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Norepinephrine and Corticosterone in the neoCLOM Animal Model of Obsessive Compulsive Disorder: Effects of Treatment and Sex

Hannah Rockwood

Binghamton University--SUNY

Jason Howard

Binghamton University--SUNY

Lea Safarpour

Binghamton University--SUNY

Kate Lerner

Binghamton University--SUNY

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Introduction

Obsessive Compulsive Disorder (OCD)

- OCD is a neurological disorder characterized by intrusive thoughts, repetitive behaviors, and anxiety¹
- Current pharmacological treatments for OCD are problematic²
Ineffective in 40-60% of patients, 8-10 week delayed onset, serious side effect

Hypothalamus-Pituitary-Adrenal (HPA) Axis

- Stress increases the activity of the axis leading to enhanced levels of the neurotransmitter norepinephrine and the hormone cortisol³

Norepinephrine

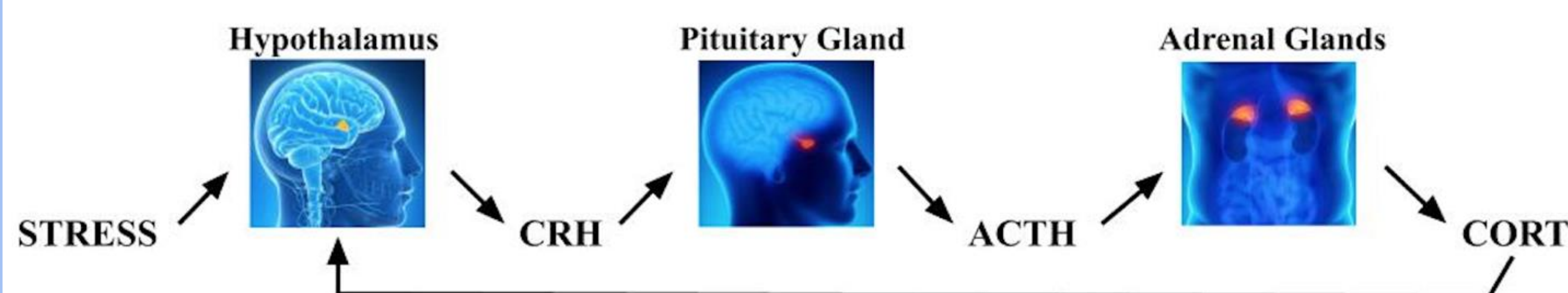
- Overall levels are elevated in OCD patients

Cortisol

- Levels are elevated in OCD patients⁴
- Corticosterone is rat analog

NeoCLOM Model

- Rats are exposed to clomipramine from Days 9-16⁶ thereby altering the rats' HPA axis during its maturation⁷



OBJECTIVE: to evaluate the neoCLOM rat model of OCD in males and females by measuring norepinephrine (NE) levels in post mortem brain regions and blood levels of corticosterone (CORT)

Methods

Subjects

72 Sprague-Dawley rats (36 male, 36 female) were used. Twice daily injections of either 15 mg/kg clomipramine (neoCLOM, 17 males, 19 females) or saline (neoSAL, 19 males, 17 females) were administered on Days 9-16.

Blood Collection for Corticosterone Analysis

Trunk blood was collected after rapid decapitation on Days 87-93, centrifuged, and serum extracted. CORT levels were measured using an ELISA kit (Immunodiagnostic Systems Limited, MD) in conjunction with spectrophotometric analysis (SpectraMax 190, CA).

Tissue Collection for Norepinephrine Analysis

Following decapitation on Days 87-93, punches of brain structures were obtained using a refrigerated cryostat⁸. Supernatants were extracted after tissue punches were homogenized and centrifuged.

