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Human attachment triggers different social buffering mechanisms under high and low early life stress rearing

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ABSTRACT

Social buffering - the attenuation of stress by maternal safety signals - is a core mammalian-general stress management mechanism implicating two ancient systems: the oxytocinergic and HPA systems. Yet, because human attachments are representation-based, understanding social buffering mechanisms in humans requires the assessment of relationship history and consideration of early life stress (ELS), which alters stress responsivity. We followed a unique trauma-exposed cohort across childhood, versus a low-stress control group, and repeatedly observed maternal sensitive, safety-promoting style. In adolescence, we used an attachment induction paradigm that exposed children to both live and reminders of attachment safety signals and measured oxytocin and cortisol baseline and response, to test how maternal safety signals impact hormonal reactivity in children reared under high- versus low-stress conditions. Only safety-promoting mothers exhibited a stress-buffering function, but their effect was system-specific and depended on the rearing context. For oxytocin, safety-promoting mothers normalized the deficient baseline oxytocin levels observed in ELS youth by implicating a *plasticity-by-affiliation* mechanism. For cortisol, safety-promoting mothering reduced the initial stress response only among youth reared in low-stress contexts via the typical *buffering-by-safety* mechanism. Results suggest that human attachments require internalized security evolving over time to trigger a stress buffering function. Under conditions of chronic early stress, the stressful rearing context overrides the maternal safety signals, normative stress buffering mechanisms fail, and safety-promoting mothers switch to an immature, affiliation-based mechanism that relies on maternal presence.

1. Introduction

The key conceptual contribution of Bowlby's attachment theory was placing the mother-infant bond as the cornerstone of human development and as the "secure base" from which infants learn to adapt to life's hardships (Bowlby, 1988). Not only was the proposition of a social foundation for human nature a radical shift from the prevailing "solipsistic" viewpoints of his time (i.e., psychoanalysis and behaviorism), it also placed humans along a continuum of mammalian young for whom the mother's body and caregiving behavior support the maturation of neurobiological systems that sustain stress management throughout life. Yet, in addition to the shared components of mammalian bonding, attachment theory also emphasized the exclusive human aspects of attachment, expressed in the mental representations infants abstract from sensitive parenting experienced over time to create internal working models of safety (Bretherton et al., 1990; Feldman, 2016). Still, decades of disconnect between animal research targeting the stress-reducing features of bonding and human studies on the role of attachment relationships in fostering representational models of security resulted in a rift among the two literatures. To date, few models provide an integrative account on how the biological, behavioral, and representational components of attachment combine over time to buffer stress in human children as they grow.

One exception to the divide among human and animal research is the "stress buffering" model, which elegantly applies findings on the stress-reducing impact of maternal presence in young mammals to understanding how human attachment modulates stress. In their seminal review, Hostinar et al. (2014) postulate a three-step mechanism of social buffering; (a) supportive early relationships establish the attachment figure as a "safety signal"; (b) this shapes putative biological mediators and moderators of social support, such as oxytocin release, and (c) the process culminates in tuning the child's lifetime HPA-axis responsivity to stress. Yet, the application of this model to humans typically translated to studies that exposed individuals to lab-based

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stressors and tested the magnitude of their stress response in the presence versus absence of attachment figures. This line of research yielded valuable data on the importance of attachment relationships for the regulation of stress; still, it left numerous questions unanswered. First, the degree to which the mother functions as a safety signal is critical to the model; however, studies measuring the participants' response to induced stress in the presence of attachment figures did not measure whether or not these figures indeed engender safety. Growing up with a mother who does not serve as a source of security is a stressor in of itself that may lead to altered stress response and stress-related disorders (Jacobvitz and Reisz, 2019). Second, while the model underscores the importance of *early* attachments to the maturation of stress-buffering, no study, to our knowledge, has followed children over lengthy periods to test their relationship history and understand how stress buffering mechanisms evolve when the mother does, or does not, function as a safety signal over time. Finally, exposure to early life stress (ELS) alters functioning of both the oxytocinergic and HPA systems (Feldman, 2015a; Gunnar and Quevedo, 2007); hence, stress buffering mechanisms should be tested under high- and low-stress rearing ecologies to examine whether maternal safety signals exert differential effects when they are internalized on the background of stressful versus low-stress rearing conditions.

To address these questions and contribute to the stress-buffering literature from a novel angle, the current study examined whether individual differences in children's oxytocin (OT) and cortisol (CT) baseline levels and reactivity patterns would vary as a function of their relational history with the mother and as a result of chronic early life stress. While most studies on human social buffering used stress inducing paradigms (e.g., the Trier Social Stress Test, see Seltzer et al., 2010), we employed a novel approach to study the effects of human attachment on stress neurobiology and used an attachment induction paradigm that exposed adolescents to both live social interactions with their mother and attachment reminders of their relationship history spanning the first decade of life (see Fig. 1). We were particularly interested in how the degree to which the mother is experienced as a safety versus stress-inducing signal impacts baseline levels and reactivity patterns of OT and CT, the two ancient stress-related systems. Our attachment induction paradigm is informed by research in animal models and humans indicating that the caregiver's presence and quality of parenting regulate the infant's OT and CT response (Feldman, 2016; Feldman et al., 2019; Champagne and Meaney, 2007). To test the effects of chronically-stressful rearing on children's OT and CT response to our attachment induction paradigm, we compared children growing up in a context of chronic war-related trauma versus those reared in low-stress ecologies. Such cohort allowed us to uniquely examine whether the maternal function as a safety signal interacts with the rearing context to shape hormonal reactivity of OT and CT.

