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BRIEF REPORT

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Vigilance for threat accounts for inter-individual variation in physiological responses to adversity in rhesus macaques: A cognition × environment approach

Tara M. Mandalaywala[1] | Lauren A. Petrullo[2,3] | Karen J. Parker[4] | Dario Maestripieri[5,6] | James P. Higham[2]

[1] Department of Psychology, New York University, New York, New York

[2] Department of Anthropology, New York University, New York, New York

[3] Interdepartmental Doctoral Program in Anthropological Sciences, Stony Brook University, Stony Brook, New York

[4] Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California

[5] Institute for Mind and Biology, The University of Chicago, Chicago, Illinois

[6] Department of Comparative Human Development, The University of Chicago, Chicago, Illinois

Correspondence
Tara M. Mandalaywala, Department of Psychology, New York University, 6 Washington Place, New York, NY 10003.
Email: tmandalaywala@nyu.edu

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Abstract

Early life adversity (ELA) can lead to poor health later in life. However, there is significant variation in outcomes, with some individuals displaying resilience even in the face of adversity. Using longitudinal data collected from free-ranging rhesus macaques between birth and 3 years, we examined whether individual variation in vigilance for threat, an early emerging attentional bias, can account for variation in long-term outcomes between individuals reared in similar environments. We found that ELA and vigilance during infancy interact to predict physiological dysregulation in Sympathetic Nervous System (SNS) and Hypothalamic-Pituitary-Adrenal (HPA) stress responses during juvenility. During high stress periods, High ELA juveniles with high vigilance exhibit less asymmetry than High ELA juveniles with low vigilance. This suggests that although increased vigilance is viewed as a negative consequence of ELA, it might also be a mechanism by which vulnerable individuals proactively buffer themselves from negative outcomes in unstable or threatening environments.

KEYWORDS
asymmetry, cognitive bias, cortisol, early life adversity, rhesus macaque, salivary α-amylase

1 | INTRODUCTION

Early life adversity (ELA), such as parental abuse or neglect, is often associated with poor mental and physical health later in life (e.g., Harlow, Dodsworth, & Harlow, 1965; Nelson, Fox, & Zeanah, 2014). However, whereas many individuals exposed to ELA develop poor health outcomes, others display relative resilience to adversity later in life. A variety of genetic and environmental factors have been proposed to explain why some individuals flourish when others in comparable situations falter (e.g., Belsky & Pluess, 2009; Caspi & Moffit, 2006; Franklin, Saab, & Mansuy, 2012; Hostinar, Cicchetti, & Rogosch, 2014; Parker & Maestripieri, 2011). The role that early emerging *cognitive* processes might play in explaining inter-individual variation in vulnerability and resilience to ELA; however, remains poorly understood.

Cognition can help individuals regulate perception of and attention to the world around them, thereby providing them with a potential means by which to cope with adversity. One aspect of cognition that might explain inter-individual variation in resilience is vigilance for threat (hereafter, vigilance), an attentional bias to

threat-relevant stimuli, which emerges early in life in both human and nonhuman primates (humans: Farroni, Menon, Rigato, & Johnson, 2007; Grossman, Striano, & Friederici, 2007; rhesus macaques (*Macaca mulatta)*: Mandalaywala, Parker, & Maestripieri, 2014). Vigilance develops in response to environmental input and is often expressed more strongly in individuals previously exposed to ELA (humans: Shackman, Shackman, & Pollak, 2007). Although extreme vigilance is implicated in anxiety disorders (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007), the emergence of vigilance in response to early experiences of adversity can also be a useful adaptation. For example, in adverse environments, active deployment of vigilance might be an effective way of managing exposure to frequent stressors (Frankenhuis & de Weerth, 2013). However, studies have not examined whether variation in vigilance can explain inter-individual variation in developmental outcomes, such that—under conditions of adversity—individuals that exhibit greater vigilance show more favorable outcomes than those with less vigilance. In the present study, we adopt a "cognition by environment approach" to assess whether ELA and vigilance for threat during infancy interact to explain inter-individual variation in developmental outcomes in juvenile rhesus macaques, a nonhuman primate model species frequently utilized in research on anxiety and emotion regulation (e.g., Kalin & Shelton, 2003; Maestripieri, Martel, Nevison, Simpson, & Keverne, 1992). Given the many physiological, behavioral, social, and cognitive similarities of rhesus macaques to humans, they are an ideal species in which to investigate how cognition might moderate the effects of adversity to lead to more or less resilient phenotypes later in life.

