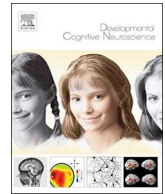




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Effects of early maternal care on adolescent attention bias to threat in nonhuman primates

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ABSTRACT

Attention bias towards threat using dot-probe tasks has mainly been reported in adults with stress-related disorders such as PTSD and other anxiety disorders, in some cases associated with early life stress or traumatic experiences. Studies during adolescence are scarce and inconsistent, which highlights the need to increase our understanding of the developmental processes that predict attentional biases, given that this is a time of emergence of psychopathology. Here, we use a translational nonhuman primate model of early life stress in the form of infant maltreatment to examine its long-term impact on attentional biases during adolescence using the dot-probe task and identify interactions with early life risk factors, such as prenatal exposure to stress hormones and emotional/stress reactivity during infancy. Maltreated animals showed higher reaction times to social threat than animals that experienced competent maternal care, suggesting interference of negative valence stimuli on attentional control and cognitive processes. Higher emotional reactivity during infancy in Maltreated animals predicted attention bias towards threat, whereas higher levels of prenatal cortisol exposure was associated with bias away (avoidance of) threat in maltreated and control groups. Our findings suggest that different postnatal experiences and early biobehavioral mechanisms regulate the development of emotional attention biases during adolescence.

1. Introduction

Childhood maltreatment is a major public health concern (Finkelhor et al., 2013) and a form of early life stress (ELS) associated with increased risk for anxiety and mood disorders -including PTSD-, physiological, neurobiological and cognitive alterations, behavioral disorders, substance abuse, and obesity, not just in humans but in nonhuman primate (NHP) species (Danese and Tan, 2014; Drury et al., 2016; Gee et al., 2013; Gunnar and Quevedo, 2007; Howell and Sanchez, 2011; Kaplow and Widom, 2007; Sanchez et al., 2001, 2007; Teicher et al., 2003). Despite the strong link between early adversity and psychopathology, the type and severity of developmental consequences is very complex and depends, in part, on the timing and duration (Kaplow and Widom, 2007; Kisiel et al., 2014; Spinazzola et al., 2014; Steinberg et al., 2014), type and severity of adversity -e.g. physical/sexual abuse, neglect, often co-morbid, and co-occurrence with psychological trauma

(Kisiel et al., 2014; Spinazzola et al., 2014). The underlying developmental and biobehavioral mechanisms are not well understood, either. Alterations in attentional control and emotional information processing have been proposed to explain some of these alterations (Foa and Kozak, 1986; Weber, 2008), including attention bias toward threat or away from it (avoidance), resulting in interference with processing of other stimuli and disruption of cognitive processes. However, findings from recent human studies are inconsistent and scarce, particularly in children and adolescents, indicating the need to understand the developmental processes that predict attentional biases to emotional valence.

Attention bias toward threat has classically been measured with the dot-probe task (Bradley et al., 2000; Waters et al., 2008), measuring reaction time (RT) to respond to a cue (e.g. a red square; see Fig. 1) that is presented following, and in the same location (congruent) or opposite location (incongruent) of an emotionally negative image (e.g.

Abbreviations: ELS, early life stress; RT, reaction time; NHP, nonhuman primate; MALT, maternal maltreatment

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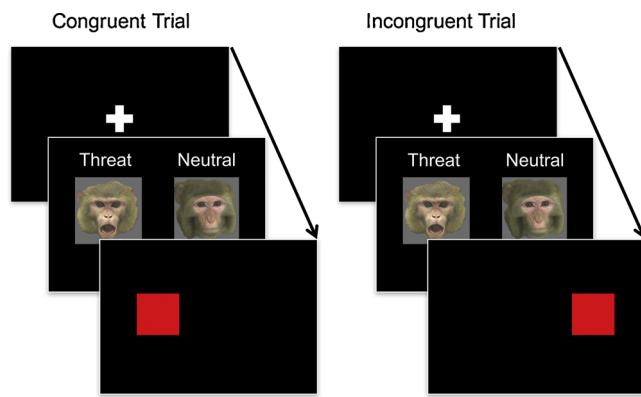


Fig. 1. Dot-Probe Paradigm. In this example of the task, the animal first touches a fixation cross in order to initiate the trial. Two images are presented for 500 ms, followed by presentation of the cue (red square). Reaction time (RT) to the final cue is measured. The cue is presented congruent (Left) or incongruent (right) to the threat face (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

threatening face) presented simultaneously with an image of different valence (neutral), from which an attention bias score can be calculated (Price et al., 2016). Differences in congruent versus incongruent RT to this cue suggests attentional bias (Cisler and Koster, 2010). Biases include vigilance and attention towards threat (shorter RT to the congruent location), avoidance of attention directed away from the threat (avoidance; longer RT to congruent location), and difficulty disengaging from the threatening image. The dot-probe has been used in studies in populations with anxiety or histories of early adversity/ELS/trauma, showing attentional bias toward threatening images (Aupperle et al., 2012; Bar-Haim et al., 2007; Cisler et al., 2009). In addition, anxious individuals identify the threat image more quickly and, therefore, have a faster RT to the congruent cue, but may also have difficulty disengaging from the threat and respond more slowly during the incongruent trials (Bryant and Harvey, 1997; Fox et al., 2001, 2002). Studies in populations exposed to trauma, including those with PTSD (Fani et al., 2012a,b; Lindstrom et al., 2011), also suggest an attentional bias to images related to the trauma (Bryant and Harvey, 1995; Foa et al., 1991).