The oxytocinergic and HPA systems are two ancient neurobiological systems that evolved to help organisms manage stress in harsh ecologies. With the evolution of mammals, functionality of both systems became tied to the maternal-infant bonding context as the primary source of stress management (Feldman et al., 2016; Johnson et al., 1992). OT and the HPA system and its components (CRH, ACTH, and glucocorticoids) presumably evolved approximately 500 million years ago (Feldman et al., 2016; Lovejoy and Balment, 1999) and have played a key role in mediating organisms' response to environmental challenges along the phylogenetic scale; in hydra, worms, mollusks, insects, reptiles, and vertebrates (Donaldson and Young, 2008; Lovejoy and Balment, 1999; Nesse et al., 2010). Most neurons controlling the two systems are located in the same hypothalamic nucleus, the paraventricular nucleus (PVN), and their influence on physiological and behavioral processes is mediated by release of hormones from the pituitary (OT and ACTH) or adrenal (corticosteroids, CT) to peripheral targets, and neuromodulation exerted by direct neural pathways to multiple brain regions (Grinevich et al., 2016; Lovejoy and Balment, 1999). The ancient origins and close proximity of these neurons underscore the ongoing crosstalk among the two systems (Jurek and Neumann, 2018); however, most human studies did not find direct correlations between CT and OT and the two systems are proposed to chart different pathways to the development of maternal attachment behavior (Feldman et al., 2007; Gordon et al., 2010).

The evolution of mammals, involving internal fertilization, gestation, and lactation, placed the mother-infant bond as the core context for the maturation, functioning, and integration of the OT and CT systems in the service of stress management (Feldman, 2017; Jurek and Neumann, 2018). Yet, the two systems evolved to cope with different types of challenges and distinctly utilize the bonding context; CT functions as a general regulator of the stress response, whereas OT supports the formation of affiliative bonds, which, in turn, serve to buffer stress. Animal studies have shown that the mother-infant bond shapes the infant's stress response and programs the regulation of OT and CT secretion and action through early parenting behavior (Champagne and Meaney, 2007). In humans, longitudinal studies indicate that peripheral levels of CT and OT are shaped by sensitive maternal behavior repeatedly experienced throughout childhood (Feldman et al., 2013b; Halevi et al., 2017; Pasco Fearon et al., 2017). Additionally, studies have shown that chronic ELS conditions, including abuse, neglect, violence, poverty, institutional rearing, or war-related trauma, exert long-term effects on functioning of the two systems, but these effects are system-specific. With regards to OT, studies in children, adolescents, and adults exposed to a variety of ELS conditions have repeatedly shown attenuated baseline OT levels in ELS participants, as measured in plasma, saliva, urine, and CSF (for review see Donadon et al., 2018). In comparison, studies testing the effects of ELS on the HPA axis have yielded mixed results; some reporting higher CT production in ELS participating, while others demonstrating low levels and flat curves (Miller et al., 2007). Still, the consistent finding across ELS conditions is that early trauma specifically impairs HPA variability and leads to reduced flexibility of the system whether it is fixated on higher or lower levels (Apter-Levi et al., 2016; Feldman et al., 2013c; Fries et al., 2005; Halevi et al., 2017; Levendosky et al., 2002; Ulmer-Yaniv et al., 2017; Yirmiya et al., 2018).

What may be the mechanisms by which maternal safety signals experienced repeatedly across childhood impact OT or CT reactivity in children reared under high- and low-stress conditions? We suggest that these systems may follow two stress-buffering mechanisms which may relate to the global and affiliation-based stress-reducing function of these systems. The oxytocinergic system, implicated in birth and lactation, evolved to trigger stress buffering via proximity to the mother's body and its provisions and these safety signals, which are initially embedded in the mother's physical presence, shape OT functionality (Champagne and Meaney, 2007; Feldman et al., 2010a). Under conditions of stress, which cause the attenuation of OT levels, maternal proximity and safety signals may lead to OT release that normalizes the deficient levels, but these normalized levels are retained only as long as contact is maintained, charting a *plasticity-by-affiliation* social buffering mechanism in which the flexible response of the OT system relies on early affiliative mechanisms and requires maternal presence (Carter and Perkeybile, 2018; Feldman et al., 2014). It has indeed been found that among children with high-functioning ASD, the low baseline OT levels were normalized following a 20-minute episode of maternal presence and sensitive interaction (Feldman et al., 2014). Among children growing in safe ecologies, it is presumed that while infants respond to maternal caregiving by increasing OT levels (Feldman et al., 2010b), by the time children reach the preschool stage and begin to leave the home, the mother's function as a safety signal has already been internalized and the OT system has been stabilized; thus, mere interactions with the mother no longer activate the system. With regards to CT, whose role in stress modulating is less intimately tied to affiliation, studies have shown that while children exhibit an initial CT response to novel settings, such as home or lab visits, this response is attenuated by the mother's presence and sensitive behavior. However,