Although there are a variety of developmental outcomes affected by ELA, we focus on the regulation of stress physiology given its established links to health outcomes. Negative mental and physical health outcomes in response to ELA may arise as a consequence of changes to the function and regulation of the stress response, especially in the Sympathetic Nervous System (SNS) and Hypothalamic-Pituitary-Adrenal (HPA) axis (McEwen, 2000). In response to a stressor, activation of the SNS, through release of catecholamines, should lead to prompt initiation of a "fight or flight" response, while activation of the HPA axis, through release of glucocorticoids, should lead to a metabolic response that mobilizes energy stored in tissues and prepares the body for future resource scarcity (Sapolsky, Romero, & Munck, 2000). In an optimally functioning system, the SNS and HPA axis should both exhibit well-regulated responses to a stressor, characterized by an acute response followed by a swift return to baseline (Chrousos & Gold, 1992). However, individuals exposed to ELA often exhibit a *dysregulated* phenotype characterized by a blunted acute response (i.e., an inability to mount an appropriate stress response) due in part to chronically elevated basal concentrations of stress hormones such as catecholamines (SNS) or cortisol (HPA) (in nonhuman primates: Sanchez, 2006; Sanchez et al., 2010). Although the SNS and HPA play different roles in the stress response system, recent research suggests that coordination between these two systems might be particularly important and thus the notion of dysregulation has been applied to the *interaction* of stress response systems. These recent studies specifically focus on the extent of asymmetry between these systems (e.g., relatively greater reactivity in one system than the other), with greater asymmetry reflecting greater cross-system dysregulation (reviewed in Kreher, Powers, & Granger, 2012). In humans, research using methods from salivary bioscience, which allow the measurement of correlates of SNS (salivary α-amylase) and HPA axis (salivary cortisol) activity non-invasively, have found that this asymmetry has functional consequences. Asymmetry has been associated with anxiety disorders (e.g., Reeves, Fisher, Newman, & Granger, 2016; Schumacher, Kirschbaum, Fydrich, & Strohle, 2013) and a suite of behavioral problems (e.g., externalizing behavior: Gordis, Granger, Susman, & Trickett, 2008). Asymmetry in SNS and HPA responses to stress has been shown to emerge in response to ELA in both humans (Gordis, Granger, Susman, & Trickett, 2006) and nonhuman primates (e.g., rhesus macaques: Petrullo, Mandalaywala, Maestripieri, Parker, & Higham, 2016). However, the extent of asymmetry in response to ELA is highly variable, suggesting that additional factors are important in determining the extent to which an individual's physiological stress systems are affected by early adversity. Here we hypothesized that vigilance for threat during infancy would moderate the effects of ELA on later physiological dysregulation in rhesus macaques. Specifically, we tested the prediction that increased vigilance during infancy promotes resilience later in life by attenuating the negative effects of adversity on SNS-HPA asymmetry in juvenility.

2 | METHODS

The study was conducted on Cayo Santiago, a small Puerto Rican island with a population of approximately 1,500 rhesus macaques. Subjects were 20 free-ranging rhesus macaques (13 male, 7 female) for whom longitudinal behavioral and physiological data were collected during the first 3 years of life as part of a larger study.

