DIFFERENTIAL IMPACTS OF ACUTE, CHRONIC, AND SOCIAL DEFEAT STRESS ON MICROGLIAL MORPHOLOGY IN THE AMYGDALA AND HABENULA

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BACKGROUND

Stress is a major risk factor for neuropsychiatric disorders, including depression and post-traumatic stress disorder (PTSD), which disrupt emotional regulation and cognitive function. Microglia, the brain's resident immune cells, play a critical role in maintaining neural homeostasis by modulating synaptic plasticity and responding to environmental challenges. Their morphological changes, such as alterations in soma size, density, and circularity, reflect distinct neuroimmune responses to stress. This study focuses on the basolateral (BLA) and central (CeA) amygdala, key for emotional processing, and the lateral (LHb) and medial (MHb) habenula, involved in motivation and reward. Understanding region-specific microglial adaptations to acute, chronic, and social defeat stress may help uncover mechanisms underlying stress vulnerability.

MAIN OBJECTIVE

Investigate microglial morphology and density changes in basolateral (BLA) and central (CeA) amygdala, and lateral (LHb) and medial (MHb) habenula under acute, chronic, and social defeat stress (SDS) to understand region-specific neuroimmune responses.

METHODS

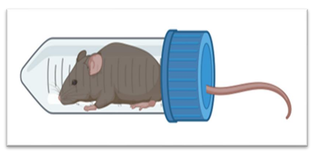
STRESS PROTOCOLS

Acute and intense stress

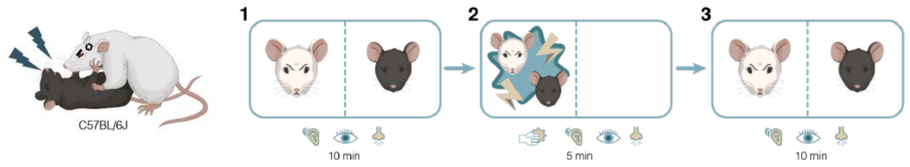
Mice were immobilized in falcon tubes, measuring 30 mm diameter × 80 mm length) and submerged to the level of the xiphoid process in a water bath maintained at 23 ± 1 °C for two hours. This procedure is known as **Water-Immersion and Restraint Stress (WIRS)** .

Chronic stress

Over 10 days, intermittently (5 days of treatment + 2 days of rest + 5 days of treatment), for a variable duration between 3.5 and 5.5 hours.