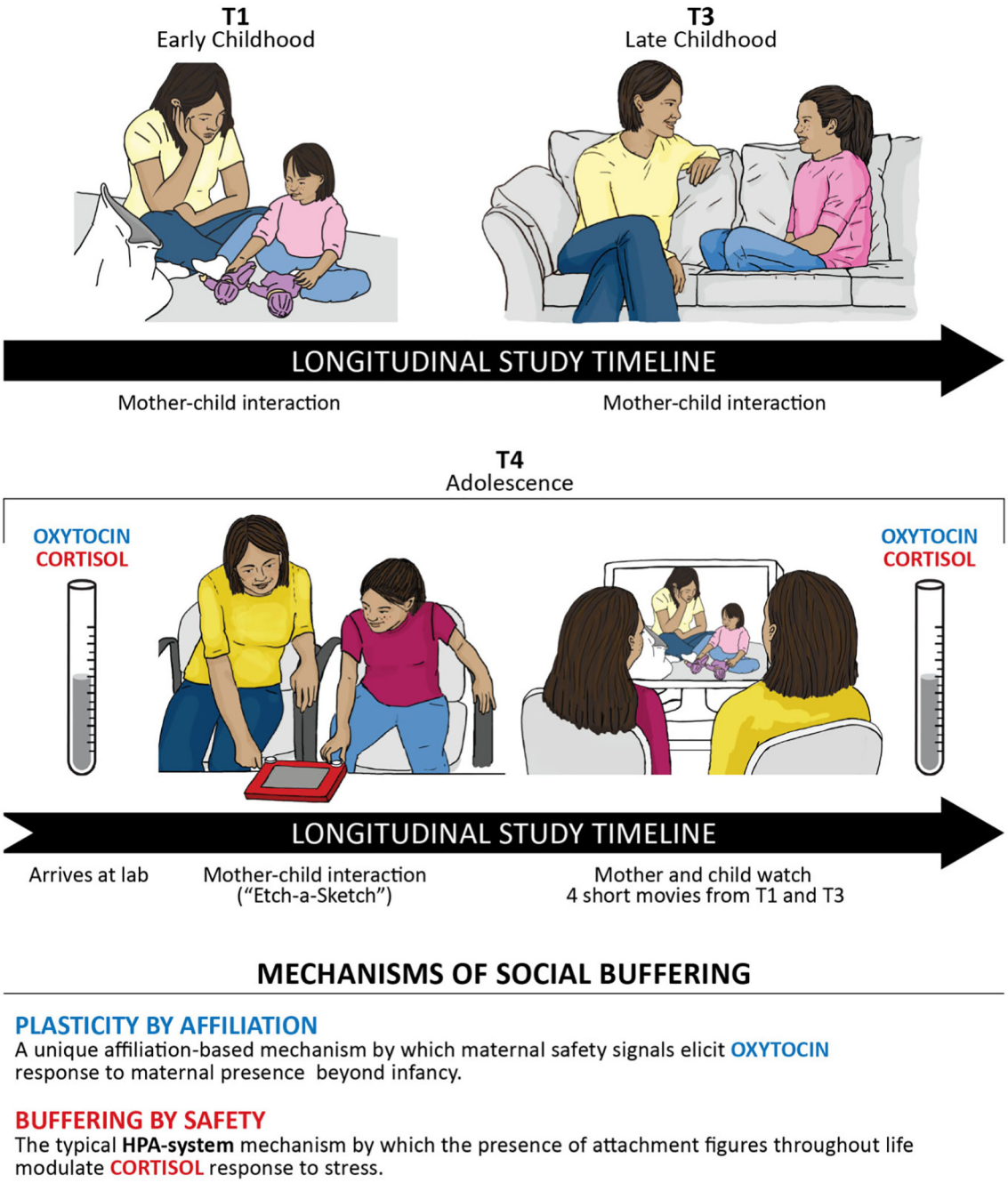

Fig. 1. Study time-line and procedures.
Footer: Note, the study also included assessment in middle childhood (age 5–8) that did not contain mother-child interaction and data from this assessment were not used here.

such stress recovery by the mother's presence was not found among children growing in ELS contexts, such as continuous war or chronic maternal depression (Apter-Levi et al., 2016; Feldman et al., 2013c). As such, with regards to the HPA-axis, we may find the typical *buffering-by-safety* mechanism but this mechanism may be triggered only when the rearing context enabled a sense of safety, but not when the highly-stressed early rearing inhibited the flexibility of the HPA system.

In the current study, we followed a unique cohort of mothers and children living in the area of Sderot, a small city located 10 km from the Gaza border. Families living in this town have been exposed to chronic war-related trauma for nearly two decades. Apart from periods of military operations, which occur every few years, families are exposed to the actual danger of missiles and rockets attacks and fire balloons that occur on a weekly or daily basis, even during periods of relative calm. To tap into children's relationship histories, we followed these children from early childhood to adolescence and used data from three time points that addressed the mother's safety-promoting behavior during mother-child naturalistic interactions. In each interaction across the three time-points, we evaluated the level of "maternal safety signals" (MSS), that is, behavior by which mothers signal to their children their availability, support, warmth, and protection, including acknowledgment of the child's non-verbal signals and verbal communication, modulation of maternal arousal and affect to match the child's level of involvement and interest, encouragement of social communication and openness, creation of a supportive environment, and expression of empathy toward the child's needs, state, and point-of-views.

In early adolescence, we exposed children to both live maternal MSS (during real-life interaction with the mother) and reminders of maternal MSS (during the observation of videos vignettes displaying their own interactions with their mother across childhood in the home ecology). We then tested the effect of these live and reminded MSS on the two stress-management systems. The study time-line and paradigm is presented in Fig. 1.

Our key hypothesis was informed by Hostinar et al.'s (2014) model, which suggests that the social buffering process is triggered by safety signals from the mother and, thus, we expected that only mothers whose behavior is safety-promoting would exhibit a social buffering function and impact the child's OT and CT response. In parallel, we also hypothesized that social buffering mechanisms would evolve differently when the mother's safety signals are internalized on the background of high- versus low-stress rearing contexts. Specifically, we expected that the interactions between the high- versus low- ELS rearing and the high versus low-MSS would express differently for the OT and CT systems. For OT, we expected to find lower baseline levels among children reared under chronic ELS, consistent with prior literature. However, when MSS are high, we expected that the live and reminders of maternal safety would trigger the *plasticity-by-affiliation* mechanism and the attenuated OT levels would normalize for the duration of the contact for children growing in ELS with safety-promoting mothers (Hypothesis 1). As to CT, we expected the typical *buffering-by-safety* mechanisms in which safety-promoting mothering leads to attenuation of the stress response following the initial CT response to novelty (in this case, arrival at the lab). However, we expected another interaction effect indicating that such attenuation is only possible when the rearing context was relatively safe. On the other hand, when the rearing context is chronically stressful, the mother's safety signals would not be able to reverse the long-term effects of ELS on inhibiting HPA-system flexibility (Hypothesis 2). These hypotheses were examined by testing the interaction effects of MSS and exposure to ELS, once for OT and again for CT reactivity.