2.1 | Behavioral data

Using continuous focal animal sampling in which each individual was observed twice weekly, behavioral data were collected across the first 12 weeks of life for 11.8 ± 0.05 hr/infant (mean ± SEM). We quantified ELA through the frequency of maternal rejection and abuse, two behaviors frequently used in studies of infant maltreatment in macaques (e.g., Maestripieri & Carroll, 1998). Maternal rejection occurred any time the mother prevented contact or access to the nipple by holding or pushing the infant away from her body, and maternal abuse occurred any time the mother physically maltreated her infant (e.g., hitting, shoving, dragging, throwing). We converted data to mean hourly rates and averaged abuse and rejection behaviors together to create a single overall frequency of maltreatment for each subject. Subjects were assigned to a high, moderate, or low ELA category based on their relative rate of ELA from a three-way split in maternal maltreatment frequencies (as in Mandalaywala, 2014). As in our previous study (Petrullo et al., 2016), we found that Low ELA

individuals exhibit SNS:HPA ratios that differ from Moderate and High ELA individuals; therefore, we combined Moderate and High ELA categories into one High ELA category (Low ELA $n = 9$; High ELA $n = 11$).

Putting agonistic interaction data from each subject's mother into a winner-loser matrix in MatMan (de Vries, Netto, & Hanegraff, 1993), we generated linear dominance hierarchies. Following 10,000 iterations, significant linear hierarchies were produced (linearity test using Landau's linearity index corrected for unknown relationships, $p = .03$). Each mother/infant dyad was categorized as high ($n = 6$), middle ($n = 8$), or low ($n = 6$) ranking by dividing mothers equally into the top, middle, or bottom third of the hierarchy, respectively.

2.2 | Cognitive data

Vigilance data were collected as part of a previous study (Mandalaywala et al., 2014). At 8.5 ± 0.08 months old (mean ± SEM) subjects were simultaneously shown two validated stimuli (Bethell et al., 2012a): stimuli were color photographs (8.25 in. long × 11.75 in. high) of an unfamiliar male displaying either an open-mouth threat or a non-emotional expression (see Mandalaywala et al., 2014, for examples of stimuli), and subject's responses were then videorecorded for 5 s using a handheld camcorder (Canon FS20). Subjects were approached while sitting calmly and away from the group, and a trial was initiated by setting up the cardboard apparatus less than 2.5 m in front of the subject. Stimuli were initially covered with colored blinders, and after the subjects attention was captured and oriented toward the center of the apparatus (equidistant from both blinders) both blinders were removed simultaneously. Observers blind to experimental aims and condition coded video data frame by frame (30 frames/sec), counting the number of frames spent looking at each stimuli separately, and converting to ms. To quantify vigilance, we subtracted the time the subject spent looking at the neutral stimulus from the time the subject spent looking at the threatening stimulus; a positive value indicated more time looking at the threatening stimulus, and a negative value more time looking at the neutral stimulus. All videos were coded by an additional coder with high inter-observer reliability (Cohen's $\kappa = 0.82$).

2.3 | Saliva collection

Saliva was collected using Salimetrics® Oral Swabs (State College, PA), following previously validated collection and processing protocols (Higham, Vitale, Rivera, Ayala, & Maestripieri, 2010) as part of a previous study (Petrullo et al., 2016). Saliva samples ($N = 217$) were collected when subjects were 2.89 ± 0.01 years old (mean ± SEM). Samples were collected during periods of "high stress" (≤15 min after a conflict with conspecifics in which the subject was the aggressed individual; $n = 90$) and "low stress" (after subject rested or had minimal conspecific engagement for ≥30 min; $n = 127$). As described in Petrullo et al. (2016), saliva samples were collected between 7:00 and 14:00 by presenting a swab, tied to a piece of rope and lightly coated in Tang, to the subject either by draping it over a rock or hanging it on a tree or other structure. The time that subjects placed the swab in their mouth was recorded using a stopwatch, and once a subject became disinterested in the swab it was cut from the rope, placed into a centrifuge tube with a retainer, and placed on ice. Samples were centrifuged after 14:00 and then frozen at −80 °C until analysis.