Numerous studies have reported altered threat responses in children with a history of maltreatment (Pine et al., 2005; Pollak et al., 1997, 2001; Pollak and Sinha, 2002; Pollak and Tolley-Schell, 2003; Shackman et al., 2007), as well as improved memory of angry facial expressions in visual tasks (Rieder and Cicchetti, 1989), and increased amygdala activity to threat cues (McCrary et al., 2011, 2013), known to mediate rapid attention to threat (Phelps and LeDoux, 2005). These differences in threat-processing have been detected as early as 15 months of age (Curtis and Cicchetti, 2013). However, inconsistent findings have been reported in dot-probe studies of maltreated children, including attentional bias away from threat (Berto et al., 2017; Kelly et al., 2015; Pine et al., 2005), or towards threat during adolescence (Gibb et al., 2009). Such attention biases may reflect strategies to improve threat detection, or to avoid exposure to threatening stimuli and attenuate emotional responses in individuals with difficulties with emotional regulation (Wald et al., 2013), respectively. However, these attentional biases can also promote maladaptive or exaggerated responses to perceived threats, including fear generalization to non-threatening stimuli (Foa et al., 1999), interfering with the evaluation of other relevant information in the environment, such as safety cues, and impairing the ability to adapt and cope with situations (Bar-Haim et al., 2007; Bar-Haim, 2010), or to properly evaluate future risks (Cisler and Koster, 2010; Messman-Moore and Long, 2003). Altered cognitive processing of threat during development may lead to increased vulnerability for psychopathology later in life, especially in response to

adult trauma exposure (Fani et al., 2010; Gibb et al., 2009). And, in the case of threat avoidance during stress exposure, this is predictive of later PTSD symptoms (Wald et al., 2011, 2013).

NHPs such as rhesus monkeys can provide a translational animal model to help address questions raised in human studies through prospective, longitudinal, studies of (a) emotional attention bias processes, using translational adaptations of the dot-probe task (Lacourse et al., 2013; Parr et al., 2013) and (b) the impact of maternal maltreatment on neurobehavioral development, including vulnerability to emotion and stress regulation. Maltreatment of infants, including abuse and rejection, occurs in NHP populations spontaneously and at similar rates (2–5% prevalence) as in humans (Brent et al., 2002; Howell et al., 2016; Johnson et al., 1996; Maestriperi, 1998a,b; Parr et al., 2012; Sanchez et al., 1998; Sanchez, 2006; Troisi and D'Amato, 1984). In macaques, infant maltreatment by the mother includes physical abuse and maternal rejection associated with infant distress (Maestriperi, 1999; Maestriperi, 1998a,b; Sanchez, 2006). In addition to transgenerational transmission of maltreatment through the maternal line, these mothers maltreat subsequent offspring in what seems to be a stable maternal trait (Maestriperi, 2005; Maestriperi, 1998a,b). Maltreated infant macaques show increased anxiety and emotional reactivity, impaired impulse control, aggression, and social deficits throughout development and into adolescence, as well as elevated levels of the stress hormone cortisol, suggesting chronic stress exposure (Drury et al., 2017; Howell et al., 2013, 2014; McCormack et al., 2006). These socioemotional alterations and activation of the stress response are consistent with alterations reported in children that experience maltreatment and other forms of adverse early care (Howell et al., 2013; Koch et al., 2014; Maestriperi, 1998a,b; McCormack et al., 2006, 2009; Sanchez, 2006; Sanchez et al., 2010).

Thus, in this study, we use a translational NHP model of infant maltreatment to (a) examine its long-term impact on attentional biases toward or away from threat during adolescence using the dot-probe task; and (b) potential interactions of postnatal adverse care (maltreatment) with other early risk factors (prenatal stress/cortisol exposure and infant's emotional and stress reactivity) that may increase vulnerability to long-term alterations in threat responses during adolescence, and explain individual variability in the outcomes. Differential attention bias has not been previously studied in maltreated monkeys, particularly during adolescence, which can provide a critical cross-species comparison with findings in human populations of children and adolescents with early adverse experiences (Berto et al., 2017; Gibb et al., 2009; Kelly et al., 2015; Pine et al., 2005; Pollak et al., 1997, 2001; Pollak and Sinha, 2002; Pollak and Tolley-Schell, 2003; Shackman et al., 2007). Although this animal model does not span all adverse experiences that human children experience (for instance, sexual abuse), one of its critical strengths lies in its ability to quantify maltreatment during a known postnatal period, providing frequency, duration, and severity of the adverse experience (e.g. abuse and rejection rates) and the concurrent levels of stress it elicits (e.g. cortisol accumulation in hair during the postnatal ELS exposure), difficult to be accurately determined in studies with children with early adverse caregiving experiences. Additionally, NHP models provide strong control over environmental variables that are known confounders of behavioral outcomes of ELS during adolescence in human studies, such as drug use, diet/obesity, prenatal stress/drug exposure, socioeconomic status, and access to medical care or therapy. Our experimental design also allows to disentangle heritability from postnatal experience by utilizing crossfostering and randomized assignment to experimental group (maltreating, competent care; (Drury et al., 2017; Howell et al., 2017)) at birth, which would be unethical in humans. These are just some of the important contributions of this translational animal model with a well-characterized adverse caregiving experience and longitudinal behavioral and biological measures of its developmental impact. Of particular interest here is the role of proper maternal care on emotional attention and regulation. Maternal care is, indeed, critical in regulating

the development of emotional/stress neural circuits in both humans and NHP species (Gee et al., 2014; Gunnar et al., 2015; Gunnar and Sullivan, 2017; Sanchez et al., 2015; Tottenham, 2015), and maltreatment experiences take place at a time when critical socioemotional skills are developing, as well as the brain regions that regulate them (Casey et al., 2010; LA, 1996; Maestripieri, 1998a,b). We are also interested in potential interactions of postnatal adverse care (maltreatment) with other early risk factors (prenatal stress/cortisol exposure and infant's emotional and stress reactivity) that may increase vulnerability to infant maltreatment. Exposure to prenatal stress and elevated cortisol -measured through maternal plasma cortisol, psychosocial stress or amniotic fluid cortisol- predicts increased reactivity and disrupted emotional regulation in human infant (Baibazarova et al., 2013; Bergman et al., 2010a, b; Davis et al., 2011; Bolten et al., 2013), and externalizing behavioral problems (Gutteling et al., 2005). Innate emotional reactivity or temperament have also been reported to affect attentional biases to threat in children, such that biases may be more prominent and fixed in children with fearful temperament (Field and Lester, 2010; LoBue and Perez-Edgar, 2014) and affect-based attention bias and temperament have a synergistic relationship leading to socioemotional maladjustment (Cole et al., 2016; Morales et al., 2015, 2016; Perez-Edgar et al., 2010, 2011). Thus, and supported by previous evidence in humans (e.g. (Gibb et al., 2009), we hypothesize that postnatal exposure to adverse caregiving will alter the development of emotional regulation, increasing attention bias towards social threat in adolescence; and that this will be further worsened by prenatal stress/cortisol exposure and infant reactive temperament. To test these hypotheses we examined differences in RT in the dot probe task in adolescent macaques with and without infant maltreatment, presenting threatening and neutral images (social vs. nonsocial). Next, we examined whether RT in the dot probe task was further predicted by prenatal cortisol exposure, and infant emotional reactivity during infancy.

