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Reported maternal childhood maltreatment experiences, amygdala activation and functional connectivity to infant cry

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Abstract

Maternal childhood maltreatment experiences (CMEs) may influence responses to infants and affect child outcomes. We examined associations between CME and mothers' neural responses and functional connectivity to infant distress. We hypothesized that mothers with greater CME would exhibit higher amygdala reactivity and amygdala–supplementary motor area (SMA) functional connectivity to own infant's cries. Postpartum mothers ($N=57$) assessed for CME completed an functional magnetic resonance imaging task with cry and white-noise stimuli. Amygdala region-of-interest and psychophysiological interaction analyses were performed. Our models tested associations of CME with activation and connectivity during task conditions (own/other and cry/noise). Exploratory analyses with parenting behaviors were performed. Mothers with higher CME exhibited higher amygdala activation to own baby's cries *vs* other stimuli ($F_{1,392}=6.9$, $P<0.01$, $N=57$) and higher differential connectivity to cry *vs* noise between amygdala and SMA ($F_{1,165}=22.3$, $P<0.001$). Exploratory analyses revealed positive associations between both amygdala activation and connectivity and maternal non-intrusiveness ($Ps<0.05$). Increased amygdala activation to own infant's cry and higher amygdala–SMA functional connectivity suggest motor responses to baby's distress. These findings were associated with less intrusive maternal behaviors. Follow-up studies might replicate these findings, add more granular parenting assessments and explore how cue processing leads to a motivated maternal approach in clinical populations.

Key words: maltreatment; mother–child relationships; infant mental health; amygdala; neuroimaging

Introduction

Exposure to childhood adversity is unfortunately common and associated with 26% of adult-onset psychiatric disorders and an even higher percentage of child- and adolescent-onset psychiatric disorders (Green *et al.*, 2010) and is associated with worse psychiatric outcomes (Melhem *et al.*, 2019), particularly in women (Goldberg *et al.*, 2019). As women reporting childhood maltreatment experiences (CMEs)—specifically those linked to interpersonal violence (i.e. abuse and witnessed domestic violence)—become mothers, there are data to suggest that they

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may be more likely to engage in less sensitive, more intrusive and harsher (i.e. more hostile) parenting behaviors (Cross et al., 2016; Lomanowska et al., 2017; Greene et al., 2020), be at higher risk for abuse of their own children (Smith et al., 2014) and have poorer offspring behavioral outcomes (Rijlaarsdam et al., 2014).

Although much work regarding suboptimal parenting behaviors has been done in maternal populations who struggle with depressive symptoms (Pridham et al., 1999; Barrett and Fleming, 2011; Ammerman et al., 2012; Apter-Levy et al., 2013; Moses-Kolko et al., 2014; Ho and Swain, 2017), less work has been done in community populations reporting CMEs, but who are not experiencing significant psychiatric symptoms. However, studies including people who report early life abuse or poor experiences of parenting have suggested that early life adverse exposures may worsen parenting outcomes for mothers, potentially in ways different from or additive to depression (Lang et al., 2010; Juul et al., 2016; Kluczniok et al., 2016). Since quality of caregiving in early life exerts an important influence on outcomes across the life span and may buffer against risks, promoting resilience (Gunnar et al., 2015), it is important to understand the underlying mechanisms of how maternal maltreatment experiences impact parenting behaviors.

One important mechanism for understanding how parenting may be affected by maternal maltreatment experiences is how mothers process and respond to their infant's distress cues, one of the most salient of which is an infant's cry. Functional MRI studies have utilized cry stimuli and matched white noise stimuli to interrogate maternal neural responses to infant distress (Kim et al., 2011, 2016; Messina et al., 2015; Bornstein et al., 2017). The amygdala has been implicated in maternal processing of infant auditory cues (Kim et al., 2011; Ho and Swain, 2017). Limited work in maternal populations reporting a history of early abuse or neglect has revealed higher activation in salience network and premotor areas to their own baby's cries (Wright et al., 2017), as well as greater physiological arousal measured by handgrip while listening to infant cries (Buisman et al., 2018). These findings are consistent with the critical function of infant distress signals for establishing and maintaining motivated maternal behaviors (Lomanowska et al., 2017).

In addition to these limited studies in mothers reporting their own CMEs, studies in community populations have found increased amygdala as well as increased response in the supplementary motor area (SMA) to cries compared to non-distress stimuli, which may be particularly accentuated in females (Seifritz et al., 2003; Sander et al., 2007; Bornstein et al., 2017). Although these tasks often do not have a behavioral component or response in the scanner, the activation of both amygdala and motor planning regions in response to infant cries evokes the question of how the amygdala may interact with other areas in response to infant distress, particularly with respect to data suggesting that a stable and adaptive maternal response across cultures to crying infants is to hold or speak to them (Bornstein et al., 2017). Further, this line of work is consistent with the known function of amygdala to mediate associations between affective stimuli and behavioral responses (Porter et al., 2015).

Beyond understanding neural responses to infant cries, given our interest in the interface between maternal detection and evaluation of infant cues and ensuing maternal behaviors, we also sought to examine the functional connectivity between the amygdala and the SMA given prior research suggesting an important role for these areas (Bornstein et al., 2017). To test whether amygdala activation and connectivity were associated with 'real world' parenting behaviors, we examined mother–infant free play observational data, which were coded using the Emotional Availability Scale which codes for four different aspects of maternal behavior during mother–infant observation (Biringen, 2000). Changes in maternal sensitivity, intrusiveness and hostility have been most associated in the literature with mothers who either struggle with psychiatric symptoms or increased life stressors (Feldman et al., 2009; Atzil et al., 2011; Kim et al., 2011, 2016, 2017; Joosen et al., 2013; Rijlaarsdam et al., 2014; Smith et al., 2014; Stacks et al., 2014; Smaling et al., 2017). Our preliminary focus on these three constructs is due to their importance in responses to infant distress, including maternal empathy (Swain et al., 2007; Lomanowska et al., 2017).

We hypothesized that mothers with higher levels of childhood maltreatment experiences would exhibit higher amygdala activation and increased differential functional amygdala-SMA connectivity to their own baby's cry *vs* other stimuli—specifically to their own baby's cry *vs* another mother's baby cry, which would in turn be associated with lower maternal sensitivity, higher maternal intrusiveness and higher maternal hostility.

