Background: Mothers' own reported adverse childhood experiences (ACEs) have been demonstrated to be associated with offspring outcomes with respect to infant brain development, stress reactivity, and child behaviors, though mechanisms are unclear. Given the role of the hypothalamic-pituitary-adrenal axis in the regulation of stress, we measured fetal adrenal volumes, hypothesizing that maternal ACEs would be associated with differences in fetal adrenal development.
Methods: Eighty-seven pregnant women recruited from an urban safety-net hospital prenatal clinic underwent ultrasound at 19 and/or 28 weeks of gestation (N=55@19w, N=66@28w, N=34@both), measuring fetal adrenal gland width, length, and depth, with volumes calculated and adjusted for estimated fetal weight. Structured clinical interview for DSM-5 and ACEs were collected and examined categorically (high 2+ vs. low 0-1 ACEs) and continuously. Linear mixed effects model included ACEs * time point + offspring-sex + side + random subject effect.
Results: Our model revealed interaction of ACEs and time point, whereby offspring of mothers with higher ACEs had lower incremental volume growth across timepoints ($F(1,217) = 7.3$, $p=0.007$). There was no effect of offspring-sex, and the model was consistent when lifetime psychiatric diagnoses and medical/delivery complications were included. Continuous ACEs analyses showed similar patterns.
Conclusions: We found that maternal ACEs were associated with changes in fetal adrenal development between 19 and 28 weeks of gestation, which was not impacted by offspring sex, maternal psychiatric diagnoses, or medical or delivery complications. These data suggest that maternal ACEs impact fetal adrenal development, the mechanism and clinical relevance of which remain to be determined.
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Keywords: Neuroendocrine, Fetal Development, Hypothalamic-Pituitary-Adrenal Axis, Adverse Childhood Experiences, Perinatal period

Research Method: Neuroimmunology

Empirically-Derived Composite Inflammation Scores: Implications for Longitudinal Depression Research

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Background: Inflammation is complex with many components, often resulting in issues with multiple comparisons when they are analyzed separately. To navigate this, some researchers use composite measures of inflammation. Typically, composites are created without the guidance of factor analysis. The utility of these theoretically derived composites and individual proteins has never been compared to empirically-derived composites, despite potentially crucial differences.
Methods: An exploratory factor analysis was conducted using CRP, IL-6, IL-8, IL-10, TNF-a, E-selectin, fibrinogen, and ICAM-1 on 1232 adults. Model fit between the empirically-identified factor structure and an "a priori" structure of all proteins equally loading onto a single factor in a different sample (N=863). Internal consistency was also compared. Next, in a longitudinal study of 315 late adolescents (922 total observations), ICCs of the empirically-identified composites were compared to the "a priori". Finally, the individual proteins and composites were compared in multilevel models predicting change in depression.
Results: A two factor solution was supported (Factor 1: CRP+IL-6+fibrinogen, and Factor 2: IL-8+IL-10+IL-6+ICAM-1+TNF-a). The composite with the highest internal consistency and temporal stability was Factor 1 (omega=.75, ICC=.53). Factor 1 predicted higher depression ($b=.36$, $p<.05$) and Factor 2 predicted lower depression ($b=-.39$, $p<.01$). The a priori aggregate and individual proteins did not predict depression ($ps>.05$)
Conclusions: Empirically-identified composites fit the data better than an "a priori" unidimensional structure, and the empirically-identified structure replicated in two other datasets (one adult, the other adolescent). Further, the highest internal consistency temporal stability, and predictive validity were associated with an empirically-identified composite.
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Keywords: Inflammation, Adolescent Depression, Measurement Model, Methodology, Physiometrics

Inflammation is Associated With Abnormal Interoceptive Processing in Major Depressive Disorder

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Background: Aberrant interoceptive awareness is observed in major depressive disorder (MDD) and thought to contribute to pathophysiology. One important yet largely ignored source of interoceptive input, the peripheral inflammatory signal, has been shown to activate the primary interoceptive region (i.e., insula), inducing fatigue in healthy subjects. However, the role of peripheral inflammatory signals in interoception has received very little attention in the context of MDD.
Methods: 212 individuals with MDD and 52 healthy comparisons (HC) completed: 1) a heartbeat tapping task, which was used to compute an interoceptive precision score; 2) a fMRI visceral interoceptive attention task in which participants paid attention to sensations from their heart and stomach, and 3) morning blood sampling to quantify interleukin [IL]-6. A robust linear regression model controlling for age, sex, BMI, and medication status was used to investigate group differences in the relationship between IL-6 and interoceptive precision.
Results: Significant IL-6-by-diagnosis interaction effects were observed on both behavioral and neuronal interoception outcome measurements. Increased IL-6 concentration was