2. Methods

2.1. Participants

The initial sample included 232 children and their mothers recruited in 2004–2005. Of these, 148 dyads comprised the trauma-exposed group and 84 the comparison low-stress group. The trauma-exposed group included a unique cohort of families living in the same frontline neighborhoods in Sderot, a small Israeli town located ten kilometers from the Gaza border. Citizens of Sderot have been exposed to continuous war- and terror-related trauma since 2001, living under a continues terror threat that involved several major military operations over the past years and missile and rockets attacks on a daily basis at times of exacerbation that occur on average every few months for a period of several weeks. Since 2001, dozens of civilians were killed, > 2000 injured, and a significant property and infrastructure damage was inflicted because of these attacks. The main defense mode is to take shelter at home or public sheltered areas. When sirens are initiated, citizen have only 7–15 s to reach shelter before possible explosion, and this functions as a major source of psychological distress and "trauma reminder". The control group comprised mother-child dyads matched on age, gender, and demographic conditions (maternal age, education, and SES) to the exposed group and living in comparable towns to Sderot in terms of size and socioeconomic condition in central Israel (for more details, see Feldman et al., 2013c). To ensure that children are exposed only to war-related trauma, we excluded families exposed to other sources of trauma (e.g., car accidents, sudden death in the family) or families with records of abuse or neglect. In the current study, children were observed three times from early childhood to early adolescence as follows: *Early Childhood* - Home visit when children were M = 2.76 years (SD = 0.91). *Late Childhood* - Home visit when children were M = 9.3 years (SD = 1.41). *Early Adolescence* – Lab visit when children were between 11 and 13 years (11.66, SD = 1.23).

A total of 111 mother-child dyads who participated in all 3 visits were included in the current study (44 males and 67 females; 58 exposed and 53 control). Attrition was related mainly to inability to locate families. No demographic differences were found between families who did or did not participate in the current stage in terms of child's age, gender, family income and maternal education. The study was approved by the local Institutional Review Board and all parents signed informed consent.

2.2. Procedures

2.2.1. Early childhood

Trained clinical psychologists conducted home visits, which included psychiatric diagnoses and mother-child free play interactions (for more information, see Feldman et al., 2013c).

2.2.2. Middle childhood

Children were seen between the ages of 5–8 years for psychiatric evaluation and these data did not contain mother-child interaction.

2.2.3. Late Childhood

Mothers and children were interviewed and engaged in interaction paradigms (Halevi et al., 2017; Ulmer-Yaniv et al., 2017). Here we used well-validated paradigm where dyads plan the "best day ever" to spend together for 7 min.

2.2.4. Early Adolescence

Mothers and children came for a lab visit, scheduled for weekday afternoons, which included interviews, hormonal assessment, and relational and individual paradigms. Upon arrival, saliva samples were collected (T1), followed by mother-child joint "Etch a Sketch" game for 7 min. In this game, parent and child each hold a knob of the toy and must cooperate to draw a house. Next, dyads watched four short videoclips of mother-child interaction in early and late childhood. The first two depicted unfamiliar dyads followed by personal relational reminders, when children observed themselves in early and late childhood interacting with their mother in their home ecology. The video clips included a short part from the beginning portions of the dyadic interactions mentioned above (free play from early childhood and planning the "best day ever" in late childhood). All three interactions could be positive, neutral or negative, depending on the dyadic relationship. After observing the video vignettes, the second saliva sample was collected for responsivity (T2).

2.3. Measures

2.3.1. Maternal safety signals (MSS)

Interactions from early childhood, late childhood, and early adolescence were all coded using the Coding Interactive Behavior Manual (CIB) (Feldman, 1998). The CIB is a well-validated tool to evaluate social behavior across ages and has shown good psychometric properties across different ages and cultures. Interactions are coded on multiple global scales from 1 (low) to 5 (high) based on frequency, intensity and duration of each behavior or social orientation. Mother sensitive safety-promoting style included five aspects across the three ages that contribute to the mother's function as a safety signals: Mother's *acknowledgment* of the child's verbal and non-verbal communications, *appropriate range of affect* – mother shows moment-by-moment matching and synchrony with the child's level of arousal, affect, enthusiasm, or verbal suggestions and, importantly, mother does not overstimulate the child, *maternal encouragement* - mother encourages, praises, and supports through verbal and non-verbal signals the child's bids, suggestions or success, and maternal positive affect; mother maintains constant positive, relaxed affective atmosphere throughout

the interaction. Finally, a key role of the maternal safety-promoting style is the *maternal supportive presence* – a code that address the degree to which mother provides a "holding environment" where the child feels safe to initiate social communication, express various affective and symbolic and, make errors, and engage in free and safe social interactions. In late childhood and adolescence, when interactions are based on verbal exchange, we also added the code of *maternal empathy* – mother is able to resonate with the child's messages and express empathy to his/her suggestions, attempts, desires, or frustration. Two trained coders, blind to other information, coded the interactions and reliability on 20% of the interactions exceeded 90% on all codes ($k > 0.82$, range 0.78–96). Variables were averaged to create the *maternal safety signals (MSS)* at each age and then averaged into a single score (alpha = 0.89; range across ages: 0.84–0.92). This combined score was divided using the median split (Median = 3.38) into high vs. low maternal sensitive safety-promoting style across childhood. To test individual continuity of the mother's sensitive safety-promoting style from early childhood to adolescence, Supplementary Table 1 shows significant correlations between *maternal safety signals (MSS*) across the three time-points. By including the mother's sensitive behavioral style over lengthy periods we aimed to support our key hypothesis – that the effects of human attachment should be measured longitudinally, taking into account the components of maternal behavior that is internalized over extended repeated experiences.