Method

Participants/Recruitment/Demographics

We recruited a community sample of English-speaking primiparous mothers between 18 and 40 years old utilizing advertisements in local and social media, the University of Denver Psychology volunteer list and Denver Health OB clinic and Women Infant and Children program ($N = 61$). Phone screening was performed, with exclusion criteria being maternal opioid/illicit drug use (self-report), neurological or psychiatric illness (except depression or anxiety disorders), self-reported peripartum medical illness or infants >1 night in NICU. Research protocol was approved by the University of Denver Institutional Review Board and informed consent was acquired. Home visits were completed, during which demographic details e.g. age, race and ethnicity, birth/nursing history, socioeconomic status and lifetime self-reported psychiatric diagnoses, Beck Depression Inventory (Beck, 1961) and Spielberger Trait and State Anxiety Inventory (Spielberger, 1970) were acquired. We examined associations between demographics and dimensional scales using independent samples t-tests or correlation with childhood maltreatment experience (CME) load, respectively, for categorical and continuous variables, to determine which factors/covariates to include in analyses, barring concerns for collinearity. During home visit, personalized infant cry stimuli were collected when babies experienced mild discomfort (i.e. diaper changing) but not when they were in pain.

Assessment of CME

CMEs of mothers were assessed using the Risky Families Questionnaire (Repetti et al., 2002). We utilized responses to three relevant questions from this scale to assess childhood maltreatment experiences: physical abuse, verbal abuse and witnessed domestic violence, all of which have been included in the prior literature (Bailey et al., 2012; Scott et al., 2012) and which affect psychiatric outcomes over the lifespan (Teicher et al., 2006). Items were rated via Likert scale, ranging from 0 (never) to 3 (all the time). We performed linear transform to avoid zero values by adding 1 to each sub-score and then adding 3 scores together to form a composite index of CME load, for a possible total score ranging from 3 to 12. The basis for examining the scale in this manner is rooted in the literature, which suggests that differences in experiences associated with direct conflict or family violence compared to other adverse experiences (e.g. divorce) have been associated with distinct outcomes in prior studies (Narayan *et al.*, 2017; Atzl *et al.*, 2019). Further, we assessed the relationships of psychological symptom scales with this maltreatment subscale in order to assess for possible limitations with using this method.

Mother–infant observation and behavioral coding

For each dyad, we obtained a 15-minute video recording of mother and infant interacting with one another. Videos were coded by two trained coders (intra-class correlation = 0.84) using the Emotional Availability Scale, a macro-coding scale which assigns one score (1–7) for each of four parent subscales (sensitivity/non-intrusiveness/structuring/non-hostility) and two child measures (child involvement/child responsiveness) (Biringen, 2000). We examined maternal sensitivity, non-intrusiveness (higher score and less intrusive) and non-hostility (higher score and less hostile) given their particular relevance to stress responses and based on prior studies (Feldman *et al.*, 2009; Atzil *et al.*, 2011; Kim *et al.*, 2011, 2016, 2017; Joosen *et al.*, 2013; Rijlaarsdam *et al.*, 2014; Smith *et al.*, 2014; Stacks *et al.*, 2014; Smaling *et al.*, 2017).

Infant cry paradigm

The functional magnetic resonance imaging (fMRI) paradigm has been previously validated in multiple samples of new mothers during the postpartum period, and a subset of these data from the Infant Development, Environment and Attachment cohort has been reported ($N = 27$ and $N = 53$) (Kim *et al.*, 2016, 2020). fMRI task was a block design with 10 20 s blocks of each stimulus type in counterbalanced order (own/other cry/white-noise stimuli), with implicit baseline modeled over two runs (∼10 min per run for a total of 20 min). The same control cry was used for all participants and was rated by a sample of unrelated adults to be average in intensity. Infant cry stimuli were created using Cool Edit Pro Version 2.0 program (Syntrillium Software, Phoenix, AZ). Personalized cry and white-noise stimuli were edited, removing background noise. Separate white-noise stimuli were matched to the sound envelope of own and other infant cry, which is a measure of amplitude corresponding to ebb and flow of each cry. Volume was adjusted to be comfortable and audible. fMRI task was administered using E-Prime Version 2.0 (Psychology Software Tools, USA) with 8–12 s interstimulus interval (mean = 10 s). Mothers were asked to attend to stimuli and to experience their feelings and thoughts.

fMRI acquisition and pre-processing

Functional and structural scans were acquired at the Intermountain Imaging Consortium at CU Boulder (3T Siemens Trio or Prisma scanner). We included a parameter reflecting which scanner was used in analysis. Functional T2* images were acquired with parameters: 3 × 3 × 3 mm voxel-size, TR = 2300 ms, TE = 27 ms, FOV = 192 mm and flip angle = 73. High-resolution magnetization-prepared rapid gradient-echo (MP-RAGE) anatomical scans were collected with slice thickness 1.0 mm (Trio) or 0.8 mm (Prisma). We conducted pre-processing and constructed single-subject models utilizing Analysis of Functional NeuroImages software (AFNI) (Cox, 1996). Pre-processing pipeline included the following steps: (i) remove four pre-steady state volumes; (ii) slice-timing correction; (iii) alignment and non-linear registration to Talaraich template and (iv) smoothing (6 mm full width half maximum); censor volumes > 0.5 mm of motion in any direction. Single-subject models included four conditions (own cry/other cry/other noise/own noise) and six motion parameters (three translational and three rotational). We excluded four participants due to censor fraction >20% ($N = 1$); Risky Families Questionnaire unavailable ($N = 2$) and wrong cry stimulus ($N = 1$).

fMRI region of interest analyses

We performed anatomical region of interest (ROI) analyses by extracting percent signal change from bilateral anatomical amygdala using DD Desai MPM atlas (Desikan *et al.*, 2006; Destrieux *et al.*, 2010). Secondary analyses of anatomical amygdala ROI were performed in R version 3.5.0 (R Core Team, 2017). We utilized linear mixed-effects models, initially including task-related fixed effects in models (sound—cry *vs* noise; identity (ID)—own *vs* other infant), fixed effects of scanner and side (right *vs* left amygdala) and random effect of participant. Following these initial analyses of main effects, we examined interactions, removing higher level interactions if not significant. Next, we sequentially added covariates/cofactors which were associated with CME. Significant interactions were decomposed utilizing within-factor *post hoc* analyses. Although we had limited lifetime self-reported psychiatric diagnostic data in this community sample, we performed a sensitivity analysis for the anatomical ROI analysis to examine whether our primary analysis indicated an effect of psychiatric diagnosis.

