Title: Early Life Adversity Potentiates Adult Response to Acute Threat: A Brain-Wide Neuroimaging and Behavior Study

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Abstract:

Adverse childhood experiences increase vulnerability to stress-provoked mental illnesses, such as anxiety/depression and substance use disorders, later in life. How these experiences shape the brain to lead to such disorders remains a mystery. Brain-wide imaging of neural activity in the adult raised with or without early life adversity (ELA) holds promise of finding clues. Longitudinal manganese-enhanced magnetic resonance imaging (MEMRI) provides a methodology to follow brain-wide neural activity dynamics over time in awake-behaving animals. Mn(II) delivered systemically is taken up through voltage-gated calcium channels throughout the brain over 24-26h. Behavior is recorded in our custom arena during Mn(II) uptake. We capture an image of basal behavior (normal exploration) at 22h, and then expose mice to acute threat, predator odor (TMT, 2,3,5-Trimethyl-3-thiazoine), and image again at 26h (Uselman et al, 2020). Here we combine this MEMRI paired with behavior protocol to investigate the effects of ELA on responses to acute threat in normally reared (n=12) and maternally deprived mice (n=12) (ELA-/+). Dams with newborn pups were deprived of adequate bedding from day P2-P9, which induces elevated cortisol in the pups (Rice et al., 2008). At 10 weeks of age, mice +/- ELA were subject our paired behavior-MEMRI longitudinal procedure for both acute and delayed responses. After imaging, mice are sacrificed, brains perfusion fixed and serial sections stained by immunohistochemistry. MEMRI images were skull-stripped, spatially co-registered, and intensity normalized. To measure the degree of activity and relationships between brain regions we performed statistical parametric mapping (SPM), segmentation of 90 brain regions, cross-correlation analysis, and Louvain community detection. Predator stress increased defensive/avoidance behavior for both groups ($p<0.05$, Tukey-Adjusted), attesting to the expected effect of the TMT. Results suggest basal neural activity of ELA mice resembles that of acute fear in normally reared mice and delayed responses among both groups are similar, with increased activity in the basal forebrain and hindbrain. Additionally, ELA resulted in decreased strength in correlation among brain segments, which fragmented further after acute threat. Staining for the norepinephrine transporter revealed a failure of distal axonal tiling, suggesting that neural activity dynamics could be due in part to ELA's effect on development of the noradrenergic system. Together our data find that ELA disrupts the arborization of noradrenergic projections, alters the coordination of basal neural activity in the basal state and in response to acute threat. Supported by NIMH RO1MH096093.