2.4 | Assay protocols

As described elsewhere (Petrullo et al., 2016), saliva samples were assayed for cortisol and sAA using commercial enzyme-immunoassays (Salimetrics), validated for use in rhesus macaques (Higham et al., 2010). For salivary cortisol, high and low inter-assay coefficients of variation (CV) were 2.4% and 3.9%, respectively, and high and low intra-assay CVs were 7% and 4%, respectively. For sAA, high and low inter-assay CVs were 2.5% and 7.2%, and high and low intra-assay CVs were 3.6% and 5.8%. sAA values were flow rate adjusted by multiplying concentrations by saliva volume (ml) deposited on the swab over the time (min) the swab was chewed during collection; sAA values are expressed in U/min. We excluded samples with undetectably low concentrations or insufficient volume to test reliably. One subject was excluded from all analyses due to having a low stress cortisol concentration average more than three times above the interquartile range, leaving a final sample size of 19 (Low ELA $n = 9$; High ELA $n = 10$), with $n = 127$ samples from 19 individuals (cortisol), and $n = 75$ samples from 13 individuals (sAA).

2.5 | Data analysis

For each individual separately, we calculated average Low Stress (LS) cortisol and LS sAA concentrations, as well as average High Stress (HS) cortisol and HS sAA concentrations across all samples. To examine individual reactivity within a biological measure, we calculated cortisol reactivity (HS cortisol: LS cortisol, $n = 19$) and sAA reactivity (HS sAA: LS sAA, $n = 13$). For cortisol and sAA reactivity, a larger value indicates a properly functioning stress response (e.g., an individual has a low baseline [LS] concentration followed by a robust response to a stressor [HS]: see Sanchez, 2006 for a review).

Finally, to utilize a multi-systems approach (e.g., Granger, Kivlighan, El-Sheikh, Gordis, & Stroud, 2007), we additionally calculated LS asymmetry (LS sAA: LS cortisol, $n = 13$) and HS asymmetry (HS sAA: HS cortisol, $n = 13$) to determine whether physiological outcomes were affected in an interactive manner. For LS and HS asymmetry, a larger number indicates a larger relative difference between sAA and cortisol concentrations for an individual, reflecting greater asymmetry, whereas a smaller number indicates a smaller relative difference, reflecting greater symmetry. A larger value, and thus greater asymmetry, is indicative of a dysregulated stress response system, where multiple components of the stress response complex do not recognize or respond to stressors in a coordinated manner (e.g., Ali & Pruessner, 2012; Gordis et al., 2006). Lack of coordination between physiological response systems has been implicated in increasing allostatic load, leading to wear and tear on the system (e.g., McEwen, 1998).

Whereas a previous study found an effect of maternal rank on vigilance in a larger sample that included these subjects (Mandalaywala et al., 2014), using General Linear Models (GLMs) with maternal rank (high, moderate, or low) as the predictor we found no effects of maternal rank on vigilance, $F_{(1,16)} = 2.10$, $p = .155$, or on any physiological variables (cortisol reactivity: $F_{(1,16)} = 0.90$, $p = .426$; sAA reactivity: $F_{(1,10)} = .26$, $p = .775$; LS asymmetry: $F_{(1,10)} = 0.05$, $p = .953$; HS asymmetry: $F_{(1,10)} = 0.99$, $p = .403$). A Chi-squared test revealed that maternal rank was also not associated with ELA, X^2 (2, $N = 19$) = 1.32, $p = .517$; therefore, rank was not included in subsequent analyses. As indicated by independent t tests with subject sex (male, female) as the predictor, there were no sex differences in rates of ELA, $t(17) = -1.32$, $p = .227$, nor were there any differences between males and females in the expression of vigilance, $t(17) = -.111$, $p = .914$, or in any of the physiological variables (cortisol reactivity: $t(17) = -.941$, $p = .374$; sAA reactivity: $t(11) = 0.192$, $p = .853$; LS asymmetry: $t(11) = 0.421$, $p = .691$; HS asymmetry: $t(11) = 0.954$, $p = .369$); therefore, subject sex was not included as a predictor in subsequent models. For the main analyses, we used GLMs including ELA, vigilance, and the interaction of ELA × vigilance as fixed factors, with the dependent variable being one of the above physiological variables (Table 1). Main and interactive effects are presented for completeness, but only interactive effects are interpreted in analyses where significant main and interactive effects are found. All analyses were undertaken in SPSS 21.0; results with a $p < .05$ will be considered significant and those with a $p < 0.10$ will be described as a trend.