Psychophysiological interaction (PPI) analyses

We performed generalized PPI analyses (McLaren *et al.*, 2012) with seeds defined by anatomical amygdala ROI (Desikan *et al.*, 2006; Destrieux *et al.*, 2010). For each run, we extracted amygdala time series (right and left separately) without censoring to prevent temporal discontinuities from interfering with modeling interactions between amygdala time series and task regressors. Next, we deconvolved seed time series and created interaction regressor including task conditions × seed time-series interaction. Single-subject models were constructed in AFNI including six motion regressors (per run), task condition regressors and PPI regressors for condition × time-series interactions. Group models were constructed using 3dLME with task conditions (sound/ID), scanner, CME load, Spielberger Trait Anxiety and random participant effect. We included similar interactions to ROI analyses. Cluster determination for group analysis was performed utilizing 3dClustSim within group 70% overlap epi_anat mask in AFNI (ACF option, $P < 0.001$, NN3), yielding $k > 33$.

Exploratory maternal behavior analyses

Given non-normally distributed Emotional Availability Scale data, we performed Spearman correlations to test whether CME and/or amygdala activation were associated with maternal sensitivity and non-intrusiveness, which are reported in the corresponding results section.

Whole brain analysis

Exploratory whole-brain analysis is included in Supplementary Data (Table S2).

Results

Participants/Demographics

Our population included primiparous mothers (Table 1) from 19 to 37 years old (mean = 26 yo). With respect to ethnicity, 46% of mothers identified as Hispanic/Latino. With respect to race, 53% identified as Caucasian, 2% Asian, 5% Black/African American, with the remaining 40% from other groups or multirace. There were no significant correlations between CME load and income-to-needs ratio (last 12 months), days postpartum, maternal age or Beck Depression Inventory scores (Pearson correlation $ps > 0.05$). There were no between-group differences in CME load (chi-square $ps > 0.05$), ethnicity or race, breastfeeding history or lifetime history of self-reported psychiatric diagnosis. There was a relationship between CME load and Spielberger Trait ($r = 0.36$; $P = 0.005$, $N = 57$) and State ($r = 0.34$; $P < 0.01$, $N = 57$) anxiety scores. There was no association of the Beck Depression Inventory with the CME load scale in this community population with low rates of psychopathology, likely due to a restricted range of Beck Depression Inventory scores. There was no association between CME and maternal sensitivity, non-intrusiveness or non-hostility ($ps > 0.05$). However, there was a relationship between amygdala activation to own baby's cry and non-intrusiveness (mothers less intrusive with higher activation, $\rho = 0.28, P = 0.03$ and $N = 57$) but not with sensitivity.

Anatomical ROI analyses

In bilateral amygdala, our final model included the following fixed effects—sound × ID × CME load + Side + Scanner + Spielberger Trait Anxiety—and random effect of participant. There was a three-way interaction of CME × sound × ID ($F_{1,392} = 6.9$, $P < 0.01$). The interaction was driven by a strong relationship between higher amygdala reactivity to own *vs* other cry and higher CME load (Pearson partial correlation including all model covariates, $r = 0.25$, $P < 0.01$). Further, there was another weaker association of higher amygdala reactivity to own cry *vs* the matched noise stimulus and higher CME load (Pearson partial correlation including all model covariates, $r = 0.22$, $P < 0.05$) (Figure 1). There was no effect of self-reported lifetime psychiatric diagnosis in a sensitivity analysis when lifetime diagnosis was added into the primary analysis. There were no other interactions and no effect of side, scanner or trait anxiety score. Identification of potentially influential points utilizing Cook's *d* yielded 2 points (results unchanged when removed). While there was no association between amygdala response to own infant cry and sensitivity or non-hostility, there was a positive correlation between non-intrusiveness and amygdala activation to own infant cry ($\rho = 0.28$, $P < 0.05$ and $N = 57$) (Supplementary Figure S1), which was robust to removal of one potential influential point. We selected own infant cry contrast as it was the primary driver of the three-way interaction. We also display sound × ID interaction to assist readers in visualizing relationships between amygdala activation during task conditions (Supplementary Figure S2).

PPI analyses

We utilized a similar model for the anatomical ROI analysis in the whole-brain PPI with the following fixed effects—sound × ID × CME load + scanner + Spielberger Trait Anxiety—and random effect of participant. Group generalized PPI analysis of left amygdala seed revealed CME × sound interaction ($F_{1,165} = 22.3$, $P < 0.001$) in R SMA ([−2, −5, 57], $k = 94$, Figure 2A) and L middle frontal gyrus (MFG) ([35–38 36], $k = 44$, Figure 2B). *Post hoc* analyses examining cry *vs* noise contrast revealed that in both areas, increased differential response to cries compared to noise was associated with CME load (all $Ps < 0.05$), which was driven by associations of increased CME load with decreased connectivity with L amygdala during noise stimuli, but no difference was observed during cry stimuli (all $Ps < 0.05$). There were also several areas with a main effect of trait anxiety for left and right

Table 1. Demographics table

	Mean (s.d.) or frequency ($N = 57$)	Range	Relationship with RFQ[a]	Relationship with own cry[a]
Age at scan (years)	26 (6)	19–37	NS	NS
Risky families' CME load	5.2 (2.3)	3–12	NS	$r = 0.24$, $P = 0.07$
Last 12 months' income-to-needs ratio	2.6 (1.5)	0.4–6.2	NS	NS
Days postpartum	135 (61)	27–324	NS	NS
Race	Asian—1 Black/African American—3 White/Caucasian—30 Other/multi-race—23	NA	NS	NS
Ethnicity	Hispanic—26 Non-Hispanic—31	NA	NS	NS
Scanner (N)	Trio—22; Prisma—35	NA	NS	NS
History of breastfeeding (N)	56	NA	NS	NS
History of psychiatric disorder (N)[b]	22	NS	NS	NS
Spielberger Trait Anxiety	35 (10)	20–60	$r = 0.36$, $P = 0.005$	NS
Spielberger State Anxiety	31 (7)	20–47	$r = 0.34$, $P < 0.01$	NS
Beck Depression Inventory	7 (5)	0–22	NS	NS
Direct sensitivity	5.4 (1.2)	3.5–7	NS	NS
Direct non-intrusiveness	5.6 (1.2)	3–7	NS	$\rho = 0.28$, $P = 0.03$
Direct non-hostility	6.2 (1.1)	2.5–7	NS	NS

[a]Pearson's correlation.
[b]All psychiatric diagnostic data were lifetime self-report. $N = 9$ missing; $N = 25$ women with undiagnosed symptoms or lifetime psychiatric diagnosis ($N = 7$ with depressive symptoms or diagnosis alone, $N = 4$ with anxiety symptoms or diagnosis alone, $N = 9$ with both depression and anxiety, $N = 1$ with eating disorder, $N = 2$ with OCD and $N = 2$ with PTSD).
NS, not significant.

