Delineating neurodevelopmental pathways from early adversity to cognitive and affective outcomes.

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Symposium

There is a large body of research robustly demonstrating that various forms of early adversity are associated with increased risk for poor cognitive, affective and mental health outcomes. However, much of this research treats different forms of adversity as interchangeable and as if the neurodevelopmental pathways and outcomes are the same regardless of the type of adversity. However, a growing body of research suggests that different forms of early adversity are associated with impairments in dissociable neurobiological pathways and cognitive and affective outcomes. Further, increasingly sophisticated neuroimaging tools are allowing researchers to better delineate the specific structural and functional brain impairments that arise as a function of specific forms of early adversity, as well as the environmental, hormonal and learning mechanisms that may be responsible for the neural outcomes. It is critical to identify these dissociable pathways, as they have very different implications for the development of the most effective and targeted intervention and prevention efforts. As such, there are several goals of this symposium. The first is to illustrate key distinctions between different forms of early adversity, with a focus on distinctions between threat/maltreatment, cognitive and emotional deprivation, and poverty. The second is to provide novel data about the distinct neurobiological outcomes associated with these different forms of early adversity, providing evidence about both differences in brain systems that are impacted (e.g., hippocampal, limbic, frontal-parietal) and brain characteristics (e.g., structural versus functional). The third is to begin to provide evidence about additional components of the mechanistic pathways from early adversity to poor cognitive and emotional outcomes, such as learning and hormonal mechanisms.

Objective

1) Understand key distinctions between different forms of early adversity, with a focus on distinctions between threat/maltreatment, cognitive and emotional deprivation, and poverty.
2) Understand the dissociable neurobiological outcomes associated with these different forms of early adversity, including evidence about both differences in brain systems that are impacted (e.g., hippocampal, limbic, frontal-parietal) and brain characteristics (e.g., structural versus functional).

Target Audience

The indented audience is any researcher who is interested in using neuroimaging tools to understand the neurobiological pathways that link early adversity to risk for poor cognitive, affective and mental health outcomes. This includes graduate students and postdoctoral fellows who may be developing their research programs and

could use this information to shape their questions and methodological choices, as well as more established researchers with interests in this domain.

Presentations

Testosterone and Hippocampal Trajectories Mediate the Relationship of Poverty to Emotion Dysregulation and Depression: A Longitudinal Study

There is robust evidence that early poverty is associated with poor developmental outcomes, including impaired emotion regulation and depression. However, the specific mechanisms that mediate this risk are less clear. Here we test the hypothesis that one pathway involves hormone dysregulation (testosterone and DHEA) that contributes to disruption of hippocampal brain development, which in turn contributes to perturbed emotion regulation, and subsequent risk for depression. To do so, we used data from 167 children participating in the Preschool Depression Study, a longitudinal study that followed children from preschool (ages 3 to 5) to late adolescence, and which includes prospective assessments of poverty in preschool, measures of testosterone, DHEA and hippocampal volume (using the Freesurfer longitudinal pipeline) across school age and adolescence, and measures of emotion regulation and depression in adolescence. We used hierarchical linear regressions to determine whether early poverty (T1 income-to-needs) predicted the variables of interest. Greater early poverty predicted lower testosterone increase over adolescence (i.e., flatter slope). In addition, greater early poverty predicted a shallower slope of hippocampal growth across development. Further, greater early poverty predicted both greater emotion dysregulation and greater depression at in adolescence. All of these significant effects survived FDR correction. Notably, poverty did not significantly interact with sex to predict any additional variance. Importantly, a greater increase in testosterone over development was associated with a greater increase in hippocampal growth over adolescence (R2Adj = .02, B = .447, bootstrapped CI 95%+/- = .068-826, t = 2.33, p = .021), again with no significant interactions with sex (ps> .64). Hierarchical linear regressions also indicated that greater testosterone increase across development predicted both lower emotion dysregulation and lower child reported depression at adolescence, and greater hippocampal volume growth across development also predicted lower emotion dysregulation, though not lower depression in adolescence. Lastly, relationship between early poverty and self-reported depression in adolescence was explained by serial mediation using PROCESS models through testosterone to hippocampus to emotion dysregulation, mediation results that held when controlling for early depression and mediation history. These results provide novel evidence about a hormonal pathway by which early poverty may contribute to disrupted brain development and risk for mental health problems later in life. Identification of such pathways provide evidence for potential points of intervention that might help mitigate the impact of early adversity on brain development.