2. Methods

2.1. Subjects

Twenty-five adolescent rhesus macaques (*Macaca mulatta*; 13 males, 12 females) between the ages of 4.5–5.5 years old were included in this study. These animals were generated and well-characterized throughout infancy and the juvenile (pre-pubertal period) as part of a bigger longitudinal study by our group on developmental outcomes of infant maltreatment in this species (Drury et al., 2017; Howell et al., 2017). They were born and lived with their mothers and families in complex social groups at the Yerkes National Primate Research Center (YNPRC) Field Station breeding colony, consisting of 75–150 adult females, their sub-adult and juvenile offspring, and 2–3 adult males. These groups were housed in outdoor compounds, with access to climate-controlled indoor areas. Standard high fiber, low fat monkey chow (Purina Mills Int., Lab Diets, St. Louis, MO) and seasonal fruits and vegetables were provided twice daily, in addition to enrichment items. Water was available *ad libitum*.

Half of the subjects experienced maternal maltreatment (MALT, $n = 14$; 8 males, 6 females), and the other half received competent maternal care (Control, $n = 11$; 5 males, 6 females); these NHP sample sizes are large in comparison to macaque studies using the dot-probe task, which have published reports with $n = 6$ animals (Lacreuse et al., 2013; Parr et al., 2013). In this model, infant maltreatment is defined by co-morbid experience of maternal physical abuse and rejection of the infant during the first three months of life –never exhibited by Control, competent mothers-, which causes pain, emotional distress and elevations in stress hormones (Drury et al., 2017; Howell et al., 2013; Maestripieri et al., 2000; Maestripieri, 1998a,b; McCormack et al., 2006, 2009; Sanchez, 2006). In this study infants were randomly assigned at birth to be crossfostered to a Control or MALT foster mother in

Table 1

Groups breakdown based on randomized crossfostering assignment at birth. The y-axis designates the crossfostering conditions (e.g. C→M identifies infants born to a control biological mother, but fostered to a MALT mother). *All animals were crossfostered except for a male control that was raised by his biological mother.

	FEMALE	MALE	
CONTROL C→C	3	0	11
CONTROL M→C	3	5*	
MALTREATED C→M	1	5	14
MALTREATED M→M	5	3	
	12	13	25

* One animal not cross-fostered.

an effort to disentangle and control for effects of heritable factors that may confound the effects of ELS, counterbalancing groups by sex, biological mother, social dominance rank and assigning infants from different matriline & paternities to provide high genetic/social diversity, as previously reported (Drury et al., 2017; Howell et al., 2017). See Table 1 for details of infant crossfostering assignment and counterbalancing of groups. Given that birth weight is a strong predictor of neurobehavioral development in humans and NHPs (Coe and Shirtcliff, 2004; Vohr et al., 2000) we only studied infants ≥ 450 gr birth weight, which is a safe veterinary clinical cut off to rule out prematurity in rhesus monkeys. While at the YNPRC Field Station, longitudinal measures were collected during the infant and juvenile periods, focusing on the following for this study: (a) behavioral observations of maternal care received and infant emotional reactivity from birth through the first three months postpartum, and (b) HPA axis basal activity, measured as cortisol accumulated in hair from birth through the first 6 months postpartum as well as prenatally (from hair samples collected at birth).

At approximately 4 years of age the 25 adolescents were transferred to the YNPRC Main Station. Upon arrival, animals were pair-housed in home cages and fed Purina monkey chow (Ralston Purina, St. Louis, MO, USA), supplemented with fruit and vegetables daily, and water was available *ad libitum*. Environmental enrichment was provided on a regular basis. The colony is maintained at an ambient temperature of 22 ± 2 °C at 25–50% humidity, and the lights set to a 12-h light/dark cycle (lights on at 7 h; lights off at 19 h). Following several months of acclimation to the move and new housing environment, the animals underwent several behavioral tasks, neuroendocrine assessments and MRI scans, including the dot-probe task to examine attention bias toward or away from threat as a part of a larger study examining long-term emotional, cognitive and neurobiological consequences of ELS during adolescence.

All procedures and animal care were in accordance with the Animal Welfare Act and the U.S. Department of Health and Human Services “Guide for the Care and Use of Laboratory Animals” and approved by the Emory Institutional Animal Care and Use Committee (IACUC).

2.2. Behavioral characterization of maternal care and measures of infant emotional reactivity

A detailed description of the infant rhesus maltreatment model and methods for selection of potential mothers and behavioral characterization of competent maternal care (Control) in contrast to infant MALT is provided in previous publications (Drury et al., 2017; Howell et al.,

2017; Maestripieri, 1998a,b; Maestripieri, 1998a,b; McCormack et al., 2006, 2009). Briefly, because MALT mothers consistently maltreat their infants, we identified potential multiparous Control and MALT mothers with known maternal care quality towards prior offspring. Following crossfostering, we performed focal observations of maternal care across the first 3 postnatal months to substantiate and measure rates of abuse and rejection towards their fostered infants. These consisted of 30 min long focal observations performed on separate days (5 days/week during month 1, 2 days/week during month 2 and 1 day/week during month 3) for a total of 16 h/mother-infant pair; this observation protocol is optimal to document early maternal care in this species, given that physical abuse is the highest during month 1 (Drury et al., 2017; Howell et al., 2017; Maestripieri, 1998a,b; McCormack et al., 2006). Behavioral observations were collected by experienced coders (inter-observer reliability > 90% agreement, Cohen $k > 0.8$). Competent maternal care is defined as species-typical behaviors such as nursing, cradling, grooming, ventral contact and protection (retrieve from potential danger, restrain) of the infant. In contrast, MALT is aberrant (prevalence rate: 2–5%), defined as the comorbid occurrence of physical abuse (operationalized as violent behaviors directed towards the infant that cause pain and distress, including dragging, crushing, throwing) and early infant rejection (i.e. prevention of ventral contact and pushing the infant away). Both abuse and rejection cause high levels of infant distress –e.g. scream vocalizations- and elevations in stress hormones (Drury et al., 2017; Howell et al., 2013; Maestripieri, 1998a,b; McCormack et al., 2006; Sanchez, 2006). Control foster mothers in this study exhibited competent/good maternal care (e.g. high maternal sensitivity, infant protection and attachment: (McCormack et al., 2015) and did not exhibit MALT behaviors -physical abuse or rejection- (Drury et al., 2017; Howell et al., 2017). Abuse and rejection rates (frequency/observation time) were calculated across the first 3 postnatal months (see Table 2). In addition to infant abuse and rejection rates, rates of infant scream (distress) vocalizations during the first 6 months of life were also included in the regression models described below as measures of infant emotional reactivity (Table 2).