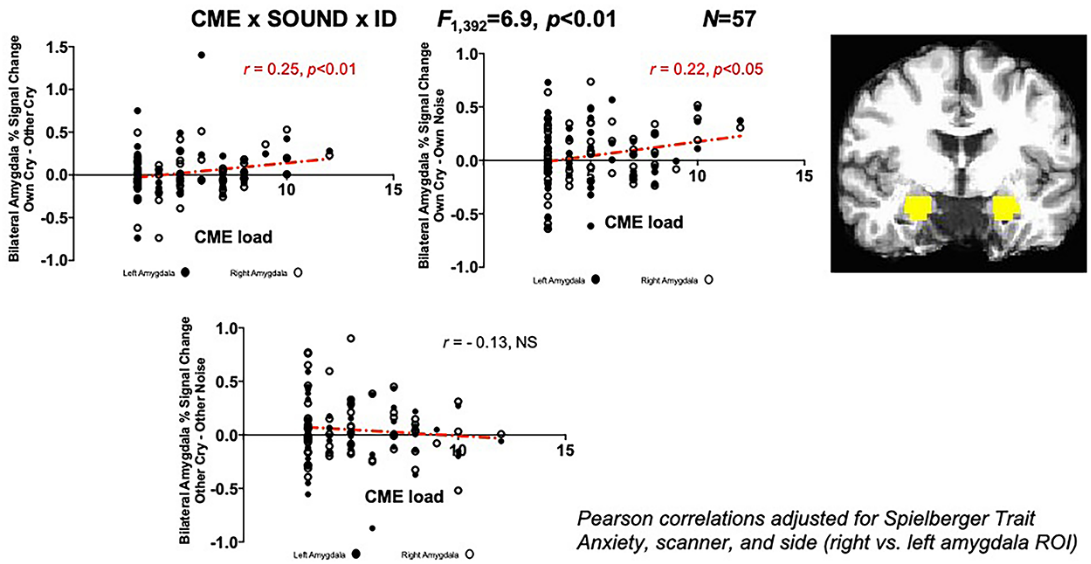

Fig. 1. Amygdala activation to infant cries by CME load.

Table 2. Generalized PPI analysis results

	Coordinates (RAI)	Cluster size (k)	Significance
L amygdala seed			
Sound × CME			
R SMA	−2, −5, 57	94	$F_{1,165} = 22.3$, $P < 0.001$
L BA9/MFG	35, −38, 36	46	$F_{1,165} = 22.3$, $P < 0.001$
Sound × ID			
L cingulate gyrus	5, 32, 33	135	$F_{1,165} = 20.7$, $P < 0.001$
L precuneus	8, 80, 42	45	$F_{1,165} = 20.7$, $P < 0.001$
Main effect and trait anxiety			
L inferior frontal gyrus	53, −32, 6	97	$F_{1,53} = 28.7$; $P < 0.001$
L middle temporal gyrus	59, 53, 6	90	$F_{1,53} = 28.7$; $P < 0.001$
L MFG	35, −29, 48	35	$F_{1,53} = 28.7$; $P < 0.001$
R amygdala seed			
Main effect and trait anxiety			
R superior frontal gyrus	−2, −62, 33	44	$F_{1,53} = 23.6$; $P < 0.001$

RAI, Right-Anterior-Inferior coordinate system.

amygdala analyses, in addition to task-related effects which did not differ based on CME load and which are reported in Table 2 and Supplementary (Figures S3, S4 and S5). There was also an association between higher amygdala-middle front gyrus functional connectivity ($\rho = 0.29$, $P < 0.05$ and $N = 57$) connectivity and lower maternal intrusiveness (i.e. greater non-intrusiveness). There was also a trend-level relationship between amygdala-SMA connectivity and lower maternal intrusiveness (i.e. greater non-intrusiveness) ($\rho = 0.22$, $P = 0.1$ and $N = 57$). There were no associations with maternal sensitivity or non-hostility.

Discussion

In this examination of maternal response to infant distress signals in a community sample of mothers reporting CMEs, we found that mothers reporting higher levels of CME had increased bilateral amygdala response to their own infant's cry compared to another infant's cry or white-noise. In the post-scan stimulus rating task, there were no differences by CME, but across mothers, they were more likely to rate cries as more urgent than noise (Supplementary Table S1). Generalized PPI analysis for left amygdala demonstrated increased differential connectivity between amygdala and two areas including R SMA and left MFG. Overall, results were driven by mothers reporting higher CME load exhibiting greater differential connectivity between amygdala and prefrontal areas associated with motor planning to cry *vs* noise stimuli. Additionally, this differential effect was driven by lower connectivity during noise stimuli in mothers reporting higher CME, which suggests that mothers reporting higher CME may be better able to tune out extraneous stimuli in their environment and to allocate greater attention to infant distress cues. The lack of an ID effect in this connectivity analysis was somewhat surprising and may have been seen if we had longer block length, providing greater power to detect subtler differences in connectivity. Further, both increased amygdala activation and connectivity with prefrontal areas were associated with fewer intrusive maternal behaviors with no differences in maternal sensitivity or hostility during mother–infant observation, which is different from our hypothesis in this regard. There were also several connectivity associations including those in amygdala in which there were task effects (sound × ID) and in left and right amygdala connectivity which were associated with trait anxiety (see Supplemental Data section and Table 2 for full results).

The amygdala activation and connectivity findings in tandem may be interpreted as a heightened response in mothers reporting higher CME both in attribution of importance and in the generation of empathic responses to their infants. The involvement of the SMA suggests planning of behavioral responses and converges with prior work that found these areas to be associated with responses to infant stimuli,

