Corticolimbic neural recruitment and behavioral changes in response to early life adversity are sex-specific in rats

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Excessive stress at any stage of life increases the likelihood that a person may develop mental health problems in the future. However, extensive stress during developmental periods such as juvenility or adolescence predisposes individuals to develop mental health disorders such as anxiety and depression in the future, and disproportionally impacts women. The early-life adversity (ELA) caused by extensive stress can contribute to maladaptive outcomes through the disruption of the development of brain regions directly related to stress and emotional regulation such as the circuit linking the prefrontal cortex (PFC) and basolateral amygdala (BLA). Males and females develop these regions differently in both humans and model systems. In response to ELA, the connections from the BLA to the PFC develop at sex-specific rates, with females experiencing stronger development of these connections earlier than their male counterparts. However, the overall local functionality and cell-types upregulated in response to these differing developments – as well as the behavioral changes as a result of this – are unclear and remain to be investigated. Using stereotaxic electrical stimulation via bipolar electrode, we introduced physiologically relevant stimulation to the BLA of adolescent rats (28 days old) to activate the region and enable the quantification and characterization of downstream circuit-specific effects. Within the PFC, we use immunohistochemistry to label cells recruited by this activation through upregulation of the immediate early gene, *c-Fos,* and leveraged cell-specific markers for inhibition (i.e., parvalbumin; PV) as a proxy to determine changes in local excitatory: inhibitory balance. Immunohistochemistry results suggest differences in overall neural, as well as cell-type, recruitment across sex and rearing condition within the PFC.

To connect the neurological results to larger scale changes, rat behavior in response to an aversive social stimulus (22kHz ultrasonic vocalization (USV) alarm calls) was assessed. Rats were placed in the open field for a total of 10 minutes, with a 5 minute baseline followed by 5 minute exposure to 22kHz rat USV playback to assess environmental vigilance within the context of potential threat. Center duration, latency to center, average velocity, and maximum velocity were compared for all conditions across both 5-minute time bins. Sex and rearing condition differences in these measures suggest an impact of sex on behaviors. Overall, these findings provide compelling evidence that point to a sex-specific effect of ELA on the neural circuitry responsible for behavioral regulation during ambiguous threat.

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