2.3. Dot-probe testing procedure

During adolescence (between 4.5–5.5 year of age), animals were trained and tested in an attention bias task –the dot-probe- in their home cage, using a touchscreen rig attached to the cage that was fully accessible when the cage door was opened. The dot-probe has been used to assess attention bias to threat in human populations exposed to trauma, including those with PTSD (e.g. (Fani et al., 2012a,b; Lindstrom et al., 2011)) as well as in a few NHP studies to examine attentional bias to social stimuli of varying emotional valence (Lacreuse et al., 2013; Parr et al., 2013). Initially, animals were habituated to the touchscreen and behavioral shaping was done using positive reinforcement (food rewards) to guide them to touch the images presented on the screen if they did not immediately do so out of curiosity. Animals were first trained to touch neutral clip art images presented centrally on the screen, and then progressed to touching images that appeared at random locations on the screen, by receiving a nutritionally-balanced food pellet as reward (Bio-Serv®), which was released into an automatic

pellet dispenser/hopper below the screen. All animals were on a delayed feeding schedule in order to prevent satiation and decreased motivation for food rewards during testing, which took place 5 days per week. Pair-housed animals were separated by a full panel partition during testing to avoid distractions and interferences due to animals' interactions and to control the number of presentations of experimental (social and nonsocial) images each animal received during testing.

Once the animals were proficient with the touchscreens, they proceeded to the training phase of the dot-probe paradigm, using the Yerkes Cognitive Battery (YCB) software, with neutral clip art images and a modification of previous protocols in macaques (Lacreuse et al., 2013; Parr et al., 2013). To initiate each training trial, the monkey touched a central fixation cross, after which two images were presented on either side of the screen for 500 ms. The target cue, a red square, was then presented congruent with one of the images (i.e. in the same location it had been briefly presented), and the animal's RT to touch this cue was recorded. Animals were closely monitored for cheating behavior throughout training, operationalized by the use of two hands to touch both sides of the screen simultaneously in anticipation of the cue. Shaping was used to enforce responding with one hand and removing the hand from the screen between trials if necessary. Over successive training sessions, the time response interval required to respond and receive the food reward was reduced, encouraging the monkeys to maintain attention, stay engaged with the task, and to respond as soon as the cue was presented. Training criterion was met and animals progressed to the experimental images when two 100-trial sessions (did not need to be consecutive) were completed with $\geq 80\%$ correct trials at a 1 s response interval.

After reaching training criterion, animals transitioned to the testing phase of the dot-probe with social or nonsocial images of negative or neutral valence. Testing trials followed a similar structure as during training, but one (or both) of the images in the pair was emotionally salient (negative: e.g. threat facial expression, snake) and the other was neutral (see Fig. 1). Animals completed one 100-trial session per day over a nine-day testing period. Response intervals were lifted to five seconds in order to allow for potentially delayed responses to the emotional saliency of the images, but still encourage responding and engagement with the task. Two categories of experimental images were presented during testing (social, nonsocial), which were separated into two different tasks. Social images were composed of unfamiliar conspecific faces with two different facial expressions classified into negative (threat) or neutral of 15 different identities (Fig. 2). Nonsocial images included familiar and unfamiliar objects with a neutral (i.e. light switch, clock), or negative (i.e. syringe, snake) valence (Fig. 2). Trials were randomly balanced per session for image valence (negative vs. neutral), location of cue presentation in relation to image with emotional valence (congruent vs. incongruent), as well as target cue presentation (left vs. right side of the screen). Three days of nonsocial image testing (300 trials) were followed by six days of social image testing (600 trials). Although most studies only use Mean Attention Bias (MAB) –a score calculated by subtracting RT during congruent trials from RT during incongruent trials- as the dependent variable, we included both MAB score and RT to touch the target cue as dependent variables. Inclusion of RT in the analyses allows to examine potential

Table 2

Descriptive data of adverse caregiving behaviors (abuse and rejection rates/hour), infant emotional reactivity (screams rates/hour) and hair cortisol concentrations (pg/mg) during the first 3–6 postnatal months. As expected based on previous publications with this model of infant maltreatment (Howell et al., 2017; Drury et al., 2017), Control mothers never exhibit abuse towards offspring and extremely low rejection rates, in contrast to Maltreating females. Data represented as mean \pm standard error of the mean (SEM). *, **, *** represent significant p values from the Mann–Whitney test.

	Abuse	Rejection	Screams	Hair Cortisol(Birth)	Hair Cortisol(6 months)
Control	0.00 \pm 0.00	0.13 \pm 0.09	0.67 \pm 0.18	515.19 \pm 24.93	134.45 \pm 9.95
Maltreated	0.98 \pm 0.25***	2.14 \pm 0.43***	2.85 \pm 0.96*	582.24 \pm 37.27	154.41 \pm 20.71

* < 0.05; ** < 0.01; *** < 0.001.

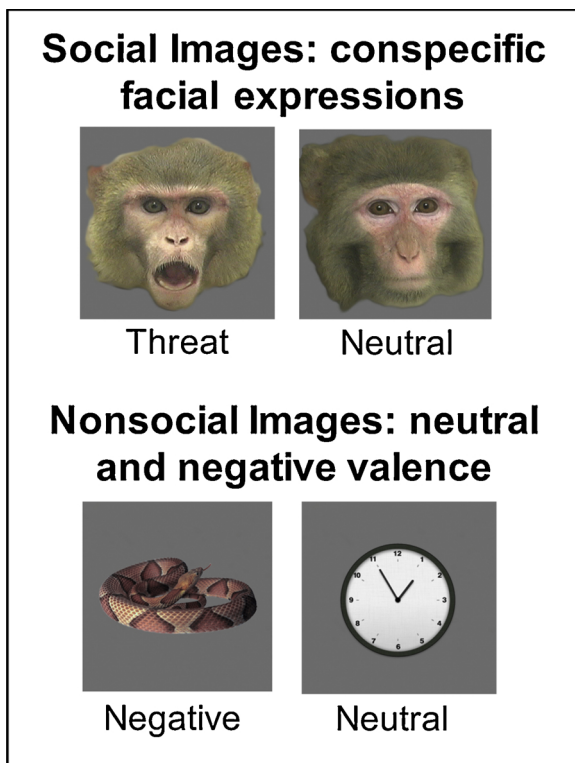


Fig. 2. Examples of images from the social and nonsocial tasks. The social task was composed of images of unfamiliar conspecifics with two different facial expressions: threat and neutral. Two images were randomly paired and presented in each trial. The nonsocial task was composed of images of negative and neutral valence and were also randomly paired and presented similarly.

