

# Perinatal hyperserotonemia influences dopamine expression in the midbrain



Zachary Zeisler, Spencer Smith, and Katharine Northcutt

Department of Biology, Mercer University, Macon, GA



## Background

Both prenatal and neonatal hyperserotonemia have been documented as risk factors for autism. Specifically, mothers taking SSRIs prescribed for depression are more likely to have children with autism.

Injecting 5-methoxytryptamine (5-MT), a serotonin agonist, daily into pregnant rat dams and then into their pups upon birth can induce autism-like symptoms, such as social deficits, sensory hyper-responsiveness, and coordination deficits. Altered serotonin levels can change the development of specific neural networks, and alterations in dopaminergic networks can produce symptoms similar to those described above. Therefore, it is fair to reason that excess serotonin during development could affect the number of dopaminergic neurons.

In the current study, we focused on the midbrain, specifically the substantia nigra (SN) and ventral tegmental area (VTA), which are important for movement and motivation. Our results could lead to a better understanding of autism's pathophysiology.

## Methods

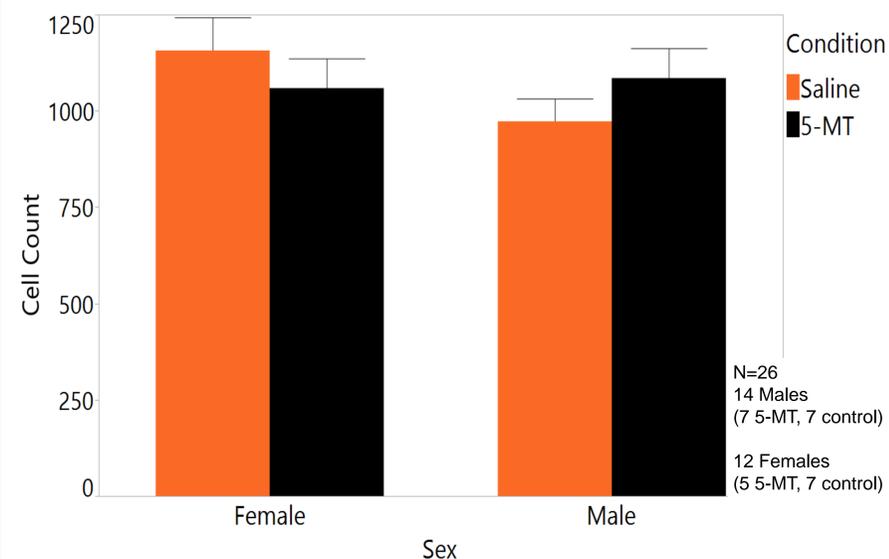
### Treatments

- Either 5-MT (1 mg/kg) or a vehicle solution was injected into the pregnant Long-Evans dams daily (days 12-21 days of gestation).
- Pups were injected similarly, with the same 1 mg/kg dose, for the first 20 days of postnatal development.
- Pups were weaned from the dams and placed into cages with same-sex siblings.
- Brains were collected on postnatal day 30-32.

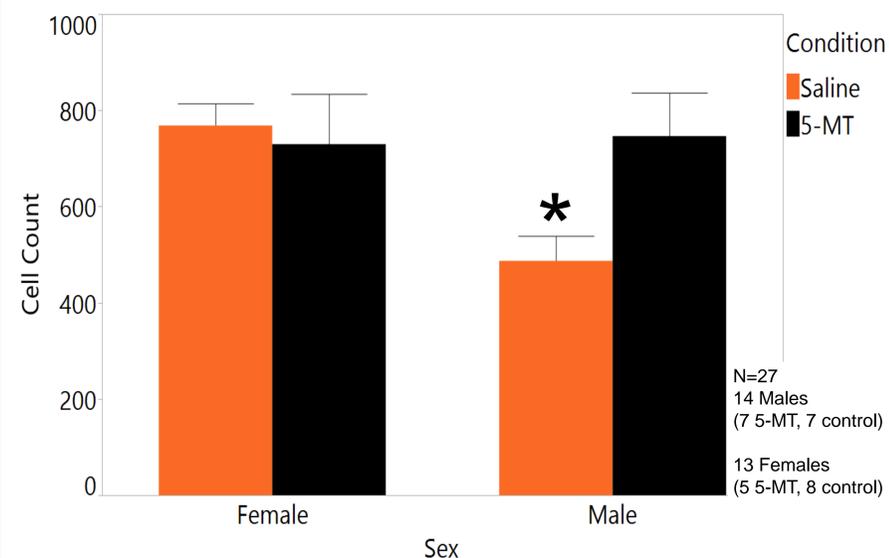
### Histology

- Brains were processed immunohistochemically to stain for tyrosine hydroxylase (to show location of dopaminergic cells).
- Cells expressing dopamine were counted, both in the VTA (SS) and the SN (ZZ).
- Two-way ANOVAs were used to analyze data.

## Results



**Figure 1.** Effect of sex and 5-MT treatment on mean number of VTA dopaminergic cells, summed from 3 sections. Error bars represent one standard error. There was not a significant main effect of sex or treatment, nor was there a significant interaction.



**Figure 2.** Effect of sex and 5-MT treatment on mean number of SN dopaminergic cells from 3 sections. Error bars represent one standard error. There was a significant main effect of treatment, as well as a significant interaction, such that 5-MT increased the number of TH-positive cells in males.

## Summary and Conclusions

•5-MT increased the number of TH-positive cells in the SN, but only in males.

•Neither sex nor treatment had an effect on the number of dopaminergic neurons in the VTA.

•Previous studies have not found a sex difference in TH-immunoreactivity in the SN, but the sex difference we observed could be a consequence of handling the newborn rats every day, particularly given that neonatal handling affects serotonin turnover (Smythe et al., 1994).

•Previous research has shown that excess dopaminergic activity from the SN can lead to hyperactivity and repetitive behaviors, similar to those seen in cases of autism (Kim et al., 2015). Therefore, the increase in TH-positive cells in the SN may relate to these repetitive behaviors.

•Autism spectrum disorders are 4.5 times more likely in boys than girls, and a differential sensitivity to perinatal conditions may help explain this.

•The lack of effect on the VTA is encouraging, in that areas important for motivation do not seem to be affected by this treatment (at least in this measure).

•Plans for future studies include analysis of other dopaminergic areas, including those with well-documented sex differences, such as the AVPV (which contains more TH-positive cells in females).

## Acknowledgements

We would like to thank the Mercer Biology Department and the Provost's Office for sponsoring this research.