Brain Structure	Motor Cortex	Lateral Thalamus	Ventral Striatum	Amygdala	Prefrontal Cortex	Anterior Cingulate Cortex	Orbitofrontal Cortex	Hypothalamus
ML coordinate	1.5 mm lateral from midline	3.0 mm lateral from midline	2.4 mm lateral from midline	4.8 mm lateral from midline	4.0 mm lateral of midline	1.0 mm lateral from midline	4.0 mm lateral of midline	0.6 mm lateral from midline
DV coordinate	1.5 mm ventral of skull	5.4 mm ventral of skull	6.0 mm ventral of skull	8.6 mm ventral of skull	5.6 mm ventral of skull	2.6 mm ventral of skull	5.6 mm ventral of skull	10.0 mm ventral of skull
Interneural coordinate	8.70 mm	6.20 mm	10.0 mm	6.20 mm	12.20 mm	12.20 mm	12.20 mm	6.20 mm

High Performance Liquid Chromatography (HPLC)

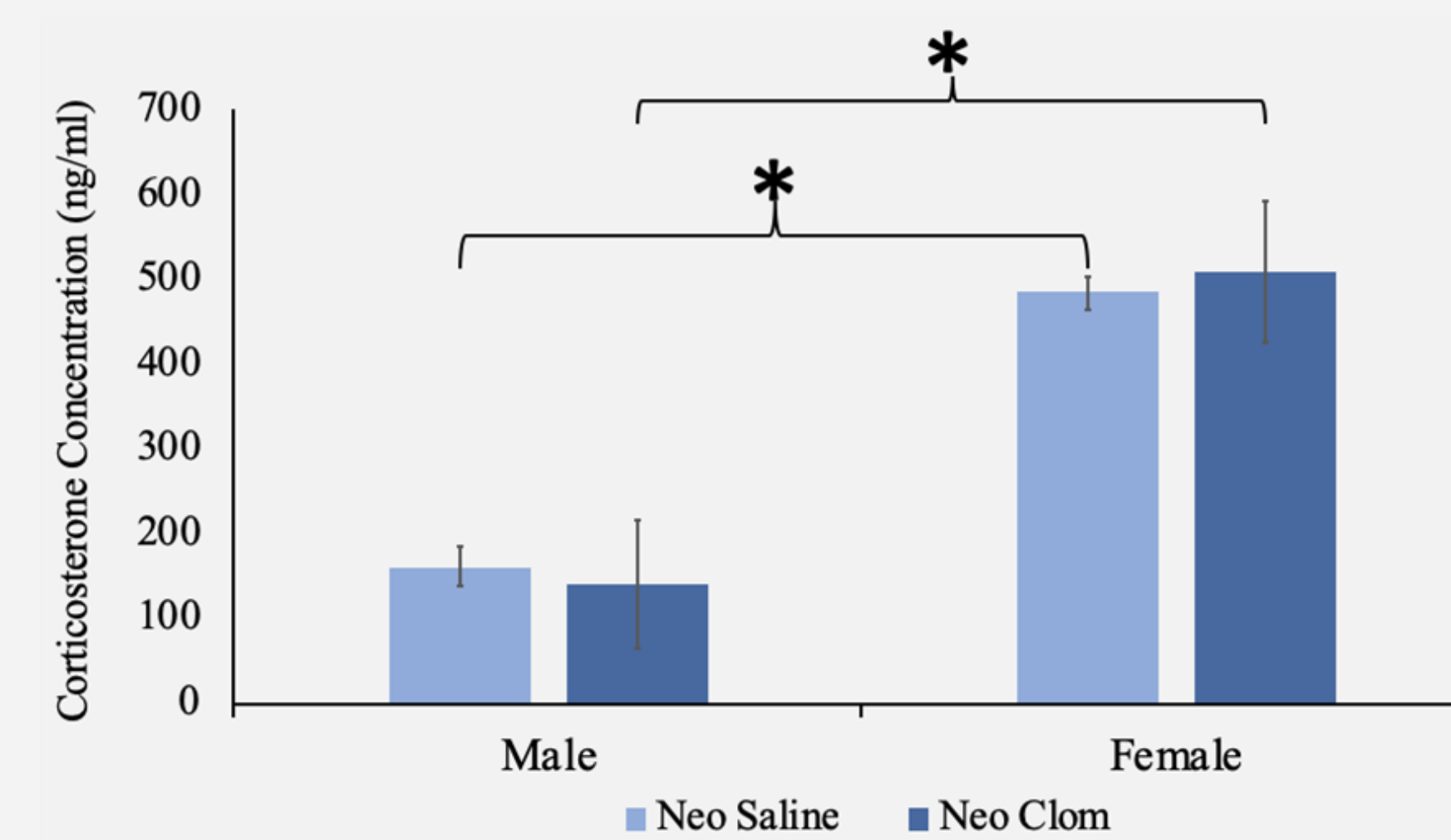
Supernatants were analyzed for NE. Peak areas were calculated using Eicom software.