2.3.2. Saliva samples collection and analysis

Salivary samples were collected by passive drooling and stored at −20 °C. To precipitate the mucus, samples underwent three freeze-thaw cycles, freeze at −70 °C and thaw at 4 °C. After the forth cycle, tubes were centrifuged twice at 1500 ×*g* (4000 rpm) for 20 min. Supernatant was collected and the aliquots stored at −20 °C until assayed.

2.3.3. Oxytocin

To concentrate the samples by four times, the liquid samples were freeze dried for 3–4 days. Prior the freeze-drying procedure the samples were stored at −80 °C, for at least three days. The dry powder then kept in −20 °C until assayed. OT levels were measured using a commercial OT Enzyme-Linked Immunosorbent Assay (ELISA) kit (Assay Design, ENZO, New-York, USA). The kit provides quantitative in vitro assay for OT in human saliva. The dry samples were reconstructed in the assay buffer immediately before the assay. Measurements were done in duplicate, according to the kit's instructions. The concentration of OT in the samples was calculated by using MatLab-7 according to relevant standard curves. The intra-assay coefficients of samples and controls are < 12.4% and 14.5%, respectively.

2.3.4. Cortisol

The concentration of Cortisol was determined by using a commercial ELISA kit (Salimetrics, USA). Measurements were performed according to the kit's instructions. In addition to the manufacture's low and high controls: 1060 + 270, 9700 + 2430 pg/ml, three in-house controls were included in each plate (250, 880, 1330 pg/ml), thus to correlate between plates measured in different periods. The concentration of cortisol was calculated by using MatLab-7 according to relevant standard curves. The intra-assay coefficient of variance (CV %) of manufacture and in-house controls low and high range controls is 7.54%. The inter-assay CV of samples is < 16.11%.

2.4. Statistical analysis

We used SPSS for Windows, version 23 (IBM, Chicago, Illinois). Of the sample ($N = 111$), one subject was unwilling to give saliva and one had blood in his saliva. Some children gave insufficient saliva and the final sample was 105 and 107 for CT (T1, T2), and 95 and 95 for OT, respectively. OT and CT levels were checked for outliers and values > 3 SD were omitted (4 CT and 5 OT samples). Salivary OT and CT levels were not distributed normally and were log- transformed. We first compared OT and CT levels at T1 and T2 using MANOVA. Repeated measure ANOVA measured changes in OT and CT as function of maternal sensitive safety promoting style and ELS. Group comparisons in sociodemographic and maternal characteristics between the exposed and comparison low-stress groups were conducted using *t*-tests (continuous variables) and X^2 tests and Phi/Cramer's V as effect size (dichotomous variables).

3. Results

Differences between groups in study variables appear in Table 1 and show no difference in sociodemographic measures, including children's age, gender, maternal age, maternal education and income. Analyses of the maternal sensitive safety promoting style throughout life score (combining the three measures) revealed that exposed mothers showed significantly less maternal safety signals toward their children compared with low-stressed mothers ($t_{(109)} = -2.67$, $p < 0.01$). Correlation between maternal safety signals (MSS) in the three study stages and their average are presented in supplementary material (supplementary Table 1).

3.1. Oxytocin: plasticity-by-affiliation stress buffering effect (hypothesis 1)

To assess the effects of live and reminders of relational behaviors, group (ELS, comparison) and maternal safety signals (High/Low MSS) repeated measures ANOVA was conducted with OT as a within-subject factor and group and maternal safety signals as between-subjects factors. Means and standard errors are presented in Table 2 and Fig. 2. Results yielded main effect of OT, indicating that OT significantly increased following the attachment manipulation: $F_{(1,82)} = 4.32$, $p = 0.04$, $\eta^2 = 0.05$, but no significant main effect emerged for group or MSS ($p_s > 0.26$). However, this significant within-subject main effect was defined by a two- and a three-way interaction effects. A two-way interaction of OT and group emerged: $F_{(1,82)} = 5.90$, $p = 0.02$, $\eta^2 = 0.07$. Post hoc analyses using the Bonferroni correction for multiple comparisons indicated baseline levels (T1) in the high-ELS group were significantly lower compared to the low-stress comparison group; $F_{(1,82)} = 5.03$, $p = 0.03$, $\eta^2 = 0.06$; however, these were attenuated and at T2 differences in OT between groups was no longer significant ($p = 0.65$). No significant interactions between MSS and OT were found ($p = 0.17$). Additionally, a three-way interaction effect of OT, group, and MSS was found; $F_{(1,82)} = 4.29$, $p = 0.04$, $\eta^2 = 0.05$. Post hoc analyses indicated that the change within the exposed group occurred only for children with high levels of MSS ($p < 0.001$) and not for those with low levels of MSS ($p = 0.53$). The change in OT levels for the comparison group remained insignificant, regardless of whether MSS were high or low.