3 | RESULTS

3.1 | Low stress cortisol, high stress cortisol, and cortisol reactivity

We found no significant effect of ELA, vigilance, or ELA × vigilance on cortisol concentration during LS. However, during HS, ELA, $F_{(1,15)} = 8.89$, $p = .009$, and ELA × vigilance, $F_{(1,15)} = 7.42$, $p = .016$, predicted cortisol concentrations. Within Low ELA subjects, greater vigilance was associated with lower cortisol concentrations. For High ELA subjects, greater vigilance was associated with higher cortisol concentrations. As in the larger dataset used in Petrullo et al. (2016), ELA predicted cortisol reactivity, with Low ELA subjects exhibiting greater cortisol reactivity than High ELA subjects, $F_{(1,15)} = 10.04$, $p = .003$. Additionally, ELA × vigilance predicted cortisol reactivity, $F_{(1,15)} = 10.17$, $p = .006$ (Figure 1a). Within Low ELA subjects, greater vigilance was associated with lower cortisol reactivity. For High ELA subjects, greater vigilance was associated with higher cortisol reactivity.

3.2 | Low stress sAA, high stress sAA, and sAA reactivity

We found trends for ELA, $F_{(1,9)} = 5.09$, $p = .050$, and vigilance, $F_{(1,9)} = 4.90$, $p = .054$, to affect sAA concentrations during LS, and there was no significant effect of their interaction. During LS periods, High ELA subjects exhibited marginally lower sAA concentrations than Low ELA subjects. Additionally, subjects with greater vigilance exhibited marginally lower LS sAA concentrations. During HS, we found no significant main effects of ELA or vigilance, but did see a trend in which the interaction of ELA × vigilance predicted HS sAA concentrations, $F_{(1,9)} = 3.78$, $p = .084$. Within Low ELA subjects, greater vigilance was associated with a slight tendency to have higher sAA concentrations. For High ELA subjects, greater vigilance was associated with a slight tendency toward lower sAA concentrations.

While we found no main effect of ELA on sAA reactivity, we did find that both vigilance, $F_{(1,9)} = 10.34$, $p = .011$, and ELA × vigilance, $F_{(1,9)} = 7.22$, $p = .025$, predicted sAA reactivity (Figure 1b), in the opposite direction to that found for cortisol reactivity. Among Low ELA subjects, greater vigilance was associated with greater sAA reactivity; among High ELA subjects, greater vigilance was associated with less sAA reactivity.

3.3 | Low stress asymmetry

Neither ELA, vigilance, nor their interaction predicted asymmetry during LS.

3.4 | High stress asymmetry

During HS, there were no significant main effects of ELA or vigilance, but ELA × vigilance significantly predicted asymmetry, $F_{(1,9)} = 10.46$,

TABLE 1 Results of GLMs for high stress (HS) and low stress (LS) samples.

