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Sex differences in stress inoculation of addiction-like phenotypes

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Early life stress that is not overwhelming can have an “inoculating” effect that promotes the development of resilience in adulthood, but the mechanisms underlying stress inoculation are unknown. Here we used the limited bedding and nesting (LBN) model—where dams and pups during the pups’ first week of life are exposed to a low resource environment—to assess how this manipulation affects addiction-like phenotypes in adulthood. We first tested whether adult male and female rats with a history of LBN exposure had altered impulsive choice in the delayed discounting task. LBN males more often chose the larger/delayed reward, indicating reduced impulsivity. LBN did not alter choice in delayed discounting in female rats. We next gave LBN-exposed rats access to morphine self-administration. LBN males took less morphine and had a lower breakpoint on a progressive ratio schedule than control males. Again LBN females were not affected. Next we assessed changes in gene expression and histone modifications in the nucleus accumbens (NAc), a region implicated in impulsivity and addiction. LBN caused sex-specific alterations in transcription and increased histone deacetylase 10 expression in the NAc of males, but not females. Using a genome-wide screen of histone post-translational modifications, we found that LBN significantly altered 1 mark in females as compared to 3 marks in males. Future studies will determine which epigenetic modifiers and histone modifications critically contribute to regulating LBN-derived changes in gene expression and behavior. Importantly, identifying factors that promote resilience to addiction-related phenotypes may reveal novel treatment options for patients.