3.2. Cortisol: buffering-by-safety stress buffering effect (hypothesis 2)

Effects of live and reminders of attachment, ELS, and MSS were similarly assessed by a three-way repeated measures ANOVA (see Table 2 and Fig. 3 for means and standard errors(. Results indicated main effect for CT: overall, children's CT levels decreased following the attachment manipulation; $F_{(1,96)} = 4.69$, $p = 0.03$, $\eta^2 = 0.05$, with no main effects for ELS or MSS ($p_s > 0.21$) and no interaction of CT and group, suggesting that CT levels at both T1 and T2 were similar across groups ($p = 0.79$). No interaction effect was found between CT and MSS ($p = 0.79$). However, the within-subject decrease of CT was modified by a three-way interaction of CT, group, and MSS; $F_{(1,96)} = 4.16$, $p = 0.04$, $\eta^2 = 0.04$. Post hoc analyses using the Bonferroni correction for multiple comparisons indicated that the reduction in CT was found only among control children who experienced MSS across childhood ($p = 0.002$). Low-stress children who received low

Table 1
Comparisons between groups in demographic variables

	Comparison	Exposed	t/χ^2	Effect size (Cohen's d/Φ)
Gender				
Female	36 (67.9%)	31 (53.4%)	$\chi^2_{(1)} = 2.42, p > 0.05$	0.15
Child Age	M = 11.55 (SD = 1.14)	M = 11.76 (SD = 1.31)	$t_{(107)} = 0.90, p > 0.05$	0.17
Mother age	M = 41.26 (SD = 4.40)	M = 40.06 (SD = 5.81)	$t_{(109)} = -1.22, p > 0.05$	0.23
Mother education				
High school education	9 (17.0%)	18 (31.0%)	$\chi^2_{(1)} = 2.97, p > 0.05$	0.16
Above high school	44 (83.0%)	40 (69.0%)		
Maternal marital status				
Married	49 (92.5%)	56 (96.6%)	$\chi^2_{(1)} = 0.91$ p > 0.05	0.09
SES (1–9)	M = 4.52 (SD = 1.42)	M = 4.13 (SD = 1.02)	$t_{(107)} = -1.66, p > 0.05$	0.31

Table 2
Means and standard errors for OT and CT according to ELS and MSS.

		Exposed		Comparison	
		SeM	M	SeM	M
OT Time 1 (log)	MSS High	0.07	1.38	05	1.46
	MSS Low	0.05	1.42	07	1.62
OT Time 2 (log)	MSS High	0.06	1.65	05	1.42
	MSS Low	0.05	1.45	07	1.63
CT Time 1 (log)	MSS High	0.05	3.38	05	3.33
	MSS Low	0.05	3.32	06	3.25
CT Time 2 (log)	MSS High	0.06	3.34	05	3.17
	MSS Low	0.05	3.25	06	2.28

Note: MSS = maternal safety signals.

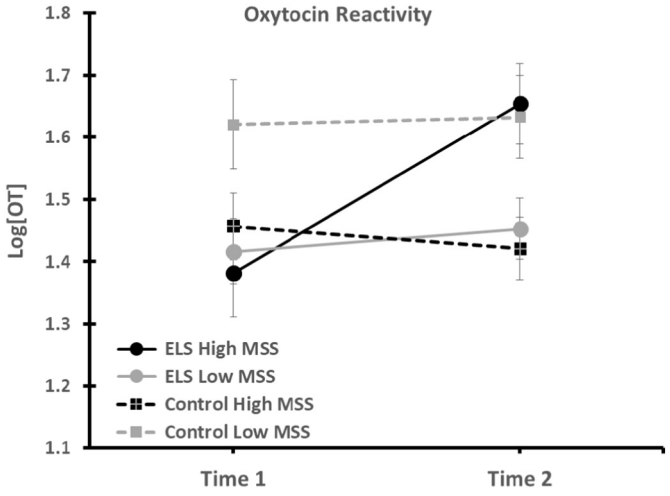

Fig. 2. Changes in OT before and after attachment manipulation as a function of exposure to Early Life Stress (ELS) and Maternal Safety Signals (MSS).

MSS showed no such significant decrease ($p = 0.54$) and ELS children, whether mothers provided high *or* low MSS, exhibited no CT reduction following live and reminders of the attachment figure ($p_s > 0.15$).

4. Discussion

The impact of maternal presence and caregiving behavior on the child's ability to manage stress throughout life – the stress buffering effect – marks a key progress in the evolution of mammals when the mother-infant bond became the central context for the organization of neurobiological systems that enable mammals to handle ecological hardships through social relationships. Yet, despite its centrality, research did not address the maturation of this core function in humans utilizing a longitudinal, multi-system approach that considers both natural variations in maternal care and variability in early stress

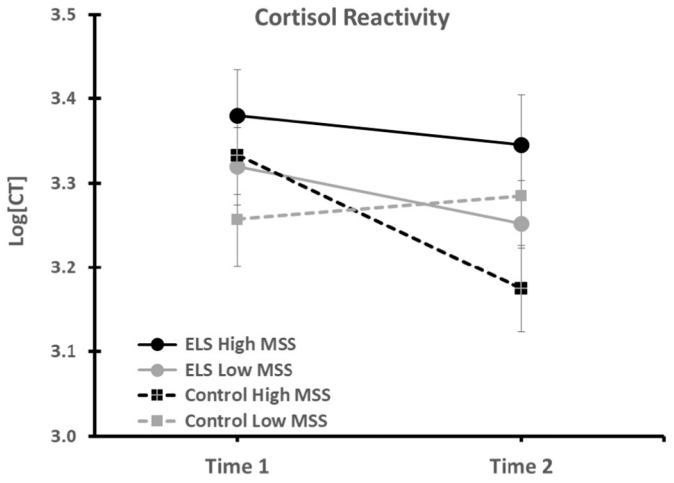

Fig. 3. Changes in CT before and after attachment manipulation as a function of exposure to Early Life Stress (ELS) and Maternal Safety Signals (MSS).

