The Developmental Cost of Stress: Infant Stress Sensitivity and the Developing Brain

Keywords: infancy; stress reactivity; stress regulation; brain development

Background: Extensive research has demonstrated that early life stress is associated with increased risk for adverse outcomes across the lifespan, including poor physical health, accelerated aging, and psychopathology, thereby posing a significant public health issue.[1] Despite clear evidence that early adversity portends disease risk, the specific mechanisms by which early experiences of stress contribute to negative outcomes are not well understood. This may be due in part to individual differences in the stress response, where certain individuals are resilient to the negative effects of stress.[2] In this application I propose to examine foundational individual stress response (infant autonomic reactivity) as it relates to brain development (change in brain connectivity). The developmental relation between stress and these biological features may provide insight into mechanisms that confer poor long-term health.

In both human and non-human animal research, autonomic function has been identified as an individual-specific mechanism linking stress and poor mental and physical health.[1,3] When exposed to stress, the sympathetic nervous system activates (the "flight or fight" response). To regulate, the parasympathetic nervous system is activated to return the body to homeostasis. Each of these systems of the autonomic nervous system (ANS) have robustly distinguished at-risk youth from their healthy peers and predict later health and functioning.[1] In infants, stress reactivity, stress regulation, and stress exposure independently predict behavior and health later in adolescence and adulthood.[3,4,5] Recently anomalous brain activation and structure has been identified in infants exposed to early stress.[6] This is consistent with non-human animal research documenting that early life stress is associated with abnormal amygdala, hippocampus, and prefrontal cortex (PFC) structural and functional development.[8,9,10] In humans, the first year of life is a marked by significant brain development, with an upsurge of activation and myelination of limbic, sensorimotor, and executive control regions of the brain.[7,8] Importantly, these features are associated with developmental gains in emotion and memory, motor skills, sense acuity, and self-control. Despite the strong evidence that stress is related to infant neural and autonomic development and, in turn, to long-term health outcomes, no study has directly related autonomic function to infant neural development. The goal of my proposed project is to directly examine, for the first time, the relation between dysregulation of the ANS and changes in the connectivity of neural circuitry involved in threat detection and emotion regulation, as well as how this relation develops over the highly plastic period of infancy.

Approach: The proposed project is a prospective longitudinal study of the relations between ANS reactivity and the development of brain regional connectivity. I will invite 60 mothers in their third trimester of pregnancy to participate in postnatal assessments of their infants. At ages 6 and 9 months, infants will undergo an MRI brain scan to assess brain connectivity and a laboratory stressor to assess ANS reactivity and regulation. To measure ANS activity, electrocardiogram (ECG) infant data will be recorded continuously during the Still Face Paradigm (SFP), a standardized laboratory stressor that reliably elicits stress responses in infants across three episodes: play (baseline); "still face" in which the caregiver withdraws from the infant and assumes a face without expression (stressor); and reunion (recovery).[11] ANS activity will be quantified minute-to-minute by extracting both sympathetic (HR) and parasympathetic (RSA) arousal from the ECG recordings, stress reactivity and regulation, respectively, during the SFP. Brain regional connectivity (BRC) will be quantified using both resting-state fMRI and diffusion tensor imaging to capture the nuanced relation between structure and function.[12] *Aim 1: Examine the cross-sectional relation between ANS activity and BRC at 6 months. Method:* ANS

reactivity (mean stressor HR minus mean baseline HR) and ANS regulation (mean recover RSA minus mean stressor) for each assessment will be entered separately into multiple linear regression models (BRC ~ age + ANS) to examine cross-sectional relations between ANS function and region of interest BRC in the infants. *Hypothesis*: ANS reactivity will be associated with heightened amygdala connectivity, and greater ANS regulation will be related to higher amygdala to PFC connectivity. *Aim 2:* Examine the relation between change in ANS and change in BRC. *Method*: Change in hippocampus, amygdala, and PFC connectivity from 6 to 9 months will be extracted (cBRC). ANS reactivity and regulation from each assessment will be modeled separately in a repeated-measures ANCOVA (ANS repeated over time; covarying age) predicting cBRC. *Hypotheses*: Improved ANS regulation will be associated with greater amygdala-PFC cBRC. Infants demonstrating greater or similar ANS reactivity at 9 months will demonstrate lesser cBRC between the amygdala and PFC. Infants who do not show improvement in ANS regulation will demonstrate higher hippocampus cBRC.

Further Study: This study is a critical step in understanding the relation between stress and health over the lifespan by elucidating the role of individual-specific stress response and brain function early in life. To gain a better understanding of the theorized moderating effect of ANS function, I will assess life stressors (verbal or physical abuse, domestic violence, or hostile communities), deprivation (neglect, malnourishment, or lack of medical care), and caregiver behaviors with these mother-infant pairs and test a moderation model among these stressors, ANS function, and brain regional connectivity. Longitudinal study is critical to understanding how early adversity produces negative mental and physical health outcomes. Therefore, additional follow-up must be conducted when these children are of school age to assess physical and mental health trajectories. **Broader Impacts**: Advancing scientific knowledge about the relations between individual differences in responses to stressors and neural development in infancy can affect public health by informing interventions with at-risk populations. Specifically, interventions that enhance regulation of the ANS may buffer infants from the negative effects of early adversity on development with greater efficacy than interventions at older ages when the brain is less plastic. Applications of these findings have the potential to foster resilience in children independent of their home life by examining the effect on brain development of methods aimed at improving ANS function. There is extensive evidence that ANS function is sensitive to activities such as massage and exercise,[12] indicating that tailored techniques could be developed for children with dysfunctional ANS. After careful study of ANS resilience, I plan to ultimately work with communities and schools to foster resilience in at-risk children. This research will improve the well-being of individuals in society by aiding in identifying critical points of early intervention and boosting desired societal outcomes. I plan to disseminate my findings to the scientific community through publications and presentations. Given the manpower required to conduct human research on this scale, this study also provides a perfect opportunity to mentor other young scientists, bolstering engagement of underrepresented minorities in science who will go on to affect science and society in a similarly meaningful way.

References: **1.** Blair, C., et.al. (2013). Psychoneuroendocrinology, 38(11), 2666–2675. **2**. Bruehlman-Senecal E, et al. J Pers Soc Psychol. 2016;111(4):610-635. **3.** Carrion, V. G., & Wong, S. S. (2012). Journal of Adolescent Health, 51(2 SUPPL.), S23–S28. **4.** Davis, E. P. et al. (2011). Journal of Child Psychology and Psychiatry and Allied Disciplines, 52(2), 119–129. **5.** Fox, N. A. (1989). Developmental Psychology, 25(3), 364–372. **6**. Graham AM, et al. J Child Psychol Psychiatry Allied Discip. 2015;56(11):1212-1222. **7.** Alcauter, S., et al. (2015). Developmental Cognitive Neuroscience, 12, 40–50. **8.** Yap, P. T. et al. (2011). PLoS ONE, 6(9). **9.** Chang, D. J., & Debiec, J. (2016). Journal of Neuroscience Research, 94(6), 526–534. **10.** Riem, M. M. E., et al. (2015). Development and Psychopathology, 27(2), 507–520. **11.** Mesman, J., et al. (2009). Developmental Review, 29(2), 120–162. **12.** Damoiseaux, J. S., & Greicius, M. D. (2009). Brain Structure & Function, 213(6), 525–33.