differences in the way the presentation of the threatening images may interfere with the animals' general performance speed, an issue that has been brought up in recent publications suggesting the use of RT (see van Rooijen et al., 2017) to provide an additional measure more related to difficulties "disengaging" from the emotional stimulus. Bias scores were computed separately for social and nonsocial tasks. Positive scores indicated a bias towards the image with negative emotional valence (i.e. faster RT to threat than neutral images), while negative scores a bias away from threat.

2.4. Hair cortisol

At birth, approximately one square inch of hair was shaved from the back of the infant's head just above the foramen magnum (nucal area), and the hair that grew in this region was shaved again at 6 months of age. At each time point the hair samples captured chronic cortisol exposure, through its accumulation into the growing hair shaft. Birth hair cortisol samples were collected to examine prenatal cortisol exposure between groups; 6 months hair cortisol concentrations were measured to examine HPA axis activations due to ELS. Both birth and 6 months cortisol measures were also used as predictors in the regression models. Hair samples were processed and assayed using previously described protocols (Meyer et al., 2014). Each sample was weighed, washed in isopropanol to remove external contamination, ground to powder, and extracted with methanol overnight. After evaporation of the methanol, the residue was redissolved in assay buffer, and cortisol was measured using the Salimetrics (Carlsbad, CA) enzyme immunoassay kit (cat. # 1-3002) according to the manufacturer's instructions. Intra- and inter-assay coefficients of variation were < 10%.

2.5. Statistical analysis

Data were summarized as mean \pm standard error of the mean (SEM) and normality tested for each variable using the Shapiro-Wilk test. Student t-test was used to compare means in normally-distributed data; because neither abuse, rejection or scream rates, nor hair cortisol concentrations at birth or at 6 months were normally distributed, the effect of maternal care (Control vs MALT) on these variables was tested using a nonparametric Mann-Whitney Rank Sum Test.

Repeated Measures (RM) ANCOVA with group as fixed factor (Control, MALT), and congruency (congruent, incongruent) as the repeated measures factor were used to examine maternal care effects on RT on each trial type (negative/threat vs neutral). Sex (male, female) was added as a covariate in the statistical models. Biological mother group (Control, MALT) was also added as a covariate to account for the potential effects of heritable/prenatal factors, but was dropped from the final models due to its lack of effects on RT. T-tests were conducted to compare MAB score in Control and MALT groups. Potential confounding/carry over effects of testing day on RT were examined on a separate RM ANOVA for group and congruency. Analyses were performed separately for social and nonsocial stimuli given they were run as separate tasks.

Multiple linear regression was used to assess early predictors of performance in the dot-probe for trial types with significant group effects: (a) abuse and rejection rates received by each infant, (b) infant emotional reactivity (screams), and (c) prenatal and postnatal cortisol exposure (measured as hair cortisol accumulation). Both RT and MAB were normally distributed. Spearman correlation was used to rule out issues of multicollinearity between regressors.

Statistical significance level was set at $p < 0.05$. Bonferroni correction was applied for multiple comparisons (Student t & Mann-Whitney tests; multiple regression models), and we present the results before and after correction, when applicable. Given the sample size of 25, we were powered at 80% power and 5% level of significance to detect moderate to large effect sizes, including for the repeated measures model effects (based on power analysis performed using PASS 15 (NCSS, 2017)) and published criteria (Cohen, 1988). Effect sizes are reported for significant results.

3. Results

3.1. Early maternal care, emotional reactivity and cortisol

Because abuse, rejection, and scream rates, as well as hair cortisol at birth and 6 months failed the Shapiro-Wilk test for normal distribution, maternal care group differences (Control vs MALT) on these variables was tested using a nonparametric Mann-Whitney Rank Sum Test. As expected based on previous publications with this model of infant maltreatment (Howell et al., 2017; Drury et al., 2017) and as shown in Table 2 there was a significant group difference in maternal abuse and rejection rates received, which were very high in MALT animals and absent or extremely low, respectively, in Control animals (Abuse: $U = 0.0$, $n_1 = 10$, $n_2 = 14$, $p < 0.001$, effect size estimate(r) = 0.86; Rejection: $U = 2.0$, $n_1 = 10$, $n_2 = 14$, $p < 0.001$, $r = 0.82$), and scream rates were also significantly greater in MALT than Control subjects ($U = 18.0$, $n_1 = 10$, $n_2 = 13$, $p = 0.04$, $r = 0.60$). However, there were not significant group differences in hair cortisol levels at birth ($U = 50.00$, $n_1 = 10$, $n_2 = 14$, $p = 0.254$, $r = 0.24$) or in hair cortisol at 6 months of age ($U = 46.0$, $n_1 = 8$, $n_2 = 12$, $p = 0.908$, $r = 0.03$; Table 2).

3.2. Dot-probe test

Trials that the animals initiated but did not respond to within 5 s were removed from the analysis. After inspecting histograms of all animal's response times, a lower cutoff of 0.2 s was set in order to

Table 3

Social & nonsocial dot-probe test: cognitive touchscreen task effectiveness. Summary of usable trials by group and sex, and breakdown of trials rejected on the basis of behavior of behavior (i.e. did not survive the lower -0.2-s- or upper - > 1.5 s- cutoffs imposed to avoid including anticipatory responding and trials in which too long of a response occurred due to an outside distractor) or of time (i.e. subject did not touch the cue within 5 s), as described in section 3.2. There was a significant main group effect on trials rejected due to time ($F_{(1,23)} = 4.4$, $p = 0.048$, $\eta^2 = 0.173$). Data represented as mean \pm SEM.