exposure. Our study, which utilized a novel attachment induction paradigm to test the social buffering effect of maternal stimuli, is novel in several aspects. First, our cohort offers a unique "natural experiment" where all children are exposed to the same chronic stressors, which is a rare condition in human ELS research that typically includes heterogeneous adversities. Yet, in our study, the source of ELS comes from outside the family and this affords the entire spectrum of safety-promoting mothering, a feature not common in ELS studies where adversity often originates in the home and early relationships are not experienced as safe. Second, the longitudinal approach enabled us to track the maternal function as a "safety signal" across the entire first decade of life. Although safety learning has long been suggested as a key social-learning mechanism, only recently has it been incorporated into human research and proposed to be mediated by the OT system (Eckstein et al., 2019). Our paradigm, which exposed adolescents to both live mother-child interactions, which reverberated the childhood patterns, and to reminders of the attachment relationship in the natural ecology, enabled us to tap into the relationship histories that underpin human attachments and to assess how these internal models of attachment impact neuroendocrine response (Bowlby, 1988; Bretherton et al., 1990; Feldman, 2016). Finally, this is this first study to examine the effects of maternal presence and attachment reminders on both the oxytocinergic and HPA systems, the two ancient systems by which organisms across the phylogenetic ladder manage stress in their ecology.

Our findings on social buffering in an attachment induction paradigm chart two distinct mechanisms of social buffering, one for the OT system, the key neurobiological system of social affiliation which is implicated in plasticity at the cellular and network assembly levels (Althammer et al., 2018; Feldman, 2015b), the other for the HPA axis, the body's main regulator of stress. Both mechanisms are sensitive to

variations in the mother's safety-promoting caregiving and to excessive stress in the rearing ecology, but their caregiving are system-specific. Thus, while our findings lend support to the "stress buffering" model (Hostinar et al., 2014), they add layers of specificity. Overall, we found that social buffering in natural attachment-related contexts is the fortune of few. Only those who received safety-promoting caregiving across childhood can alter their stress neurobiology in response to real-life experiences and reminders of the attachment relationship. In contrast, when the mother does not function as a safety signal, her role as a "stress shield" falters. Furthermore, our findings show that even the role of the safety-promoting mother depends on the rearing context; it impacts the OT system in harsh contexts and the HPA-system in low-stress ecologies, the first via normalizing the attenuated OT levels in stress-exposed youth, the second by maintaining system flexibility in children growing in safe contexts. These findings indicate that stress buffering mechanisms, a key function of close attachments, are relationship-specific, context-specific, and system-specific. It is important to note that our findings represent only a first step in this line of research and much further research is required to untangle the effects of attachment induction on stress reactivity across multiple attachment bonds, stressful moments, personal histories, and neural, epigenetic, and microbiological stress-management systems. Furthermore, prior research on the effects of attachment style and sensitive caregiving on hormonal responses has mainly investigated infants or young children, and very few neuroendocrine studies addressed adolescents, with nearly none utilizing longitudinal cohorts (Gunnar and Hostinar, 2015; Hostinar et al., 2014). Much further research is needed to examine the maturation of the OT and HPA-axis systems across later childhood and adolescence in relation to caregiving over time in health and high-risk conditions.

Adolescents exposed to ELS showed attenuated baseline OT levels, consistent with much research in various ELS conditions (Donadon et al., 2018). However, when children experienced high MSS throughout childhood, OT levels increased and normalized after the attachment manipulation consistent with the *plasticity-by affiliation* mechanism. This was not found among controls, for whom attachment cues did not alter the high initial OT levels. The overarching role of the OT system in stress management is due, in part, to its role in neural plasticity. OT neurons can co-express with multiple neurotransmitter systems, including dopamine, serotonin, and opioids, and oxytocin-expressing neurons include multiple cell types, including GABAergic interneurons, glutamatergic pyramidal cells, and other peptidergic cells (Althammer et al., 2018). OT integrates brain and periphery, intersects with the immune and reward systems, functions as both a hormone and neurotransmitter, reaches multiple brain target, and incorporate massive epigenetic inputs (Althammer et al., 2018; Feldman et al., 2016). OT is a key neuromodulator in the mammalian brain, increases the salience of social information and circuit plasticity in the hippocampal network (Tirko et al., 2018), and early attachment experiences shape OT receptors availability (Froemke and Carcea, 2017) and hippocampal plasticity (Zheng et al., 2014), highlighting the role of early attachment experiences in the lifelong plasticity of the system.

Our results suggest that only in the context of chronic trauma, safety-promoting mothers can continue to function as a social buffer, adaptively regulating children's OT responsiveness. In low-stress ecologies, attachment relationships are internalized toward the end of the first year with the maturation of the prefrontal cortex circuitry (Hostinar et al., 2014). These developmental changes enable the mother–child attachment to become less dependent on phasic hormonal alterations and to be maintained by higher-order neural mechanisms that sustain humans' representation-based attachments (Feldman, 2015b, 2017; Taylor, 2006). Early trauma may not allow attachment security to consolidate into representations, possibly due to abnormalities in frontal cortex maturation (Hostinar et al., 2014). Children exposed to chronic ELS showed phasic changes in OT secretion following our attachment induction, but only when mothers provided high MSS, suggesting that in these children the OT system may still exhibit flexible adaptation to maternal presence and absence.