Statistical Analysis

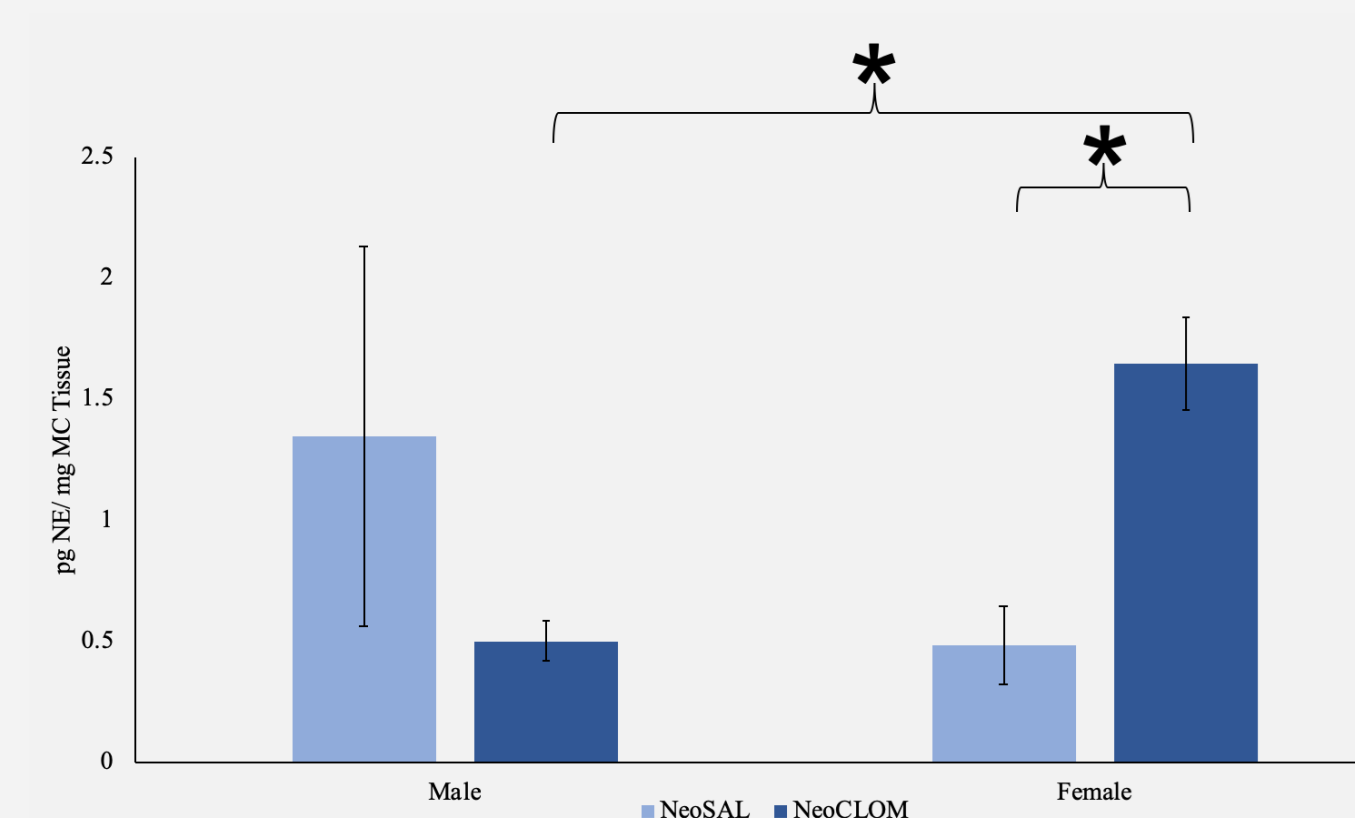
Data was subjected to a 2x2 ANOVA with between subject factors of neonatal treatment (neoSAL, neoCLOM) and sex (male, female) with significance set at $p < 0.05$. Two-tailed Student's T-tests were used for pairwise comparisons.