	LS cortisol	LS sAA	HS cortisol	HS sAA	HS cort: LS cortisol (*Cortisol reactivity*)	HS sAA: LS sAA (*sAA reactivity*)	LS sAA: LS cortisol (*LS Asymmetry*)	HS sAA: HS cortisol (*HS Asymmetry*)
ELA	n.s.	$F_{(1,9)} = 5.09$	**$F_{(1,15)} = 8.89$**	n.s.	**$F_{(1,15)} = 10.04$**	n.s.	n.s.	n.s.
		$p = .050$	**$p = .009$**		**$p = .003$**			
Vigilance	n.s.	$F_{(1,9)} = 4.90$	n.s.	n.s.	n.s.	**$F_{(1,9)} = 10.34$**	n.s.	n.s.
		$p = .054$				**$p = .011$**		
ELA × Vigilance	n.s.	n.s.	**$F_{(1,15)} = 7.42$**	$F_{(1,9)} = 3.78$	**$F_{(1,15)} = 10.17$**	**$F_{(1,9)} = 7.22$**	n.s.	**$F_{(1,9)} = 10.46$**
			$p = .016$	$p = .084$	**$p = .006$**	**$p = .025$**		**$p = .010$**

Results are bolded where $p < .05$.

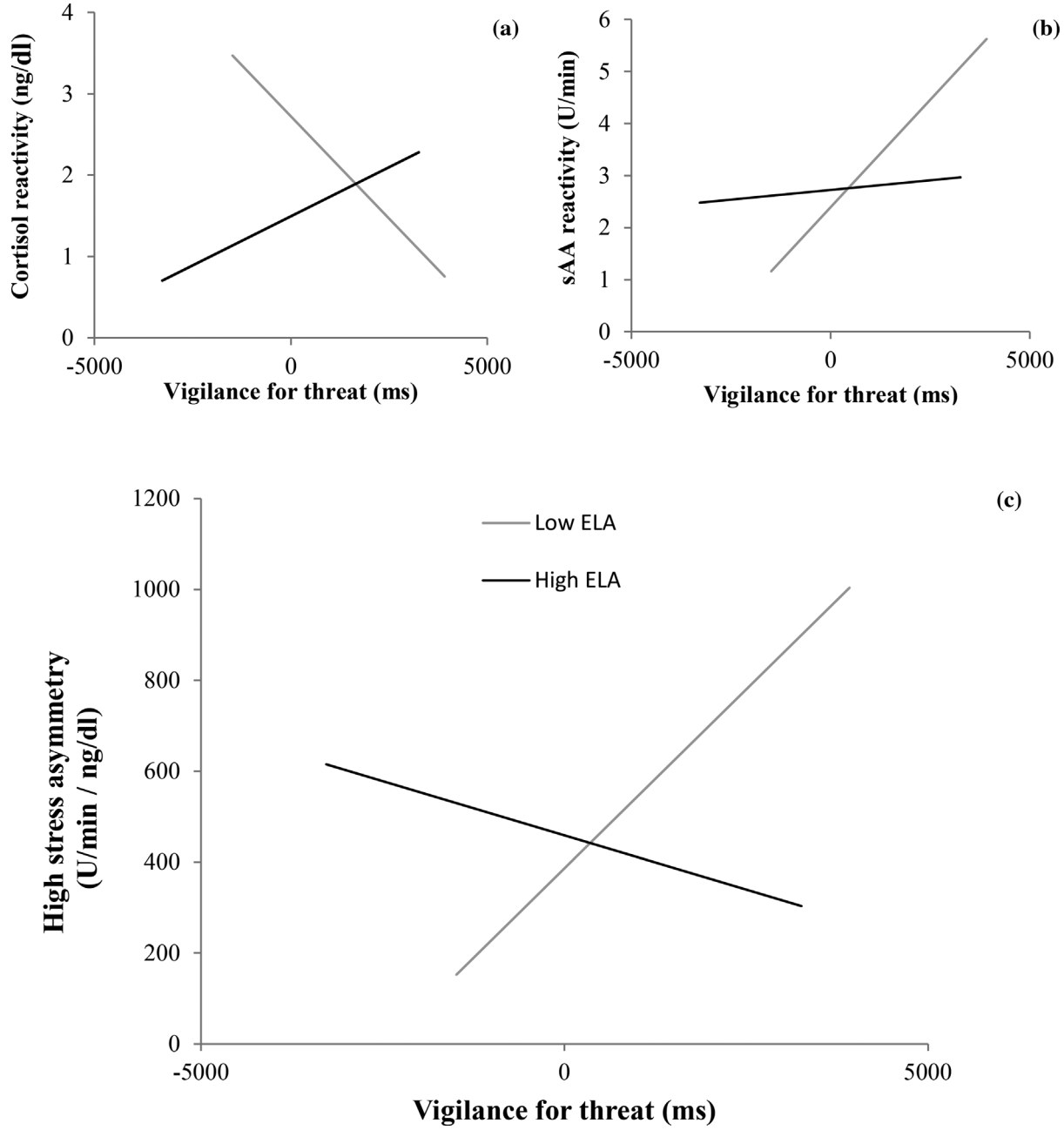

FIGURE 1 Model predicted plots (with best-fitting regression lines of the fixed predicted values from GLM for Low and High ELA subjects separately) showing the relationship between vigilance and: (a) cortisol reactivity (HS cort:LS cort); (b) sAA reactivity (HS sAA:LS sAA); and (c) HS asymmetry (HS sAA:HS cort)

$p = .010$. Within Low ELA subjects, greater vigilance was associated with greater asymmetry, whereas for High ELA subjects, greater vigilance was associated with less asymmetry (Figure 1c).

4 | DISCUSSION

Among rhesus macaques, ELA and vigilance for threat during infancy predicted asymmetry in SNS-HPA activity in periods of high stress during juvenility. High ELA individuals exhibited blunted cortisol reactivity, a suboptimal physiological profile. However, this effect was moderated by vigilance, such that High ELA individuals with greater vigilance exhibited greater cortisol reactivity. Moreover, High ELA individuals with greater vigilance exhibited less asymmetry in SNS-HPA activity than Low ELA individuals with greater vigilance, lending support to our hypothesis that being vigilant toward threats might be recruited as a cognitive mechanism to attenuate the consequences of ELA.