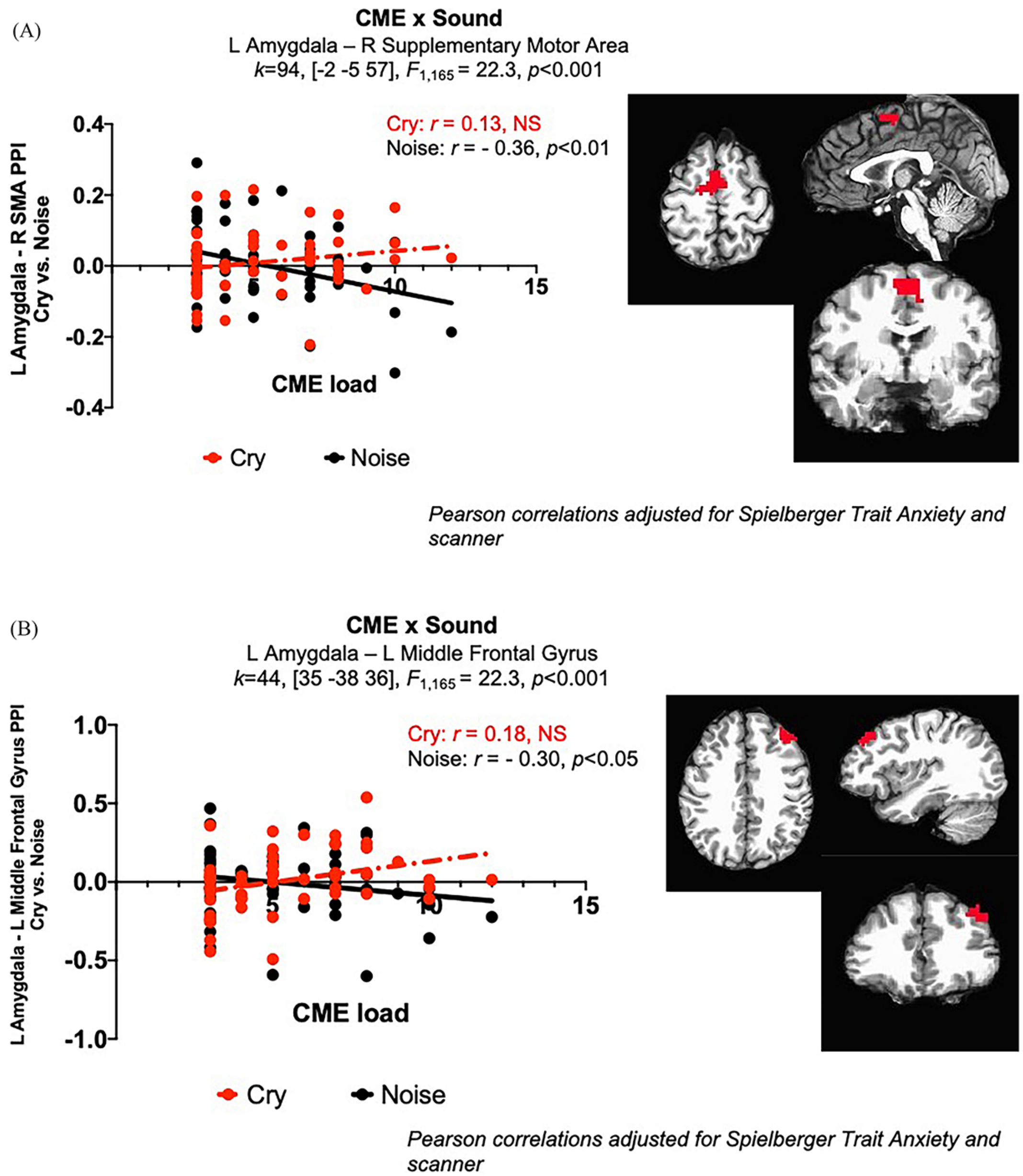

Fig. 2. (A) PPI analysis—CME × sound: L amygdala—R SMA. (B) PPI analysis—CME × sound: L amygdala—L MFG.

in particular, to infant cries (Bornstein *et al.*, 2017). Further, there was heightened positive connectivity to cry *vs* noise stimuli with higher reported CME between left amygdala and left MFG, an area which has been demonstrated in multiple studies to be involved with the processing of empathic responses in various social fMRI tasks (MFG) (Lamm *et al.*, 2007; Seehausen *et al.*, 2014, 2016). Another line of research which may inform the interpretation of these data is maternal mentalization, which is in essence how mothers interpret baby emotional states. One study found that mothers with greater frequency of verbal statements describing baby emotions during mother–infant interaction exhibited increased responsivity in the SMA and amygdala to own *vs* other infant cry during an fMRI task (Hipwell *et al.*, 2015). Similarly, results in this study suggest that in mothers reporting higher CME, there is both heightened amygdala activation to infant distress and increased connectivity between amygdala and areas associated with motor planning and empathy, which may represent an adaptive response emphasizing increased protection or sensitivity toward the infant. Interestingly, these findings are in contrast to those of mothers with depressive symptoms, who have been shown to exhibit a more blunted pattern of amygdala activation in response to their own infant's cries compared to a control sound (Laurent and Ablow, 2012), and these neural patterns have been associated with a more disengaged parenting style (Esposito *et al.*, 2017). Interestingly, our maternal behavioral findings during mother–infant observation suggest that the amygdala activation and connectivity findings may not be associated with more intrusive behaviors; in fact, our results suggest the contrary that mothers with higher amygdala activation and connectivity with SMA may have decreased intrusive behaviors. These results are in a small sample and will need to be replicated. Additionally, the results need to be interpreted in light of prior data in a partially overlapping sample, finding higher amygdala reactivity to distressed infant faces to be associated with more intrusive maternal behaviors (Kim *et al.*, 2017). There are several reasons why that prior finding may be different than our current results. This study differed from the current one in that it used non-personalized stimuli and that it focused on socioeconomic status rather than CME, which may be associated with distinct changes in the brain compared to prior early maltreatment experiences. While mothers' reported that CMEs do not represent a current active threat, they nonetheless may inform empathic responses to infants in a way that seeks to repair their own prior childhood experiences as has been suggested in qualitative analyses (i.e. 'I want my infant's life to be different than mine') (Chamberlain *et al.*, 2019).

Another connectivity relationship which may inform interpretation of our findings is the greater differential connectivity between amygdala and MFG in mothers reporting higher CME to cry *vs* noise stimuli (Figure 2B), an area that also exhibited a main effect of trait anxiety, in which higher trait anxiety was associated with increased connectivity between amygdala and MFG (Supplementary Figures S3C, S4A and S4B). Thus, the finding in MFG may be associated with more of an anxious pattern of response to infant distress cues, which might be related to empathy level in mothers, which is not directly measured in our study.