Results

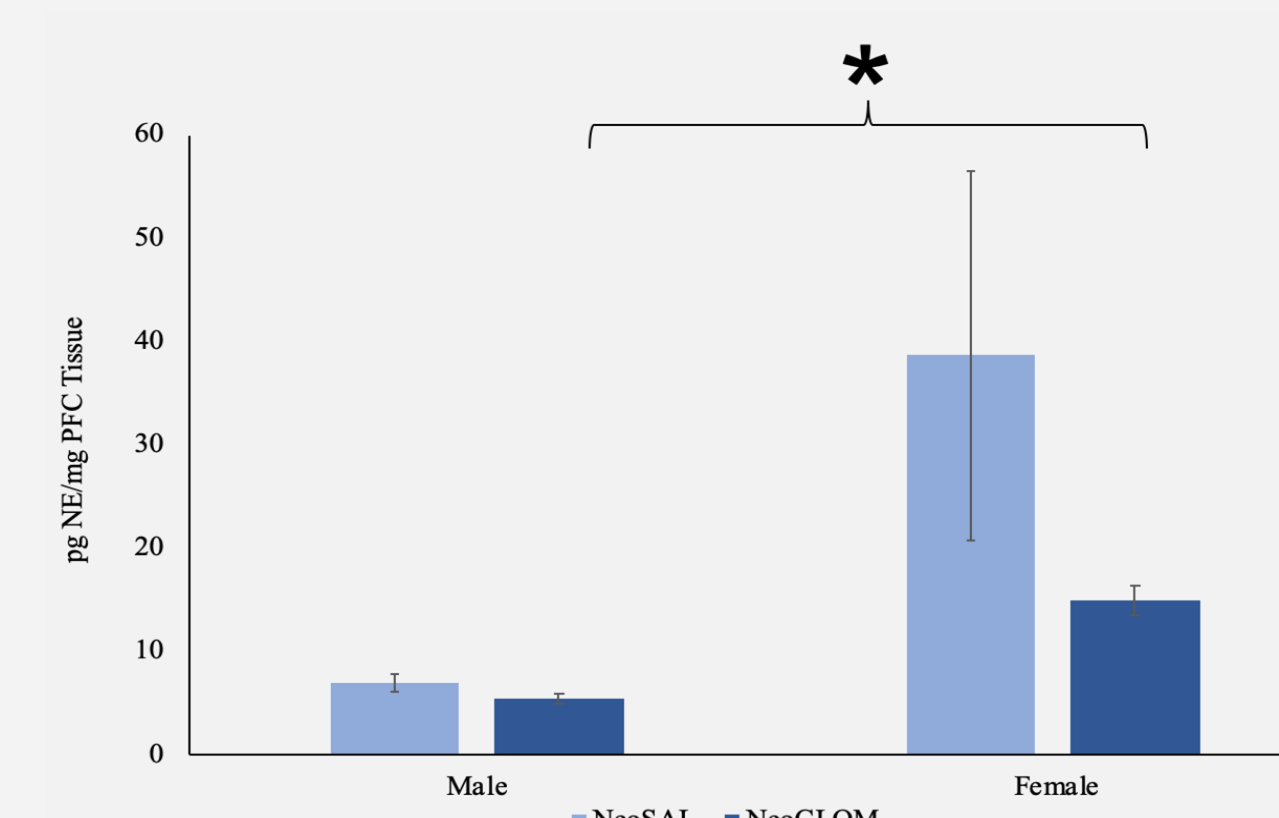
Blood CORT Levels