Presenter

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Early-life trauma is associated with altered inhibition of threat via learned safety during development

Early-life trauma is a potent risk factor for psychopathology, including anxiety disorders. Delineating the

neurodevelopmental mechanisms linking early-life trauma to psychopathology is critical for early risk identification and for optimizing interventions. Youth exposed to trauma show altered threat learning and difficulties discriminating between threat and safety, yet much remains unknown about the active inhibition of threat responding via learned safety. Moreover, given cross-species evidence for diminished fear extinction during adolescence, novel approaches to fear reduction (e.g., safety cues) may be particularly useful during development. Using a conditioned inhibition paradigm, the present fMRI study examined safety cue learning and its association with early-life trauma and anxiety among individuals ages 8-30 (N=80). Participants viewed stimuli predictive of threat or safety during acquisition and then viewed compound cues (i.e., threat and safety cues presented simultaneously) to test inhibition via learned safety. Skin conductance response was assessed during fMRI as an index of conditioning. Childhood trauma was assessed using the UCLA PTSD Reaction Index, and psychopathology was assessed using the Anxiety Disorders Interview for DSM-5. A GLM tested the main effects and interactions between childhood trauma and age on activation in hippocampal-frontoamygdala circuitry during safety learning. Analyses revealed interactions between childhood trauma exposure and age for activation in the ventromedial prefrontal cortex (vmPFC) and hippocampus. Individuals with lower trauma exposure showed an age-related increase in vmPFC activation to learned safety, whereas individuals with higher trauma exposure did not show age-related change. In addition, individuals with lower trauma exposure showed an age-related decrease in hippocampal activation to learned safety, whereas individuals with higher trauma exposure did not show age-related change. Individuals with higher levels of trauma exposure also showed alterations in physiological responding to learned safety. These findings suggest that trauma exposure may interfere with normative development of safety cue learning. Altered function in hippocampal-frontoamygdala circuitry may underlie difficulties learning or integrating environmental cues signaling safety, and deviations from age-expected trajectories could increase risk for anxiety during development among trauma-exposed youth.

Presenter

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Neural structure, cognition, and psychopathology are independently predicted by deprivation and threat in early childhood

Objectives: The impact of childhood adversity on risk for psychopathology is commonly examined using a cumulative risk model. In a recently proposed alternative approach, the dimensional model of adversity and psychopathology (DMAP), different dimensions of adversity are hypothesized to impact health and well-being through different neural pathways. This model has initial evidence from a number of studies in adolescence but has been understudied in early childhood. We expect deprivation to impact thickness in areas of cortex involved in higher order cognition such as the prefrontal cortex and to selectively be associated with impairments in cognitive function. In contrast, we expect threat to selectively impact subcortical structures associated with increased reactivity to emotional stimuli and disrupted emotion regulation. We further expect that both deprivation and threat will impact psychopathology. Methods: To examine these patterns we review analyses in two datasets recruited to be weighted back to a representative sample of preschool children in the United States. First, we examine associations among threat, deprivation, cognitive function, and psychopathology in the Fragile Families and Child Wellbeing study (FF). Here, we examine a sample of 2566 parent/child dyads (47.9% female) who were recruited into the Fragile Families and Child Wellbeing study and participated in a home visit during the second wave of data collection in 2000. The FF sample was recruited to over-sample single parent families with the first visit happening shortly after birth at 75 hospitals in 20 cities across the United States. By wave 2, these children were 3 years old. Second, we examine associations among deprivation, threat, neural structure and

