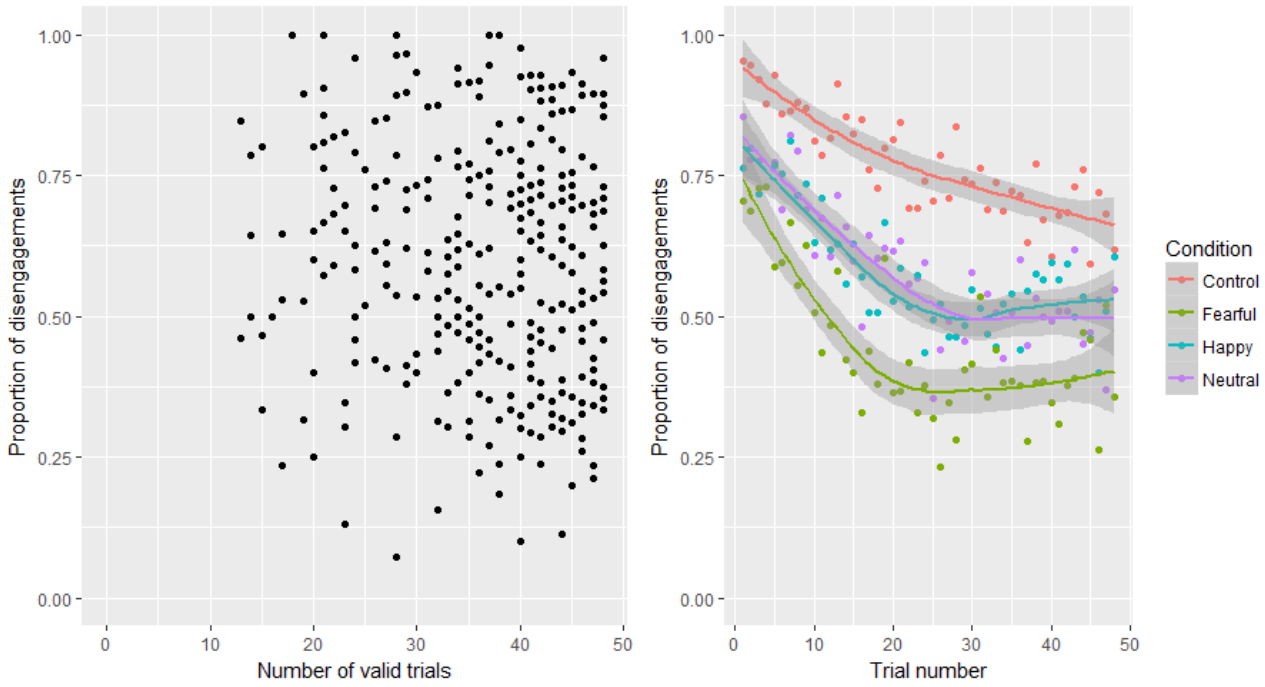

Figure S1a Each infant's observed disengagement proportions plotted against the number of valid trials, illustrating the large individual differences in the infants' overall DPs. *Figure S1b* The observed proportions of disengagements (for the whole sample) are plotted as a function of trial number for each condition, illustrating the dependence of the DPs on the trial number.