We recently reported that mothers with CME have lower amygdala activation to non-personalized infant face stimuli compared to mothers unexposed to CME in a partially overlapping sample to this cohort (Olsavsky *et al.*, 2019). There are several reasons why the results may differ from the photo stimuli task. First, the cry stimuli are very clearly a distress signal, as opposed to the infant picture stimuli (happy, neutral and distressed). Further, the infant picture finding was across emotional face stimuli, regardless of valence. Additionally, cry blocks are 20 s long, which constitute a more intense experience for participants than 2 s photographic face stimuli. Lastly, the cry task contains personalized stimuli, which may be more relevant to mothers, and potentially also more ecologically valid, as the scanner environment of lying down may mimic to a greater extent the 'at home' circumstances of laying in bed at night and hearing one's baby crying, as opposed to the picture stimuli, given that visual stimuli are more likely to be experienced in an awake and active state during the daytime. Additionally, the fact that the amygdala activation finding for own infant's cry but not for other infant's cry was associated with non-intrusiveness also may speak to some specificity to these personalized compared to standardized stimuli, which may also help to explain some of the differences between this and prior findings.

While we have found increased amygdala reactivity to be associated with higher childhood maltreatment experiences in mothers in a community sample with relatively low psychopathological symptoms, more work is needed to determine whether these differences in the neural processing of distressed infant stimuli are associated with differences in parenting behaviors. Further, these data leave open the question of how mothers with higher levels of anxiety and/or anxiety disorders differ in their neural processing of infant stimuli and subsequent engagement in parenting behaviors.

Limitations

There are several limitations to the current study. First, mothers in this cohort exhibited limited psychiatric symptoms and thus the result may have been different were the data collected in a clinical population (e.g. mothers with CME and depressive symptoms), given that differences in neural processing have been identified in mothers with a variety of psychopathology (Moses-Kolko *et al.*, 2014). There are also some important limitations in retrospective assessment of CMEs due to poor agreement between retrospective and prospective measures for a variety of reasons (Scott *et al.*, 2012; Baldwin *et al.*, 2019). Nonetheless, these experiences may be linked to psychopathology and thus are important for understanding the subjective experiences of mothers (Danese and Widom, 2020). In future studies, including a deeper phenotyping of trauma with multiple assessments including specifically interviews and other types of prospective informants (e.g. child protective services reports, medical records and parent reports for mothers) may be helpful for a more rigorous assessment (Newbury *et al.*, 2018). It may well be that a multi-pronged approach with deeper phenotyping of traumatic experiences, psychiatric diagnoses, micro- and macro-coding approaches and narrative/qualitative techniques may provide subtler insights into how maternal cue processing may relate to approach behaviors. With respect to concerns that have been raised in the past about connectivity analyses (Haller *et al.*, 2018), cry and noise stimuli were presented as blocks, which is a sensitive technique in fMRI to obtain signal *vs* noise contrast and which has been suggested to be more sensitive for PPI analyses (O'Reilly *et al.*, 2012). Notably, our task length and quality conform to initial recommendations for examining task-condition variation in connectivity (task length >20 min) (Gratton *et al.*, 2018). As in any preliminary finding, convergence with prior work and replication will support its validity. Lastly, we did not measure genetic factors or the specific frequencies of cries, which also are known to contribute to mothers' infant cry responses (Out *et al.*, 2010; Esposito *et al.*, 2017). Lastly, the task is a passive one, and thus, there are concerns for attentional focus of mothers. However, this issue is mitigated by the fact that this task has been used in multiple studies (Kim *et al.*, 2011, 2016; Messina *et al.*, 2015; Bornstein *et al.*, 2017; Esposito *et al.*, 2017) and has been shown to evoke consistent neural activation across samples and studies in a network of limbic and motor areas which have been posited by multiple groups to constitute a parental brain network.

Future directions

Overall, our findings regarding the relationship between maternal CME and how infant stimuli are processed in maternal brain, in terms of both activation and connectivity, inform our understanding of infant cue processing, while generating additional questions to be targeted with different research approaches. First of all, this heightened amygdala activation to infant cries, interpreted in the context of prior work suggesting decreased amygdala reactivity across infant face emotions (Olsavsky *et al.*, 2019), emphasizes the importance of studying stimuli with different characteristics and valence. Second, increased amygdala reactivity to distress, as well as increased connectivity with regions associated with motor response, may reflect an increased tendency to approach and console baby in times of distress, which may be adaptive at earlier points in development. Thus, perhaps there may be increased intrusive parenting with CME, but our sample does not capture this phenomenon as all women were within the first-year postpartum; it is possible that intrusive behaviors would manifest more clearly as children acquire the ability to be mobile and engage in more exploration. However, at later developmental stages when baby is engaging in expected exploratory behaviors, the increased responsiveness to infant distress may increase maternal anxiety and result in more intrusive parenting behaviors, which has been described in a prior study examining mothers' response to infant emotions and associations with socioeconomic status (Kim *et al.*, 2016).

Given these intriguing findings, which need to be interpreted in the context of the study limitations, two approaches to the study of mother–infant systems may be helpful. First, it would be informative to design specific tasks which parse out mothers' responses to distress in general compared to mothers' responses to infant distress. Second, studies using standardized behavioral and imaging paradigms in clinical populations which may examine the subcomponents of parental behaviors may be useful in understanding at which point the process may go awry for mothers struggling with psychopathology. Mothers' reported CMEs are an area for study as early adverse experiences cross diagnoses, potentially worsening symptoms across disorders, and may likely inform treatment and increase the effectiveness of early-life behavioral interventions for mothers and young children.

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest

All authors report no potential conflicts of interest. A.K.O.'s husband works for Thermo Fisher Scientific.

References

Ammerman, R.T., Shenk, C.E., Teeters, A.R., Noll, J.G., Putnam, F.W., Van Ginkel, J.B. (2012). Impact of depression and childhood trauma in mothers receiving home visitation. *Journal of Child and Family Studies*, ***21***(4), 612–25.

Apter-Levy, Y., Feldman, M., Vakart, A., Ebstein, R.P., Feldman, R. (2013). Impact of maternal depression across the first 6 years of life on the child's mental health, social engagement, and empathy: the moderating role of oxytocin. *American Journal of Psychiatry*, ***170***(10), 1161–8.

Atzil, S., Hendler, T., Feldman, R. (2011). Specifying the neurobiological basis of human attachment: brain, hormones, and behavior in synchronous and intrusive mothers. *Neuropsychopharmacology*, ***36***(13), 2603–15.

Atzl, V.M., Narayan, A.J., Rivera, L.M., Lieberman, A.F. (2019). Adverse childhood experiences and prenatal mental health: type of ACEs and age of maltreatment onset. *Journal of Family Psychology*, ***33***(3), 304–14.

Bailey, H.N., DeOliveira, C.A., Wolfe, V.V., Evans, E.M., Hartwick, C. (2012). The impact of childhood maltreatment history on parenting: a comparison of maltreatment types and assessment methods. *Child Abuse and Neglect*, ***36***(3), 236–46.