What exactly is it about vigilance that confers this physiological advantage later in life for those experiencing high ELA? One possibility is that vigilance during infancy is associated with preferable physiological outcomes in juvenility because infants that experienced

greater ELA learned earlier how to regulate emotion and arousal in the face of threat (e.g., Bauer, Quas, & Boyce, 2002; Parker & Maestripieri, 2011), giving them the tools early on to cope with adversity across the lifespan. Conversely, High ELA individuals who exhibited relatively weaker vigilance showed significant dysregulation, suggesting that these individuals were ill equipped to deal with subsequent adverse experiences. In line with this explanation, we found that vigilance and ELA were more likely to be associated with subsequent physiological dysregulation during high stress periods, after the individual was exposed to a social stressor. During periods of low stress, stress physiology was relatively unaffected by either vigilance or ELA. This suggests that meaningful differences between groups emerge most strongly when there is a social threat that necessitates a response. Interestingly, even during high stress periods not all aspects of stress physiology were similarly affected by vigilance, adversity, or their interaction. Rather, we found that SNS-HPA asymmetry in response to early life adversity and vigilance was driven by the HPA component of the stress response. This finding is consistent with previous research across species showing that the HPA axis shows attenuation in response to chronic stress over time (Heim & Nemeroff, 2001; Meaney & Szyf, 2005; Sanchez, 2006).