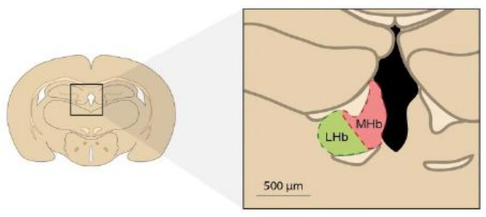
Social defeat stress



BRAIN REGIONS

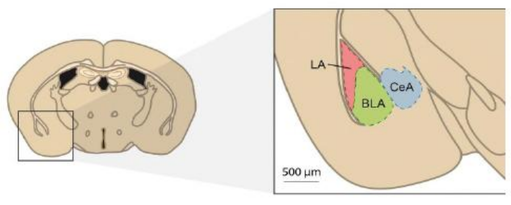
Habenula

Lateral (**LHb**) and medial (**MHb**) habenula

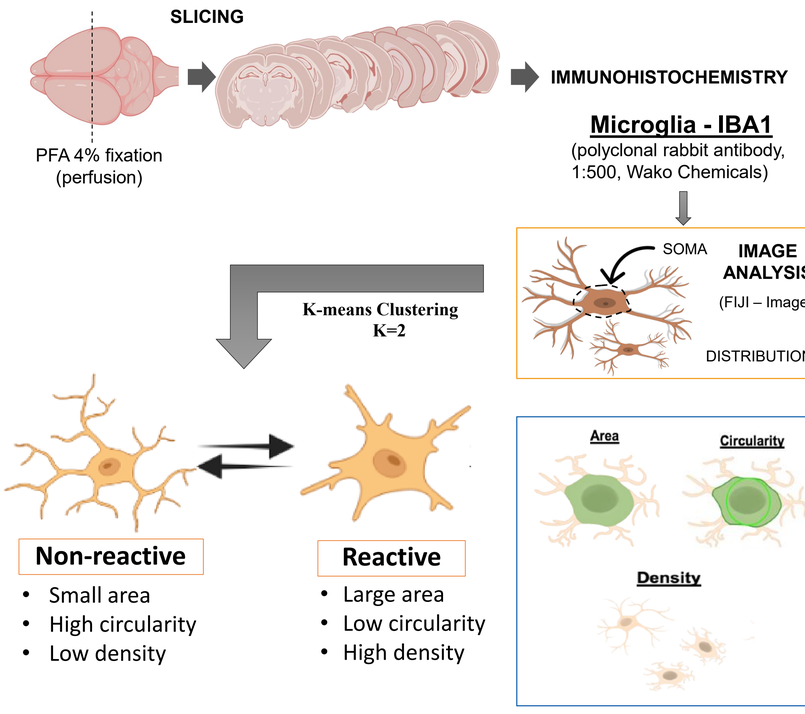


Amygdala

Basolateral (**BLA**) and central (**CeA**) amygdala



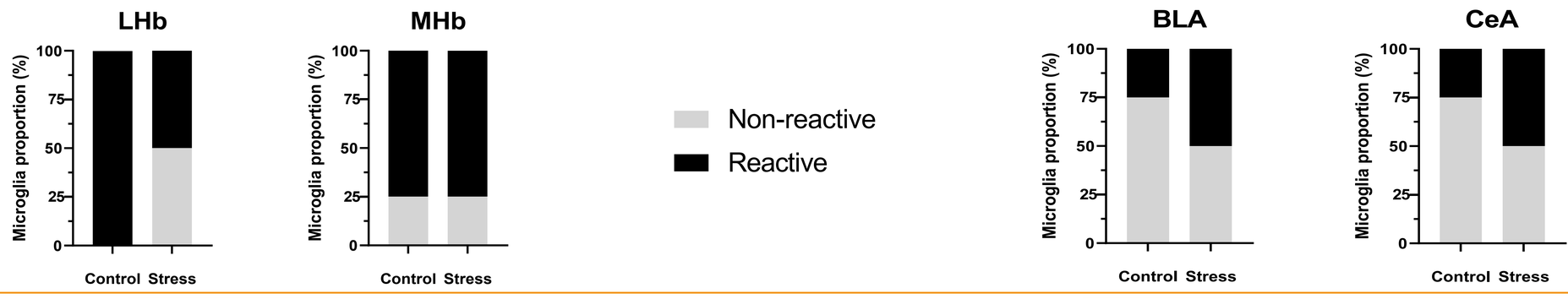
HISTOLOGICAL PROCESSING



RESULTS

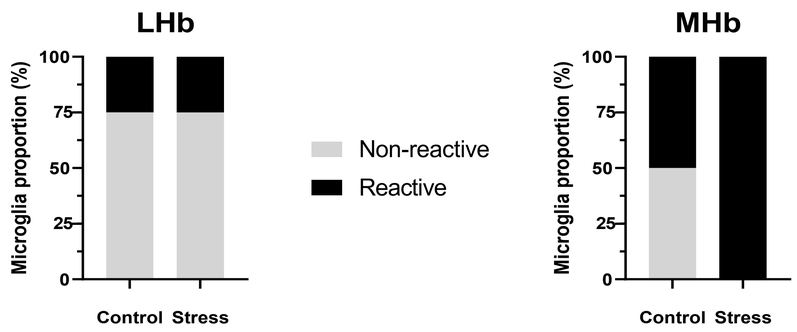
ACUTE STRESS

- Acute stress reduced microglial density in the LHb, with a shift from 100% to 50% reactive profiles, suggesting a regulatory modulation that may have destabilized emotional circuits. The MHb showed stability, indicating regional resilience. Both the BLA and CeA exhibited early reactivity, potentially escalating with prolonged stress.