Baldwin, J.R., Reuben, A., Newbury, J.B., Danese, A. (2019). Agreement between prospective and retrospective measures of childhood maltreatment: a systematic review and meta-analysis. *JAMA Psychiatry*, ***76***(6), 584–93.

Barrett, J., Fleming, A.S. (2011). Annual research review: all mothers are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, **52**(4), 368–97.

Beck, A.T., Mendelson, M., Mock, J., Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, **4**, 53–63.

Biringen, Z. (2000). Emotional availability: conceptualization and research findings. *American Journal of Orthopsychiatry*, ***70***(1), 104–14.

Bornstein, M.H., Putnick, D.L., Rigo, P., et al. (2017). Neurobiology of culturally common maternal responses to infant cry. *Proceedings of the National Academy of Sciences*, **114**(45), E9465–73.

Buisman, R.S.M., Pittner, K., Compier-de Block, L., van den Berg, L.J.M., Bakermans-Kranenburg, M.J., Alink, L.R.A. (2018). The past is present: the role of maltreatment history in perceptual, behavioral and autonomic responses to infant emotional signals. *Child Abuse and Neglect*, ***77***, 23–34.

Chamberlain, C., Ralph, N., Hokke, S., Clark, Y., Gee, G., Stansfield, C. (2019). Healing The Past By Nurturing The Future: a qualitative systematic review and meta-synthesis of pregnancy, birth and early postpartum experiences and views of parents with a history of childhood maltreatment. *PLoS One*, ***14***(12), e0225441.

Cox, R.W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, ***29***(3), 162–73. https://www.ncbi.nlm.nih.gov/pubmed/8812068.

Cross, D., Kim, Y.J., Vance, L.A., Robinson, G., Jovanovic, T., Bradley, B. (2016). Maternal child sexual abuse is associated with lower maternal warmth toward daughters but not sons. *Journal of Child Sexual Abuse*, **25**(8), 813–26.

Danese, A., Widom, C.S. (2020). Objective and subjective experiences of child maltreatment and their relationships with psychopathology. *Nature Human Behaviour*, **4**(8), 811–8.

Desikan, R.S., Segonne, F., Fischl, B., et al (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, **31**(3), 968–80.

Destrieux, C., Fischl, B., Dale, A., Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage*, **53**(1), 1–15.

Esposito, G., Manian, N., Truzzi, A., Bornstein, M.H. (2017). Response to infant cry in clinically depressed and non-depressed mothers. *PLoS One*, **12**(1), e0169066.

Feldman, R., Granat, A., Pariente, C., Kanety, H., Kuint, J., Gilboa-Schechtman, E. (2009). Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. *Journal of the American Academy of Child and Adolescent Psychiatry*, **48**(9), 919–27.

Goldberg, X., Serra-Blasco, M., Vicent-Gil, M., et al. (2019). Childhood maltreatment and risk for suicide attempts in major depression: a sex-specific approach. *European Journal of Psychotraumatology*, **10**(1), 1603557.

Gratton, C., Laumann, T.O., Nielsen, A.N., et al. (2018). Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. *Neuron*, **98**(2), 439–452.e5.

Green, J.G., McLaughlin, K.A., Berglund, P.A., et al. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. *Archives of General Psychiatry*, **67**(2), 113–23.

Greene, C.A., Haisley, L., Wallace, C., Ford, J.D. (2020). Intergenerational effects of childhood maltreatment: a systematic review of the parenting practices of adult survivors of childhood abuse, neglect, and violence. *Clinical Psychology Review*, **80**, 101891.

Gunnar, M.R., Hostinar, C.E., Sanchez, M.M., Tottenham, N., Sullivan, R.M. (2015). Parental buffering of fear and stress neurobiology: reviewing parallels across rodent, monkey, and human models. *Social Neuroscience*, **10**(5), 474–8.

Haller, S.P., Kircanski, K., Stoddard, J., et al. (2018). Reliability of neural activation and connectivity during implicit face emotion processing in youth. *Developmental Cognitive Neuroscience*, **31**, 67–73.

Hipwell, A.E., Guo, C., Phillips, M.L., Swain, J.E., Moses-Kolko, E.L. (2015). Right frontoinsular cortex and subcortical activity to infant cry is associated with maternal mental state talk. *Journal of Neuroscience*, **35**(37), 12725–32.

Ho, S.S., Swain, J.E. (2017). Depression alters maternal extended amygdala response and functional connectivity during distress signals in attachment relationship. *Behavioural Brain Research*, **325**(Pt B), 290–6.

Joosen, K.J., Mesman, J., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H. (2013). Maternal overreactive sympathetic nervous system responses to repeated infant crying predicts risk for impulsive harsh discipline of infants. *Child Maltreatment*, **18**(4), 252–63.

Juul, S.H., Hendrix, C., Robinson, B., et al. (2016). Maternal early-life trauma and affective parenting style: the mediating role of HPA-axis function. *Archives of Women's Mental Health*, **19**(1), 17–23.

Kim, P., Capistrano, C., Congleton, C. (2016). Socioeconomic disadvantages and neural sensitivity to infant cry: role of maternal distress. *Social Cognitive and Affective Neuroscience*, **11**(10), 1597–607.

Kim, P., Capistrano, C.G., Erhart, A., Gray-Schiff, R., Xu, N. (2017). Socioeconomic disadvantage, neural responses to infant emotions, and emotional availability among first-time new mothers. *Behavioural Brain Research*, **325**, 188–96.

Kim, P., Feldman, R., Mayes, L.C., et al. (2011). Breastfeeding, brain activation to own infant cry, and maternal sensitivity. *Journal of Child Psychology and Psychiatry*, **52**(8), 907–15.

Kim, P., Tribble, R., Olsavsky, A.K., et al. (2020). Associations between stress exposure and new mothers' brain responses to infant cry sounds. *Neuroimage*, **223**, 117360.

Kluczniok, D., Boedeker, K., Fuchs, A., et al. (2016). Emotional availability in mother-child interaction: the effects of maternal depression in remission and additional history of childhood abuse. *Depression and Anxiety*, **33**(7), 648–57.

Lamm, C., Batson, C.D., Decety, J. (2007). The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience*, **19**(1), 42–58.

Lang, A.J., Gartstein, M.A., Rodgers, C.S., Lebeck, M.M. (2010). The impact of maternal childhood abuse on parenting and infant temperament. *Journal of Child and Adolescent Psychiatric Nursing*, **23**(2), 100–10.