Unlike younger children, for whom sensitive mother-child interactions induce OT release (Feldman et al., 2010b; Galbally et al., 2011), only in atypical development mothers continue to impact their children's OT reactivity at later stages. Adolescents exposed to ELS may show developmental immaturity and may thus be unable to maintain high oxytocinergic set-points without constant reinforcement from the caregiver. In such youth, the mother's sensitive caregiving and mother-child endocrine synchrony of OT production (Ulmer-Yaniv et al., 2017) continue to function as an external regulator, similar to the maternal biobehavioral regulation of physiological systems in infancy (Feldman, 2015a, 2017). We previously showed that among preschoolers with ASD, proximity to a sensitive mother normalized the low OT levels, but these increased levels returned to the low baseline 20 min after the mother-child contact terminated (Feldman et al., 2014). These findings highlight the maternal role as an "external regulator", which functions in all mammals to tune biobehavioral systems in early infancy (Hofer, 1995; Feldman and Eidelman, 1998). As seen, under ELS, safety-promoting mothers continue to externally-regulate OT's plasticity well beyond its maturational window by employing the *plasticity-by-affiliation* mechanism, which, while beneficial, fixates an early, immature function.

In the HPA-system, on the other hand, we found the typical *buffering-by-safety* mechanism, consistent with studies showing CT reduction by multiple attachment figures from infancy and across development (Gunnar et al., 1989; Hostinar et al., 2014). However, unlike the oxytocinergic system, maternal safety-promoting caregiving buffered stress only among children growing in low-risk ecologies. Previous studies on adolescents demonstrated that positive mother-child relationship is associated with attenuation of CT response and quicker return to baseline after a stressor (Cameron et al., 2017; Pasco Fearon et al., 2017). However, in children exposed to various environmental and affiliative hazards, including chronic maternal depression, war-related trauma, abuse, and adoption, evidence points to reduced flexibility of the CT stress response (Apter-Levi et al., 2016; Elzinga et al., 2008). Similar to our paradigm, studies have shown that when children arrive at the lab or during a home visit, there is an initial CT response to novelty, but CT levels are reduced during the visit when mothers are sensitive (Apter-Levi et al., 2016; Davies et al., 2007; De Bruijn et al., 2009; Feldman et al., 2013a; Smeekens et al., 2007), suggesting that although our paradigm did not involve a stressor, HPA reactivity to mother-child interaction may index the degree to which mother serves as a safety signal. Similarly, several studies have shown that CT levels are attenuated to stressors when mothers are sensitive. For instance, neglected children showed CT elevation following interaction with their parent, whereas controls exhibited CT decrease (Fries et al., 2008). This is consistent with animals studies linking early caregiving to the development of the HPA-axis stress response (Gunnar and Quevedo, 2007; Meaney and Szyf, 2005).

The two stress buffering mechanisms may reflect a fundamental difference in the evolutionary nature of the oxytocinergic and HPA systems. In typical development, the HPA stress response continues to be buffered by the presence of supportive attachment relationships throughout life, including partners and close friends (Heinrichs et al., 2003; Kirschbaum et al., 1995). When the environment is safe and attachment secure, mothers can serve as social buffers and reduce CT levels throughout development, possibly via mechanisms of endocrine fit found for infants, children, and adolescents (Halevi et al., 2017; Pratt et al., 2017; Yirmiya et al., 2018). However, when the source of trauma is external to the family and the global rearing environment is unsafe, the social buffering effect is not manifested via the typical HPA channel even when the mother functioned as a safety signal across childhood. In such cases, the mechanism shift to the OT system, which momentarily applies the *plasticity-by-affiliation* social buffering mechanism that requires the physical presence of the caregiver.

Adolescence is a period of biobehavioral reorganization, associated with both heightened risk and new opportunities (Crone and Dahl, 2012). Adolescence is also a time of heightened risk for psychopathology (Gunnar et al., 2009). Profiling adolescents' hormonal reactivity and understanding how attachment relationships can buffer stress at this stage may be important for understanding how relationships influence the biological stress response and may buffer the emergence of stress-related disorders.

Several study limitations should be mentioned. First, the individual stability of the MSS across the three time points in our study was low-to-moderate. Although attachment theory rests on the assumption that maternal caregiving behavior is individually stable, very few studies repeatedly observed maternal behavior across lengthy periods, particularly in high-risk contexts, and the correlations found here are consistent with other studies that measured maternal sensitivity from infancy to adolescence (Feldman, 2010; Feldman et al., 2013a). Second, the current study did not examine hormonal reactivity of children exposed to chronic stress at various points across development, only at the adolescent time-point. Future studies may benefit from assessing physiological regulation in children exposed to a variety of ELS conditions across the first years of life. Another point to keep in mind is the validity of salivary OT, an issue that has been previously raised (Valstad et al., 2017), despite the fact that studies have shown links between salivary OT with plasma OT, intranasal administration, genetic variability on the oxytocin receptor gene, and activation in brain areas rich in oxytocin receptors (Feldman, 2016). Still, more longitudinal studies that include multiple samples and test OT in different fractions are important. Another limitation is that we did not assess the participants' perceived level of stress. Such measures could have enriched our understanding of the factors influencing hormonal reactivity under objective environmental stress. Future studies will benefit from including other attachment figures that can serve as social buffers in adolescence, especially fathers, mentors, close friends, and emerging romantic relationships. In addition, patterns of sensitive-caregiving are culture-specific and thus our study needs replication across cultures that utilize other forms of sensitive caregiving, such as touch-based caregiving (Feldman et al., 2006). Finally, to strengthen the validity of the saliva hormone measurements (Valstad et al., 2017), future studies should also measure the influence of MSS on blood OT and CT.

As millions of the world's children are growing up under conditions of chronic war, ethnic strife, immigration, and poverty, building targeted interventions that can bolster the mother's capacity to function as safety signals amidst hardship is among the most pressing endeavors for future research.

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Declaration of competing interest

None.

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