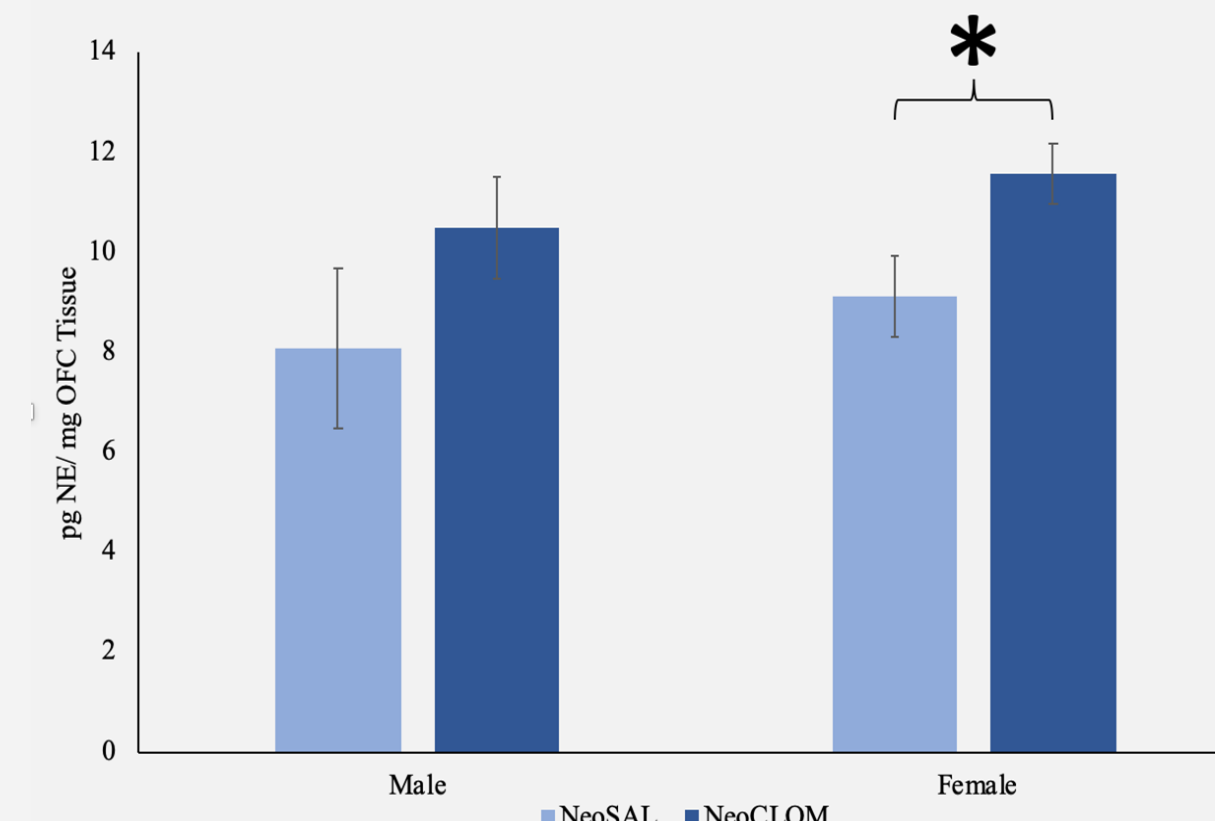
Motor Cortex



