Title: Reconfiguration of adult brain responses to threat after early life adversity

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ABSTRACT:

Introduction: Early life adversity (ELA) correlates with vulnerability to mental disorders later in life. Effects of psychotropic drugs, both pharmacotherapies and drugs of abuse, point to the noradrenergic system (NS) as a contributing factor. How ELA impacts the brain to heighten risk and what roles NS plays, largely remain a mystery. Longitudinal manganese-enhanced magnetic resonance imaging (MEMRI) provides a methodology to investigate impacts of ELA on neural activity in awake-behaving animals. **Methods:** Here, newborn mice are exposed to ELA, fragmented maternal care, then brain activity studied in adulthood. For ELA, dams were deprived of adequate bedding from P2-P9. Separate cohorts with and without ELA were allowed to age to 10 weeks (n=24) in normal housing and then subjected to longitudinal MRI paired with video recordings captured before, immediately and longer times after exposure to acute threat (TMT, 2,3,5-Trimethyl-3-thiazoline). Mn(II) delivered systemically (0.3 mmol/kg) enters neurons via voltage-gated calcium channels. Accumulated Mn(II) thus reports on neural activity retrospectively in T1-weighted MRI. Mice activity is video recorded in our custom arena during Mn(II) accumulation. At conclusion of our longitudinal imaging timeline, mice are sacrificed, brains perfusion fixed, and serial sections stained by immunohistochemistry. MEMRI images were skull-stripped, spatially co-registered, and intensity normalized prior to statistical parametric mapping (SPM), segmentation, and network analysis. Noldus Ethovision XT 15 was used to analyze activity recordings. **Results:** ELA mice showed increased motility and reduced inter-individual variability in baseline exploration. Defensive-avoidance behavior increased for both groups with TMT, attesting to the expected effect of threat. SPM of 3D brain images found heightened neural activity of ELA mice in ventral pallidum prior to threat, in hindbrain nuclei immediately after threat, and in hypothalamus and ventral hippocampus a week later. Additionally, ELA exposure decreased Mn(II)-enhancement in prefrontal cortex and medial thalamic nuclei throughout the timeline as compared to non-ELA mice. Network analysis revealed a decrease of coordinated neural activity between many brain regions and shifts in network structure. Staining for norepinephrine transporter suggested a breakdown of distal tiling in various brain regions. **Conclusions:** Our data find that ELA heightens neural activity of various brain regions basally and in responses to stimuli like predator odor, an ethological threat. Consistently low prefrontal cortical and thalamic activity in ELA mice across the timeline suggests influential roles for these regions in altered brain states after ELA. Disruption of NS anatomy might partially explain these shifts in brain activity and regional coordination after ELA. Supported by NIMH RO1MH096093 and Harvey Family Endowment.