	Total Trials	Usable trials	Bad behavior	Rejected for time
Control				
Male	900	743.2 \pm 5.73	4.2 \pm 1.32	152.6 \pm 4.96
Female	900	735.33 \pm 14.36	7.67 \pm 1.56	157.0 \pm 13.17
Maltreated				
Male	900	719.38 \pm 20.33	10.88 \pm 5.57	169.75 \pm 15.47
Female	900	681.67 \pm 9.54	26.33 \pm 11.29	192.0 \pm 4.46

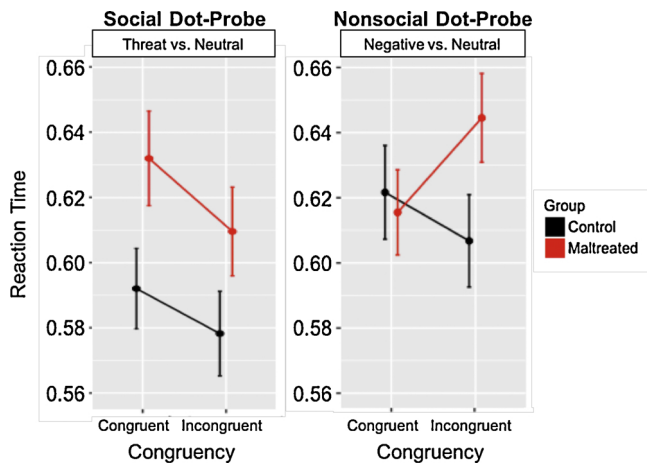


Fig. 3. Social and Nonsocial Dot-Probe: Reaction Time. Here reaction time (RT) is plotted, subdivided by the location of the cue (congruent or incongruent). A main effect of group was found for the Threat vs. Neutral comparison in social trials, with maltreated animals responding more slowly irrespective of the congruency of the cue. No main or interactions effects of group were found in nonsocial trials when collapsing across trials, but see text for group x testing day interaction effects. Data represented as mean \pm SEM.

remove a small peak of responses that occurred immediately after the image was presented, as there is a risk that there were most likely anticipatory responses, consistent with other studies (Joormann and Gotlib, 2007). An upper cutoff of 1.5 s was selected based on previous macaque studies (Parr et al., 2013) in order to capture delayed responding due to image salience and not to distractions (e.g. from other animals). Social and nonsocial trials were assessed in separate tasks, and all trials within these categories were collapsed across days of

testing. See Table 3 for details.

Results of the two-way RM ANCOVA conducted to examine the effect of group and congruency on RT (with sex included as a covariate) detected a significant main effect of group on RT ($F_{(1,22)} = 4.5$, $p = 0.0463$, $\eta^2 = 0.17$) for the threat vs. neutral social image trials, with MALT animals showing slower RT than Controls (see Fig. 3). No main effects of congruency ($F_{(1,23)} = 1.8$, $p = 0.188$, $\eta^2 = 0.07$), group x congruency interaction effects ($F_{(1,23)} = 0.0$, $p = 0.998$, $\eta^2 = 0.00$) or covariate (sex) main or interaction effects were detected ($F_{(1,22)} = 0.5$, $p = 0.4787$, $\eta^2 = 0.02$). The slower RTs in MALT animals seem specific of the threat vs. neutral face trials because no RT group differences are detected during presentations of positive vs. neutral face pairs (unpublished data). No confounding/carry over effects of testing day were detected on RT, either (main day effect: $F_{(1,23)} = 2.4$, $p = 0.139$, $\eta^2 = 0.093$; day x group: $F_{(1,23)} = 2.1$, $p = 0.161$, $\eta^2 = 0.084$; day x congruency: $F_{(1,23)} = 0.7$, $p = 0.412$, $\eta^2 = 0.029$).

No main or interaction effects of group, congruency or sex were detected for RT in the nonsocial Negative vs. Neutral trials (group when collapsing across testing days ($F_{(1,22)} = 0.5$, $p = 0.506$), congruency ($F_{(1,23)} = 0.7$, $p = 0.4237$), group x congruency ($F_{(1,23)} = 3.7$, $p = 0.0681$), sex ($F_{(1,22)} = 0.02$, $p = 0.878$)). However, a significant group x testing day was detected ($F_{(1,23)} = 4.6$, $p = 0.042$, $\eta^2 = 0.168$) with control, but not MALT animals, becoming faster with time (no other testing day ($F_{(1,23)} = 0.7$, $p = 0.406$, $\eta^2 = 0.03$), or day x congruency ($F_{(1,23)} = 0.06$, $p = 0.809$, $\eta^2 = 0.003$) effects were detected).

There was not a significant group difference in MAB score for threat vs. neutral social ($t_{(23)} = -0.003$, $p = 0.99$, $g = -0.112$; Bonferroni-adjusted p value = 0.025) or negative vs. neutral nonsocial images ($t_{(23)} = -1.9$, $p = 0.08$, $g = -0.733$; adjusted p value = 0.025), either.

3.3. Early predictors of reaction time in the dot-probe

A multiple linear regression model was used to assess early predictors (infant abuse, rejection and scream rates; hair cortisol at birth and 6 months) of RT during social threat vs. neutral trials in the dot-probe task, where MALT had higher RT than Controls. Because independent variables were not normally distributed there were log-transformed before analysis. No issues of multicollinearity were detected using Spearman correlations. A significant regression equation was found for social threat vs. neutral, congruent ($F_{(5,10)} = 10.0$, $R = 0.95$, $R^2 = 0.91$, $p = 0.012$ —Bonferroni-adjusted p value: 0.025—), but not incongruent trials ($F_{(5,10)} = 0.7$, $R = 0.64$, $R^2 = 0.41$, $p = 0.649$). In the significant multiple regression “congruent” model, the RT for threat vs neutral congruent trials was predicted from a linear combination of two of the independent variables: screams during infancy ($\beta = -0.14$, $t = -6.1$, $p = 0.002$; Fig. 4A) and hair cortisol at birth ($\beta = 0.27$, $t = 2.8$, $p = 0.037$; Fig. 4B). Higher screams rates during infancy was predictive of faster RT to the threat congruent cue, effect seemingly driven by maltreated animals (Fig. 4A), whereas higher