psychopathology in the Duke Preschool Anxiety Study, a cross-sectional study of 2–6 year olds enrolled through primary care from 2007–2011. A subset of these participants (N = 71; 42% male) participated in a longitudinal imaging follow-up about two years later (ages 4 - 9.5 years old). In both studies, threat and deprivation were operationalized using questions from the Conflict Tactics Scale-2 (CTS-2), CTS-PC, HOME interview, or Preschool Age Psychiatric Assessment. Threat measured physical or sexual abuse, domestic violence, and violent neighborhood. Deprivation measured neglect and lack of cognitive stimulation. In study 1 we use network analysis and structural equation modeling to identify linkages among variables. In study 2, using FreeSurfer we automatically segmented the brain and estimated cortical thickness, surface area, and volume of subcortical structures and used OLS regression to identify independent associations between deprivation and threat and brain structure. Results: Study 1. In the first study we observed that using both network and strucutural equation modeling approaches, deprivation clustered independently of threat with cognitive function. Interestingly, threat clustered independently of deprivation and was uniquely associated with psychopathology in early childhood. Study 2: We observed that deprivation, net of the effect of threat, predicted cortical thickness in the orbital frontal cortex, insula, precuneus, parahippocampus, and lateral occipital cortex, but not surface area or subcortical volume. In contrast, threat predicts volume of the amygdala, hippocampus, and putamen, and global reductions in surface area. Interestingly, in this sample we also observed that threat but not deprivation predicted psychopathology in early childhood. Conclusion: These disparate associations among threat, deprivation, cognition and brain structure are consistent with our predictions and extend observations in adolescence to early childhood. The differential association of threat but not deprivation with psychopathology in early childhood was not predicted but may be due to the continued maturation of neural structures which support healthy psychological functioning and signal the potential for intervention across childhood.

Presenter

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Distinct neural signatures of adverse early environments characterized by threat and deprivation

Objectives: An extensive literature on childhood adversity and neurodevelopment has emerged over the past decade. Although most studies combine distinct adversity types together when examining neural outcomes, we have argued that such an approach is likely to obscure meaningful variation in patterns of neurodevelopment following distinct types of adverse early experiences. Neural plasticity mechanisms are sensitive to particular types of experiences. The specific nature of environmental experiences determines the types of changes that occur, both in neural circuits and ultimately behavior. Here we examine the predictions of a theoretical model arguing that early experiences characterized by threat (e.g., violence exposure) influence neural circuits involved in salience processing and aversive learning, whereas experiences of deprivation (e.g., neglect) influence circuits underlying higher-order cognition, including the fronto-parietal network. Methods: To examine these predictions we use data from a longitudinal study of children recruited to have wide variability in socio-economic status (SES) at age 3 years. Information on exposure to threat and deprivation was collected prospectively over time, and children completed MRI scans at age 11 years (N=187). We examine neural recruitment during fMRI tasks assessing threat processing (i.e., viewing of fearful relative to neutral faces) and working memory (i.e., a high-load relative to low-load condition). Threat and deprivation were measured as continuous variables. Exposure to threat included physical or sexual abuse, domestic violence, and neighborhood violence. Deprivation exposure included physical and emotional neglect, material deprivation (e.g., food insecurity), and lack of cognitive stimulation. All analyses examine threat and deprivation as predictors of neural responses in the same model to isolate effects

that may be unique to particular types of early experience, controlling for age, sex, and SES. Results: Consistent with our hypotheses, we observed unique associations of early environments characterized by threat and deprivation with neural function in late childhood. Children with higher levels of early threat exposure exhibited greater activation in the amygdala and several nodes of the salience network—including anterior insula and dorsal anterior cingulate cortex—to fearful relative to neutral faces in whole-brain analysis after controlling for deprivation; deprivation was unrelated to salience network recruitment during this task after controlling for threat. In contrast, greater exposure to deprivation was associated with reduced recruitment in fronto-parietal network for trials with high versus low working memory load after controlling for threat, which was unrelated to neural recruitment during this task. Conclusion: Our results suggest that different types of adverse early environments are associated with distinct changes in neural function later in childhood. These patterns are broadly consistent with evidence on typical development indicating that neural plasticity in early life varies as a function of the type and timing of particular environmental experiences. More broadly, these results highlight the importance of taking a more nuanced approach to characterizing how the early environment shapes brain development.

Presenter

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