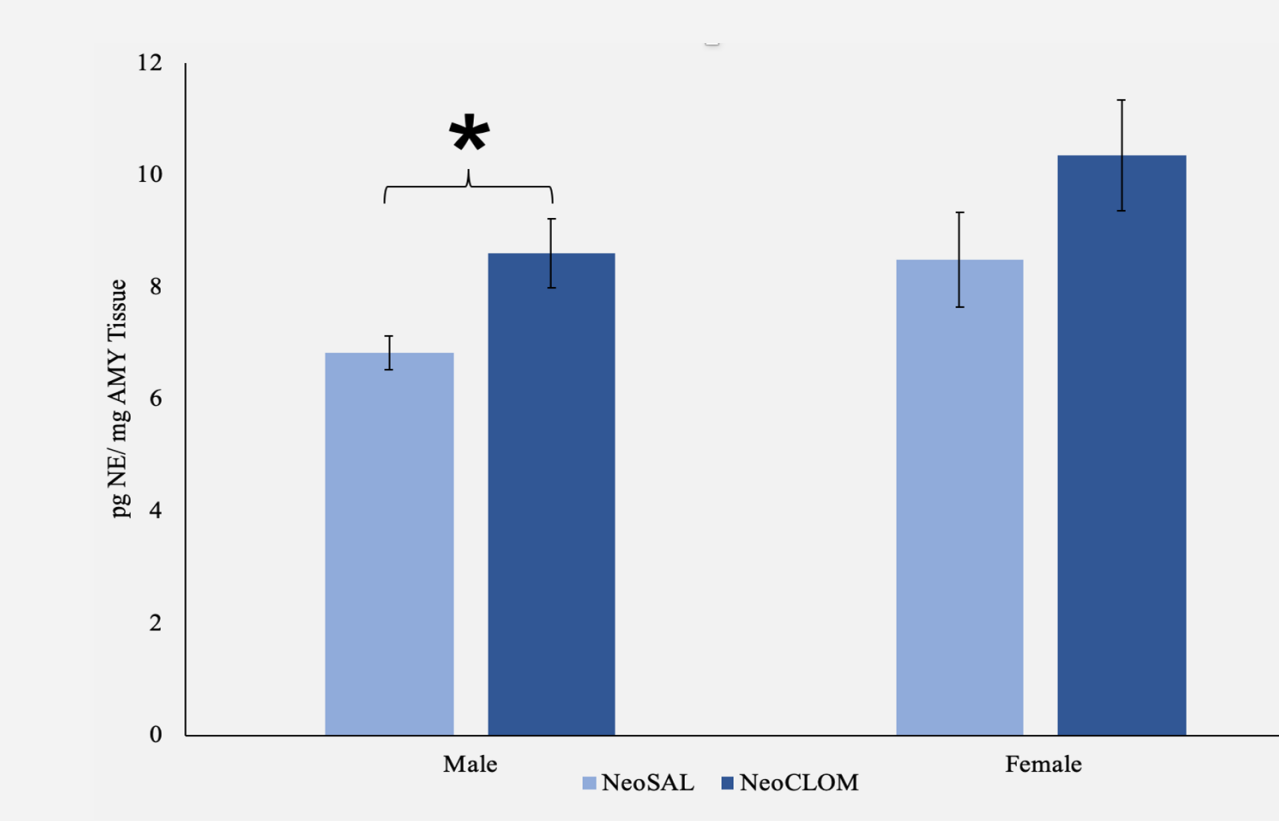
Prefrontal Cortex



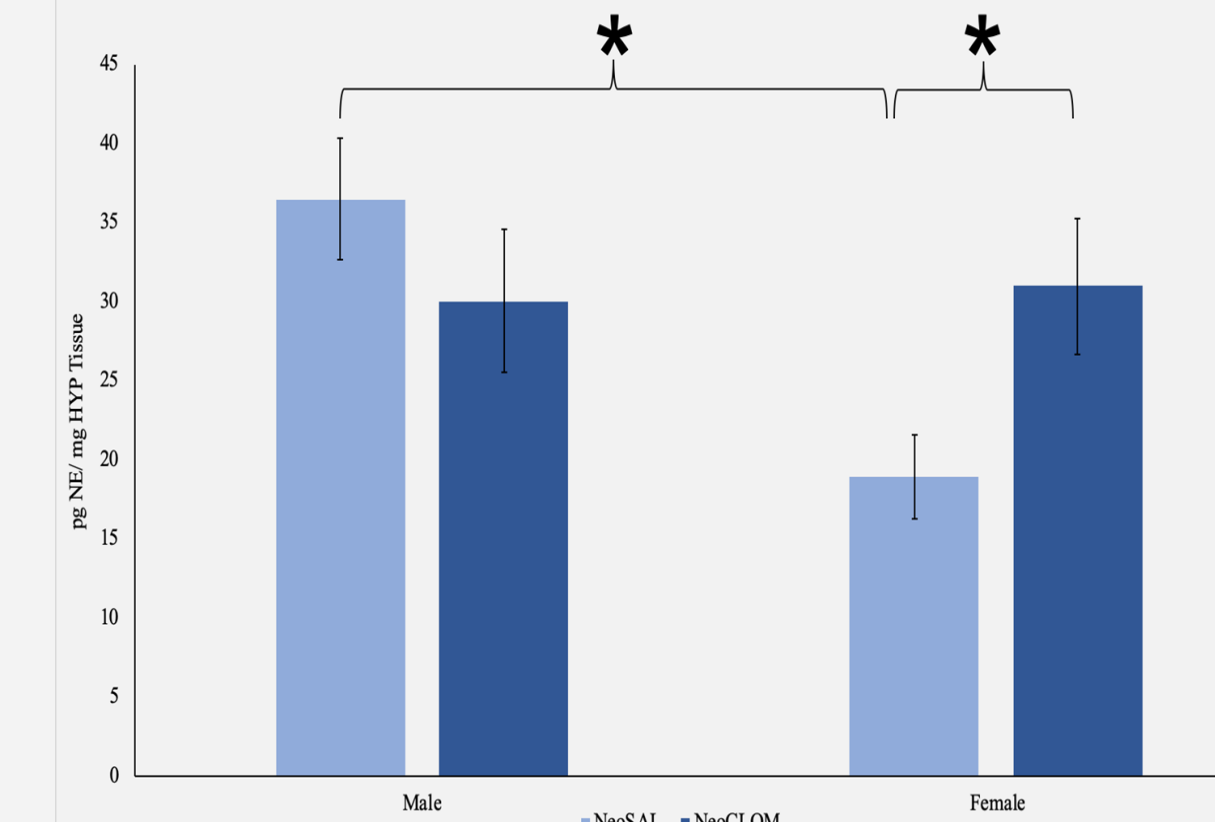