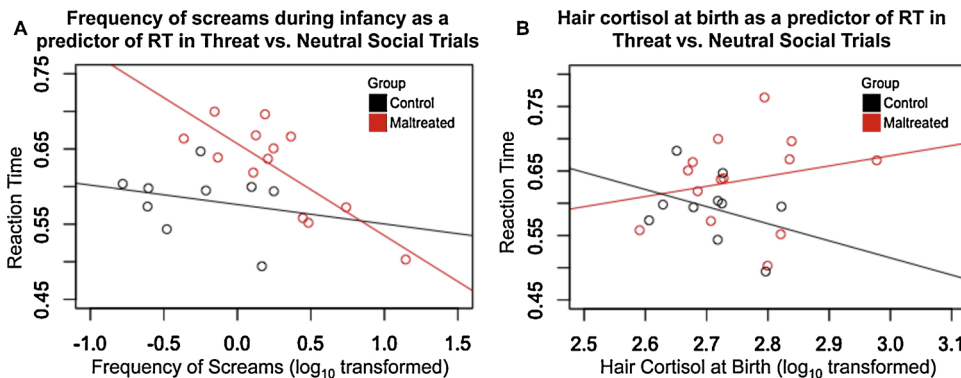


Fig. 4. Early life predictors of reaction time in Threat vs. Neutral Social Trials: scatterplots per group (from the omnibus multiple regression model). **A.** Screams were predictive of RT, such that higher screams rates during infancy was predictive of faster RT to the threat congruent cue ($\beta = -0.14$, $t = -6.1$, $p = 0.002$), and this effect seemed driven by maltreated animals. **B.** Prenatal cortisol exposure (measured as hair cortisol at birth) predicted slower RT ($\beta = 0.27$, $t = 2.8$, $p = 0.037$), which again seems to be driven by the maltreated group.

prenatal cortisol exposure predicted slower RTs (Fig. 4B).

4. Discussion

In this study we used a translational NHP model of infant maltreatment to examine its impact on RT and attentional biases toward or away from threat during adolescence using the dot-probe task. We also examined potential interactions of postnatal adverse experience with other early risk factors, particularly measures of emotional and stress reactivity during infancy and prenatal/postnatal cortisol exposure. RT to a cue following the presentation of two social or nonsocial images of different emotional valence (threatening vs. neutral) was measured. Findings indicated group differences in RT during the social, but not the non-social, threat vs. neutral images presentation, with maltreated animals responding slower than controls, both during congruent and incongruent trials. This suggests potential interference of the social threat image in cognitive processing and attentional control. In the nonsocial trials, control, but not MALT, animals' RT became faster over testing days. Higher emotional reactivity (increased rates of distress vocalizations –screams–) during infancy, predicted faster RTs, whereas prenatal cortisol exposure (measured as hair cortisol at birth), was associated with slower RTs. These findings suggest a complex regulation by postnatal experiences, temperament and prenatal biological factors on emotional attention control during adolescence.

Differences in attention bias have been reported using the dot-probe task in children and adults with stress-related disorders, such as anxiety and PTSD, sometimes associated with ELS/trauma (Aupperle et al., 2012; Bar-Haim et al., 2007; Bryant and Harvey, 1995, 1997; Cisler et al., 2009; Dalgleish et al., 2003; Elsesser et al., 2004; Fani et al., 2010, Fani et al., 2012a,b; Foa et al., 1991; Fox et al., 2001, 2002; Lindstrom et al., 2011; Pine et al., 2005). However, findings from these studies are inconsistent, especially among pediatric maltreated populations, with some individuals showing an attentional bias towards threat (Gibb et al., 2009), and others away from threat –determined using bias score– (Berto et al., 2017; Kelly et al., 2015; Pine et al., 2005). Studies of the effects of childhood maltreatment on attention bias during adolescence are also scarce, leaving a gap in our understanding of this measure during development. Here we used a macaque model to test the hypothesis that the directionality of the effects may be partially explained by interactions between postnatal adverse caregiving and other early risk factors, namely prenatal stress/cortisol exposure and infant stress/emotional reactivity.

Very few NHP studies have focused on attention bias towards threat using the dot-probe task, mostly to compare human and monkey attention bias and memory for emotional stimuli, and to study the effect of intranasal oxytocin on attention bias to negative facial expressions (Lacreuse et al., 2013; Parr et al., 2013). To our knowledge this is the first NHP study of the long-term effects of ELS on adolescent attention bias to threat. Although no group differences were found for attention bias scores, MALT animals showed higher (slower) RT than controls in the social, but not in the non-social, threat vs. neutral trials, independent of congruency. The specificity of the slower RT during social threat vs. neutral trials in MALT than Controls is further supported by the lack of group differences during presentations of positive vs. neutral face pairs (unpublished data). This suggests that threatening social stimuli may specifically interfere with cognitive processing and attentional control in animals with ELS, increasing the time that it takes to process or respond to stimuli that follow the presentation of threatening faces. Perhaps these aversive emotional faces engage attention control networks, tying up cognitive resources and delaying responses, as previously suggested in individuals with PTSD (Fani et al., 2012a,b). Recent publications have suggested to examine RT, in addition to MAB (see van Rooijen et al., 2017) to provide a measure more related to difficulties “disengaging” from the emotional stimulus. Although social threat vs. neutral trial-specific, generalized (i.e., independent of congruency), slower RTs have not been reported in other studies in

macaques (Lacreuse et al., 2013; Parr et al., 2013), our findings could be attributed to early adversity-related alterations in the development of emotional attention and regulation neural circuits and processes, resulting in interference with cognition.

We also examined the potential interaction of postnatal adverse care (maltreatment) with other early risk factors, specifically prenatal stress/cortisol exposure and infant's stress and emotional reactivity, that could increase vulnerability to long-term alterations in processing and responding to threatening stimuli during adolescence (i.e. differences in RT during the threat vs. neutral face presentations). Despite the high abuse and rejection experienced by MALT animals, and their high emotional reactivity (screams) during infancy, postnatal cortisol accumulation in hair was not significantly higher in MALT than control groups. This finding was unexpected and we believe is a power issue, as we have previously reported significantly higher postnatal hair cortisol accumulation in MALT than control infants in the bigger, full, dataset ($n = 42$), suggesting chronic stress in the adverse caregiving group (Drury et al., 2017).

