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Developmental effects of maternal separation on oxidative stress accumulation in fast-spiking parvalbumin neurons in prefrontal cortex of male and female rats

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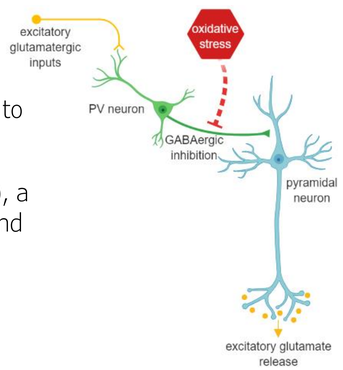
OPPORTUNITY

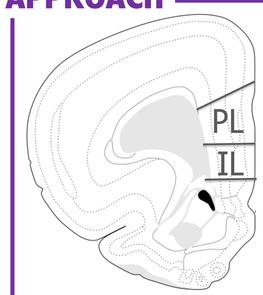
- Early life adversity affects many people[1] and is linked to an increased risk of psychiatric disorders later in life, including depression, bipolar disorder, and schizophrenia.[2] There are sex differences in outcomes, demonstrating a need to compare data across sexes.[3,4]
- The maternal separation (MS) paradigm models early life stress in rats and has been linked to sex-dependent neurological and behavioral deficits.[5]
- These deficits affect parvalbumin (PV)-expressing interneurons in the prefrontal cortex (PFC), a brain region shown to be particularly vulnerable to developmental stress in both humans[6] and rats.[7]
- Oxidative stress has been linked to downregulated PV immunoreactivity in genetic,[8] pharmacological,[9] and psychosocial[10] manipulations.
- Oxidative stress can be quantified using anti-8-oxo-dG, a marker for oxidized guanine.[8]

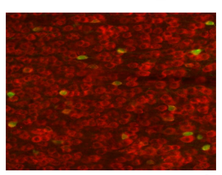
Aim: Measure accumulation of oxidative stress in PV-expressing interneurons in the PFC of juvenile and adolescent rats of both sexes subject to MS.



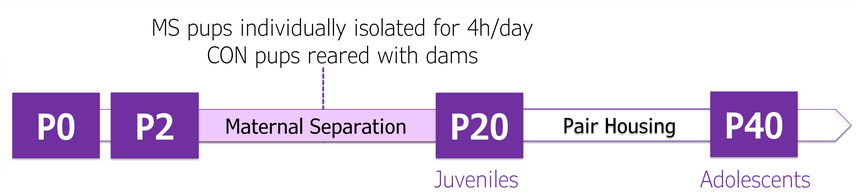
Simplified circuit showing PV neuron function and role of oxidative stress

APPROACH



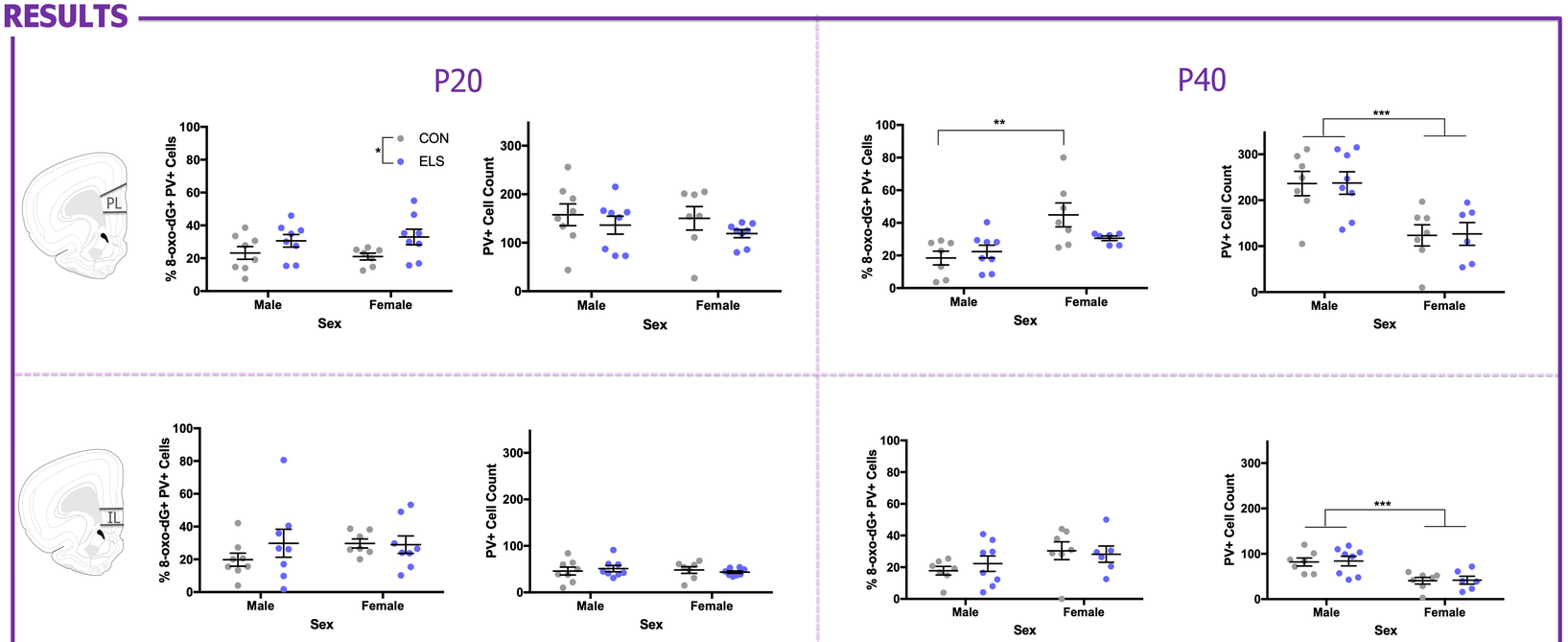


A representative image of the PL of a P20 ELS male (8-oxo-dG shown in red, PV shown in green)



- Juvenile and Adolescent Sprague-Dawley rats sacrificed and perfused with 4% paraformaldehyde
- Brains collected, cryoprotected, and sliced on a freezing microtome to 40µm sections
- Sections containing prelimbic (PL) and infralimbic (IL) PFC incubated in RNAse A and then stained with anti-8-oxo-dG and anti-PV antibody with respective fluorescent secondary antibodies (Alexa Fluor 568 and 488) to visualize oxidized DNA and PV-expressing interneurons
- Images obtained at 20x using Zeiss Axio Imager M2
- Number of PV-expressing neurons and 8-oxo-dG-expressing PV neurons quantified in ImageJ

RESULTS



IMPACT

- The unique feature about my innovation is its demonstration of developmental metabolic dysfunction following early life adversity
- This solves the problem of understanding onset and development of mental illness following early life adversity
- Our findings demonstrate that colocalization of 8-oxo-dG and PV is increased in the PL of animals subject to MS at P20, suggesting that oxidative stress is increased in PV neurons of juveniles that experience early life adversity.
- We found an increase in colocalization in the PL of female CON animals compared to male CON animals at P20, but this may be driven by an overall decrease in PV cell count among females.
- There is no significant difference in colocalization at P40; future work will seek to address this by studying potential differences in antioxidant enzyme regulation.
- These studies provide evidence that early life stress increases oxidative damage in GABAergic PV interneurons of the PFC, which may drive the PV dysfunction and associated neuropsychological deficits seen in animals and humans subject to early life adversity.

FUNDING

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