Unlike Low ELA individuals with weaker vigilance, which showed little dysregulation, Low ELA individuals with greater vigilance exhibited dysregulated stress profiles, characterized by decreased cortisol reactivity and increased SNS:HPA asymmetry. In humans, having a hyperactive vigilance for threat in relatively stable and predictable environments is associated with greater physiological asymmetry (e.g., Reeves et al., 2016; Schumacher et al., 2013), and as such, is also implicated in the etiology of anxiety disorders (e.g., Bar-Haim et al., 2007). It remains an open question precisely why certain individuals exposed to adversity developed greater vigilance in the first place, whereas others exposed to adversity developed less, as robust attention to threat should be equally useful among any individuals exposed to adversity. To understand better why individuals sometimes develop vigilance profiles that are mismatched to their experience, we can look to studies exploring the genetic basis for cognitive phenotypes. Previous work on the genetic basis of vigilance has shown that genetic factors shape an individual's propensity to *express* vigilance (e.g., Fox, Zougkou, Ridgewell, & Garner, 2011; Pérez-Edgar et al., 2010), and genetic factors might be similarly likely to influence the very *development* of a vigilant phenotype as well. By integrating an individual's genotype into our studies on the development of cognition in response to particular environments, we can better understand when, how, and why individuals develop cognitive and behavioral phenotypes that are best suited to their environment.

Implicit in the above proposed adaptive explanations is the assumption that the early environment is predictive of the future environment, such that individuals who encountered adversity early in life are also likely to encounter adversity later (in line with theories such as the Predictive Adaptive Response hypothesis: see Bateson, Gluckman, & Hanson, 2014). Given that we did not collect data on the environment during the juvenile period, we cannot explicitly test this assumption, and future studies should examine how environmental continuity or change across time influences the effects of vigilance (for a similar approach, see Frankenhuis & Del Giudice, 2012; Schmidt, 2011). Similarly, the adaptive account assumes some level of stability in vigilance across development. Although intra-individual variation in the expression of vigilance across time has not been well studied (but see Schehner & Bar-Haim, 2016), this particular cognitive bias displays hints of flexibility. Studies across multiple species, including humans, and both captive and free-ranging rhesus macaques, have found short-term modification of vigilance in response to stressful situations (bumblebees: Bateson, Desire, Guardside, & Wright, 2011; chickens: Salmeto et al., 2011; humans: Mogg, Bradley, & Hallowell, 1994; Wald, Lubin, Holoshitz, & Muller, 2011; captive rhesus macaques: Bethell et al., 2012b; free-ranging rhesus macaques: Mandalaywala, 2014). However, whether individuals can more permanently alter the expression of vigilance in response to changes in the environment remains to be determined.

Nonetheless, our results suggest that among individuals with High ELA, increased vigilance during infancy serves as an adaptive response that results in comparatively less physiological dysregulation later in life. Moreover, by adopting a more comprehensive developmental approach, integrating measures of cognition, behavior, physiology, and environmental context, we can also begin to clarify the developmental timeline and the causal direction of these relations. In the correlational results presented here, it is not possible to infer a causal direction; therefore it is possible that developmental differences in SNS-HPA activity during infancy led to inter-individual differences in vigilance rather than the other way round. Future studies incorporating multi-system measures of stress physiology earlier in life are necessary to better understand these complex interactions. Even with these limitations, our results show that early life experience and cognitive processes interact to shape physiological development, helping to explain inter-individual variation in long-term outcomes and illustrating the utility of the cognition by environment approach.

AUTHORS' CONTRIBUTIONS

DM and KJP designed the longitudinal study, TMM developed the cognitive development component, collected cognitive and behavioral data, and carried out statistical analyses with JPH. LAP collected and analyzed endocrine data under the supervision of JPH. TMM and JPH drafted the manuscript while DM, KJP, and LAP provided revisions.

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ETHICS STATEMENT

This research was approved by the Institutional Animal Care and Use Committees of New York University, University of Chicago, Stanford University, and University of Puerto Rico.

ORCID

Tara M. Mandalaywala http://orcid.org/0000-0003-0035-4311

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