Higher emotional reactivity (i.e. distress vocalizations) during infancy was a negative predictor of RT to the cue congruent to threat, particularly in the maltreated group. In contrast, exposure to higher prenatal cortisol predicted slower RT to the congruent cue. For this type of trial, a faster RT to the threat congruent cue suggests an attention bias towards threat in animals with higher emotional reactivity, (Bryant and Harvey, 1997; Fani et al., 2012a,b; Lacreuse et al., 2013; Parr et al., 2013), whereas a slower RT could mean either a bias away from threat, or general difficulty disengaging from the threat and therefore slow time responding in animals with higher prenatal cortisol exposure. Neuroimaging studies have shown alterations in activation of the hippocampus during threat disengagement in anxious individuals (Price et al., 2014). Additionally, in an exogenous cueing task, people with anxiety have been found to have difficulty disengaging from a threat cue, related to non-facilitated attention that is distinct from vigilance (Fox et al., 2001; Koster et al., 2004; Yiend and Mathews, 2001). Given the high levels of abuse and rejection that maltreated animals endured over the first few months of life, consistent with previous reports (Drury et al., 2017; Howell et al., 2017; Maestripieri, 1998a,b; McCormack et al., 2006), the long-term effects may be akin to those of complex trauma (Courtois, 2008), and may not present with the classical symptoms of hyperarousal and vigilance (i.e. attention bias toward threat) expected from a traumatized population (D'Andrea et al., 2013) in all maltreated animals. Thus, MALT animals with more externalizing behavior (i.e. those with higher distress vocalizations –screams–), may be more vigilant/hyperaroused and faster to identify and respond to threat (i.e. exhibit faster RT in the threat trials). A link between emotional reactivity and attention bias to threat has also been shown in maltreated children, suggesting attention bias as a potential marker of later development of psychopathology (Kelly et al., 2015). Maltreated animals that showed less emotional reactivity during infancy (i.e. screamed less) might exhibit more internalizing problems, blunted autonomic responses and attention bias away from (avoidance of) threat during adolescence. Although there was also some variability in RT among control animals, in general, they responded more quickly than the maltreated animals and had low scream rates.

Higher hair cortisol levels at birth (a measure of prenatal cortisol exposure), predicted longer RT. Previous studies in animal models (Coe et al., 1996, 2003; Maccari et al., 2003; Schneider et al., 1992; Weinstock, 2001) and humans (Bergman et al., 2007; Davis et al., 2007; Huizink et al., 2003; Laplante et al., 2004; O'Connor et al., 2003; Talge et al., 2007; Van den Bergh and Marcoen, 2004) have shown adverse impacts of high prenatal cortisol on infant cognitive, motor, and socioemotional development. Exposure to prenatal stress and elevated cortisol predicts increased reactivity and disrupted emotional regulation in human infants (Baibazarova et al., 2013; Bergman et al., 2010a, b; Bolten et al., 2013; Davis et al., 2011), and externalizing behavioral problems (Gutteling et al., 2005), highlighting the programming role

that prenatal cortisol plays on the development of emotional attention and regulatory processes. Furthermore, it has been suggested that these effects may be attenuated by secure infant attachment to the mother (Bergman et al., 2010a, b).

Despite the strengths of this study, there are also limitations. Notably, although our sample size is large for macaque cognitive studies (Abzug and Sommer, 2018; Acikalin et al., 2018; Basile and Hampton, 2011; Ferrucci et al., 2019) – particularly those using the dot-probe task (Lacourse et al., 2013; Parr et al., 2013) –, it is small in comparison to human studies and limited our statistical power to detect only moderate to large effect sizes (e.g. abuse, rejection, screams, social RT group effects) and to adequately test for other complex relationships (interactions) between factors, such as the effect of (1) genetic/heritable factors (biological mother), (2) sex, and (3) crossfostering and related postnatal environmental mismatches with ancestral environment. Such mismatches have been proposed to result in “recalibration” of emotional regulatory systems –dysfunctional or maladaptive behaviors– from the ancestral programmed pattern (“mismatch theory”: (Barker, 1995; Del Giudice et al., 2011; Gluckman et al., 2005; Hostinar and Gunnar, 2013)). In this “mismatch theory”, individuals are behaviorally and biologically programmed to benefit from a match of postnatal and ancestral environments, even if they are adverse (Nederhof and Schmidt, 2012). A similar “3-hit hypothesis” has been suggested, such that heritable genetic factors play a role as the first “hit” (de Kloet et al., 2007).

Smaller sample sizes are used in NHP than in human research based on the high experimental control over environmental factors that are known confounders in human studies such as drug use, diet, prenatal environment, health care, etc. Although our sample size only allowed to test the potential effect of biological inheritance/prenatal factors (via crossfostering) as a covariate in the statistical models, we did not detect significant effects of biological mother on our measures (RT). Although previous crossfostering studies between competent and maltreating macaque mothers have not reported impact of the manipulation on maternal care (Maestripieri, 2005) and our foster mothers displayed similar maternal care to that observed by our group with prior offspring, the potential impact of crossfostering itself on infant’s emotional reactivity has not been previously studied. Another limitation is the potential effect of animal transfer to the Main Station; although both groups were exposed to the same relocation stress experience, it is possible that more reactive animals were more impacted by this move.

Lastly, although group differences in RT were found for the social threat vs. neutral trials, the images used in our dot-probe studies were not ranked based on the degree of the stimulus threat, which may have added noise to our measures. Indeed, previous studies have shown differences in attention bias between mild- and high-threat stimuli (i.e. bias towards mild threats, which are more ambiguous and require more attention for evaluation; in contrast to bias away from high intensity-threats, which may be more likely to provoke avoidance) (Bryant and Harvey, 1997; Herzog et al., 2018). Based on the subgroups of MALT animals identified based on infant emotional reactivity, it would have been important to examine responses to images with different degrees of threat, in order to determine attention bias to high intensity-threats vs. ambiguous threats, or even whether the effects are generalized/transferred across different types of threatening faces.

In summary, our findings suggest altered attentional processing of threat in maltreated animals, evident in delayed RT in the dot-probe task, which is further modified by emotional reactivity during infancy and prenatal cortisol/stress exposure. We propose that there may be two subgroups of maltreated animals, one that was more emotionally reactive during infancy, outwardly expressing distress, and another that internalized and developed attention bias away from threat during adolescence. Future work is necessary to determine the relationships between these attentional biases and underlying neurobiological functional mechanisms related to emotional regulation and fear learning circuitry, which may be altered during development.

Conflict of interest

None.

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