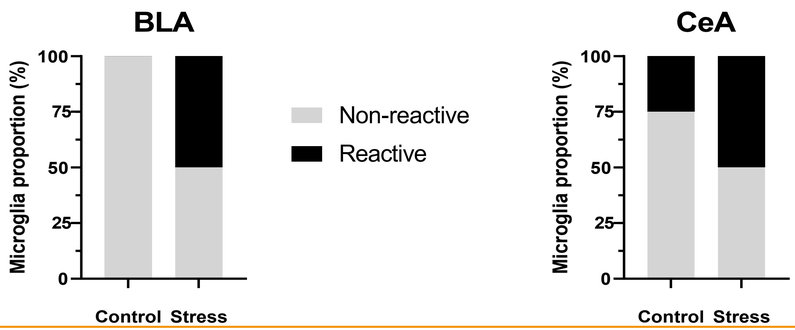


CHRONIC STRESS

- LHb maintained stability at 25% reactive with limited remodeling, suggesting a restricted adaptation to chronic stress. MHb showed a transition to 100% reactive with significant morphological changes, indicating increased functional demand or sustained inflammation.

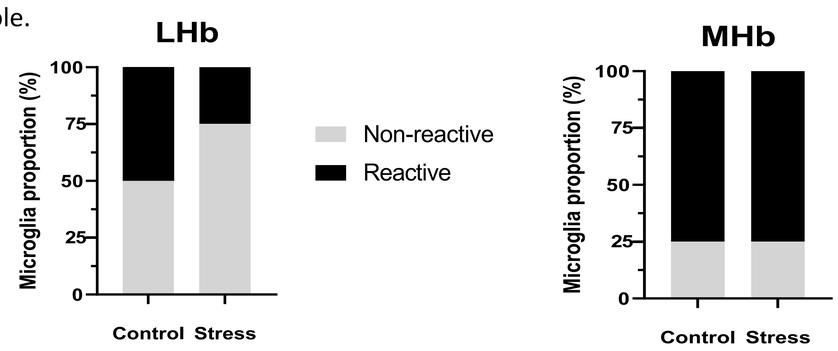


- Chronic stress shifted BLA from 100% non-reactive to 50% reactive, and CeA from 75% non-reactive to 50% reactive, suggesting a partial neuroimmune modulation influencing prolonged emotional regulation with implications for stress-related disorders.

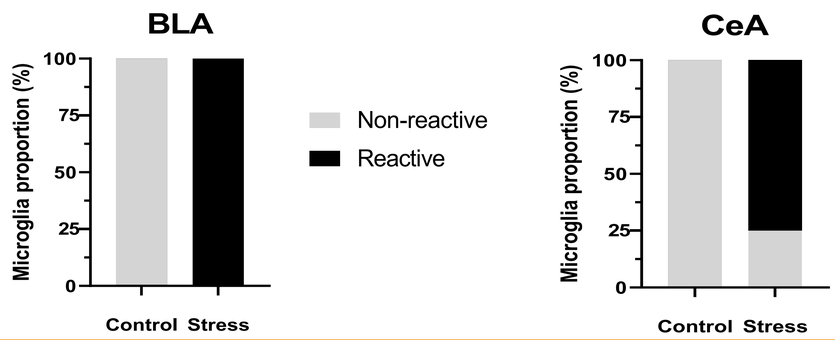


SOCIAL DEFEAT STRESS

- Social stress reduced reactive-like microglial profiles in the LHb from control levels to 25%, with altered circularity, suggesting a shift from a vigilant to a quiescent state, indicating an adaptive response. The MHb showed no changes, reflecting regional resistance to stress and a distinct functional role.



- SDS stress induced significant morphological changes in BLA (100% reactive) and CeA (75% reactive), suggesting strong neuroimmune activation linked to intense emotional responses.



CONCLUSION

Our findings highlight a marked microglial reactivity in the basolateral amygdala (BLA) under chronic and social defeat stress, consistent with its emotional sensitivity to emotional challenges. In contrast, the habenula exhibited divergent responses: the lateral habenula (LHb) showed reduced reactivity under stress, suggesting compensatory adaptation, while the medial habenula (MHb) remained stable after acute stress but responded to chronic stress with increased reactivity and morphological changes. These structure-specific neuroimmune responses may shape vulnerability to stress-related disorders and support microglial plasticity as a therapeutic target.

ACKNOLEDGEMENTS

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