Orbitofrontal Cortex



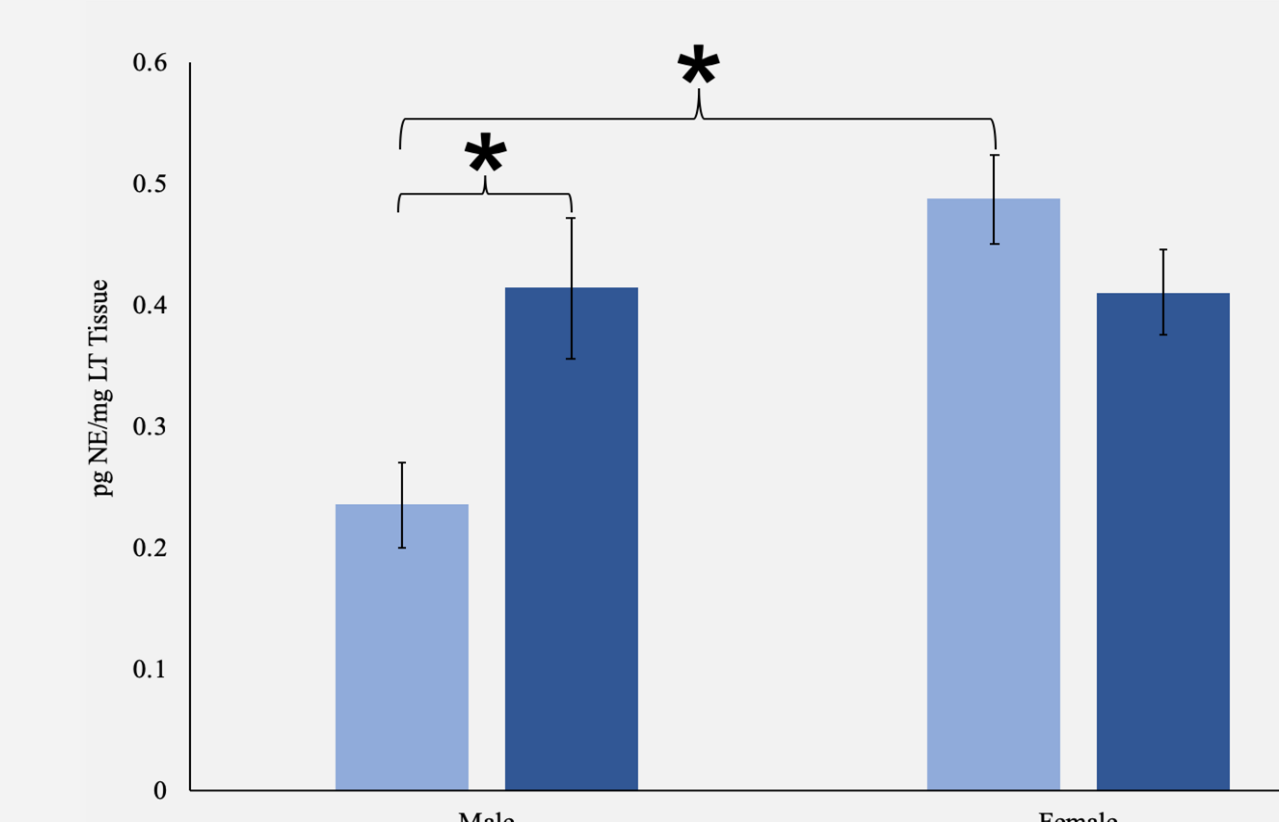