Laurent, H.K., Ablow, J.C. (2012). A cry in the dark: depressed mothers show reduced neural activation to their own infant's cry. *Social Cognitive and Affective Neuroscience*, **7**(2), 125–34.

Lomanowska, A.M., Boivin, M., Hertzman, C., Fleming, A.S. (2017). Parenting begets parenting: a neurobiological perspective on early adversity and the transmission of parenting styles across generations. *Neuroscience*, **342**, 120–39.

McLaren, D.G., Ries, M.L., Xu, G., Johnson, S.C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *Neuroimage*, **61**(4), 1277–86.

Melhem, N.M., Porta, G., Oquendo, M.A., et al. (2019). Severity and variability of depression symptoms predicting suicide attempt in high-risk individuals. *JAMA Psychiatry*, **76**(6), 603–13.

Messina, I., Cattaneo, L., Venuti, P., et al. (2015). Sex-specific automatic responses to infant cries: TMS reveals greater excitability in females than males in motor evoked potentials. *Frontiers in Psychology*, **6**, 1909.

Moses-Kolko, E.L., Horner, M.S., Phillips, M.L., Hipwell, A.E., Swain, J.E. (2014). In search of neural endophenotypes of postpartum psychopathology and disrupted maternal caregiving. *Journal of Neuroendocrinology*, **26**(10), 665–84.

Narayan, A.J., Kalstabakken, A.W., Labella, M.H., Nerenberg, L.S., Monn, A.R., Masten, A.S. (2017). Intergenerational continuity of adverse childhood experiences in homeless families: unpacking exposure to maltreatment versus family dysfunction. *American Journal of Orthopsychiatry*, **87**(1), 3–14.

Newbury, J.B., Arseneault, L., Moffitt, T.E., et al. (2018). Measuring childhood maltreatment to predict early-adult psychopathology: comparison of prospective informant-reports and retrospective self-reports. *Journal of Psychiatric Research*, **96**, 57–64.

O'Reilly, J.X., Woolrich, M.W., Behrens, T.E., Smith, S.M., Johansen-Berg, H. (2012). Tools of the trade: psychophysiological interactions and functional connectivity. *Social Cognitive and Affective Neuroscience*, ***7***(5), 604–9.

Olsavsky, A.K., Stoddard, J., Erhart, A., Tribble, R., Kim, P. (2019). Neural processing of infant and adult face emotion and maternal exposure to childhood maltreatment. *Social Cognitive and Affective Neuroscience*, **14**(9), 997–1008.

Out, D., Pieper, S., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H. (2010). Physiological reactivity to infant crying: a behavioral genetic study. *Genes, Brain, and Behavior*, ***9***(8), 868–76.

Porter, J.N., Roy, A.K., Benson, B., et al. (2015). Age-related changes in the intrinsic functional connectivity of the human ventral vs. dorsal striatum from childhood to middle age. *Developmental Cognitive Neuroscience*, ***11***, 83–95.

Pridham, K.F., Schroeder, M., Brown, R. (1999). The adaptiveness of mothers' working models of caregiving through the first year: infant and mother contributions. *Research in Nursing and Health*, **22**(6), 471–85.

Repetti, R.L., Taylor, S.E., Seeman, T.E. (2002). Risky families: family social environments and the mental and physical health of offspring. *Psychological Bulletin*, ***128***(2), 330–66. https://www.ncbi.nlm.nih.gov/pubmed/11931522.

Rijlaarsdam, J., Stevens, G.W., Jansen, P.W., et al. (2014). Maternal childhood maltreatment and offspring emotional and behavioral problems: maternal and paternal mechanisms of risk transmission. *Child Maltreatment*, ***19***(2), 67–78.

Sander, K., Frome, Y., Scheich, H. (2007). FMRI activations of amygdala, cingulate cortex, and auditory cortex by infant laughing and crying. *Human Brain Mapping*, ***28***(10), 1007–22.

Scott, K.M., McLaughlin, K.A., Smith, D.A., Ellis, P.M. (2012). Childhood maltreatment and DSM-IV adult mental disorders: comparison of prospective and retrospective findings. *The British Journal of Psychiatry*, ***200***(6), 469–75.

Seehausen, M., Kazzer, P., Bajbouj, M., et al. (2014). Talking about social conflict in the MRI scanner: neural correlates of being empathized with. *Neuroimage*, ***84***, 951–61.

Seehausen, M., Kazzer, P., Bajbouj, M., et al. (2016). Effects of empathic social responses on the emotions of the recipient. *Brain and Cognition*, ***103***, 50–61.

Seifritz, E., Esposito, F., Neuhoff, J.G., et al. (2003). Differential sex-independent amygdala response to infant crying and laughing in parents versus nonparents. *Biological Psychiatry*, **54**(12), 1367–75. https://www.ncbi.nlm.nih.gov/pubmed/14675800.

Smaling, H.J., Huijbregts, S.C., van der Heijden, K.B., Hay, D.F., van Goozen, S.H., Swaab, H. (2017). Prenatal reflective functioning and development of aggression in infancy: the roles of maternal intrusiveness and sensitivity. *Journal of Abnormal Child Psychology*, **45**(2), 237–48.

Smith, A.L., Cross, D., Winkler, J., Jovanovic, T., Bradley, B. (2014). Emotional dysregulation and negative affect mediate the relationship between maternal history of child maltreatment and maternal child abuse potential. *Journal of Family Violence*, ***29***(5), 483–94.

Spielberger C.D., Gorsuch, R.L., Lushene, R.E. (1970). *STAI Manual for the State Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Stacks, A.M., Muzik, M., Wong, K., et al. (2014). Maternal reflective functioning among mothers with childhood maltreatment histories: links to sensitive parenting and infant attachment security. *Attachment and Human Development*, **16**(5), 515–33.

Swain, J.E., Lorberbaum, J.P., Kose, S., Strathearn, L. (2007). Brain basis of early parent-infant interactions: psychology, physiology, and in vivo functional neuroimaging studies. *Journal of Child Psychology and Psychiatry*, **48**(3–4), 262–87.

Teicher, M.H., Samson, J.A., Polcari, A., McGreenery, C.E. (2006). Sticks, stones, and hurtful words: relative effects of various forms of childhood maltreatment. *American Journal of Psychiatry*, ***163***(6), 993–1000.

Wright, D.B., Laurent, H.K., Ablow, J.C. (2017). Mothers who were neglected in childhood show differences in neural response to their infant's cry. *Child Maltreatment*, **22**(2), 158–66.