Amygdala



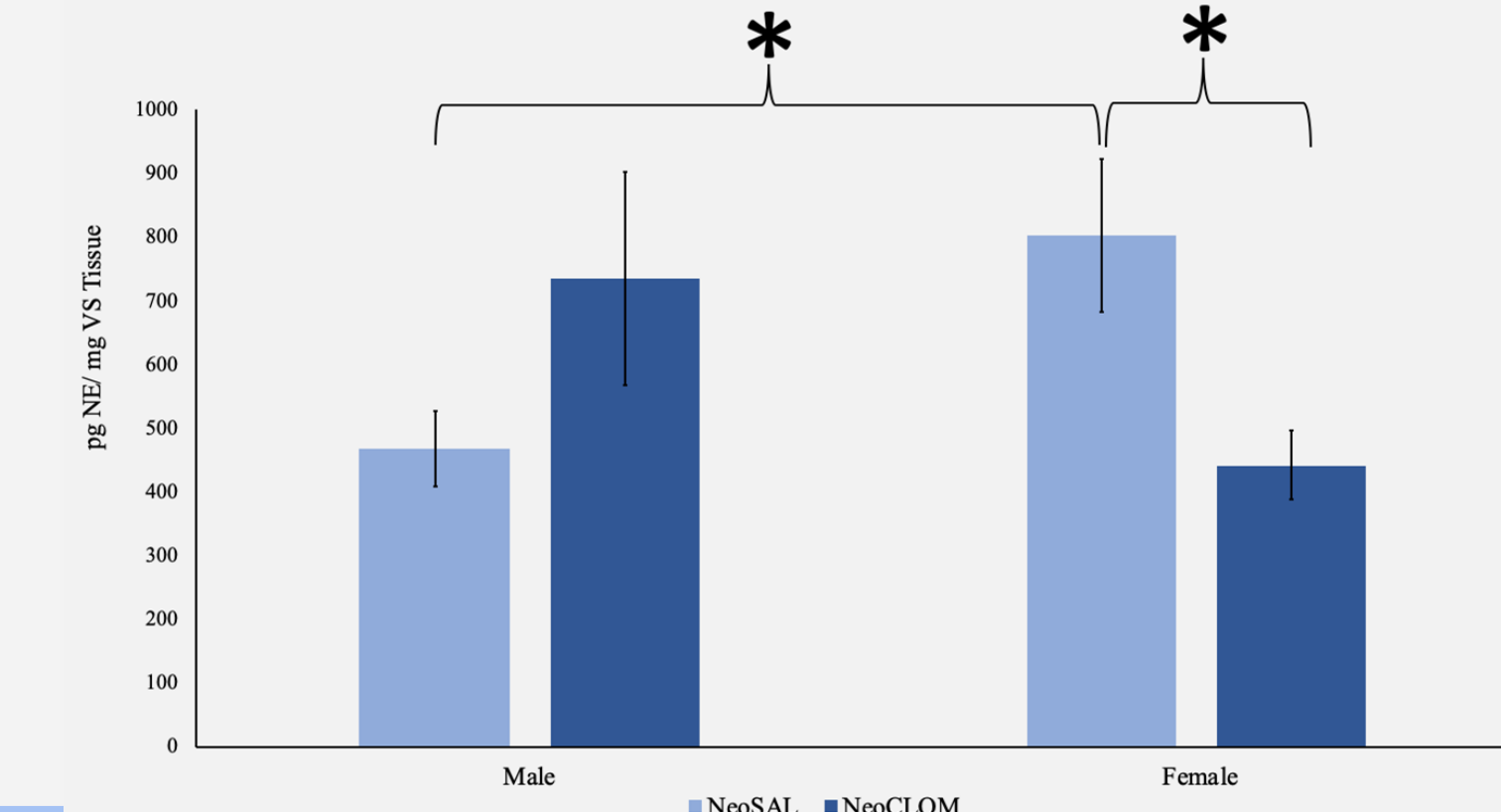
Hypothalamus



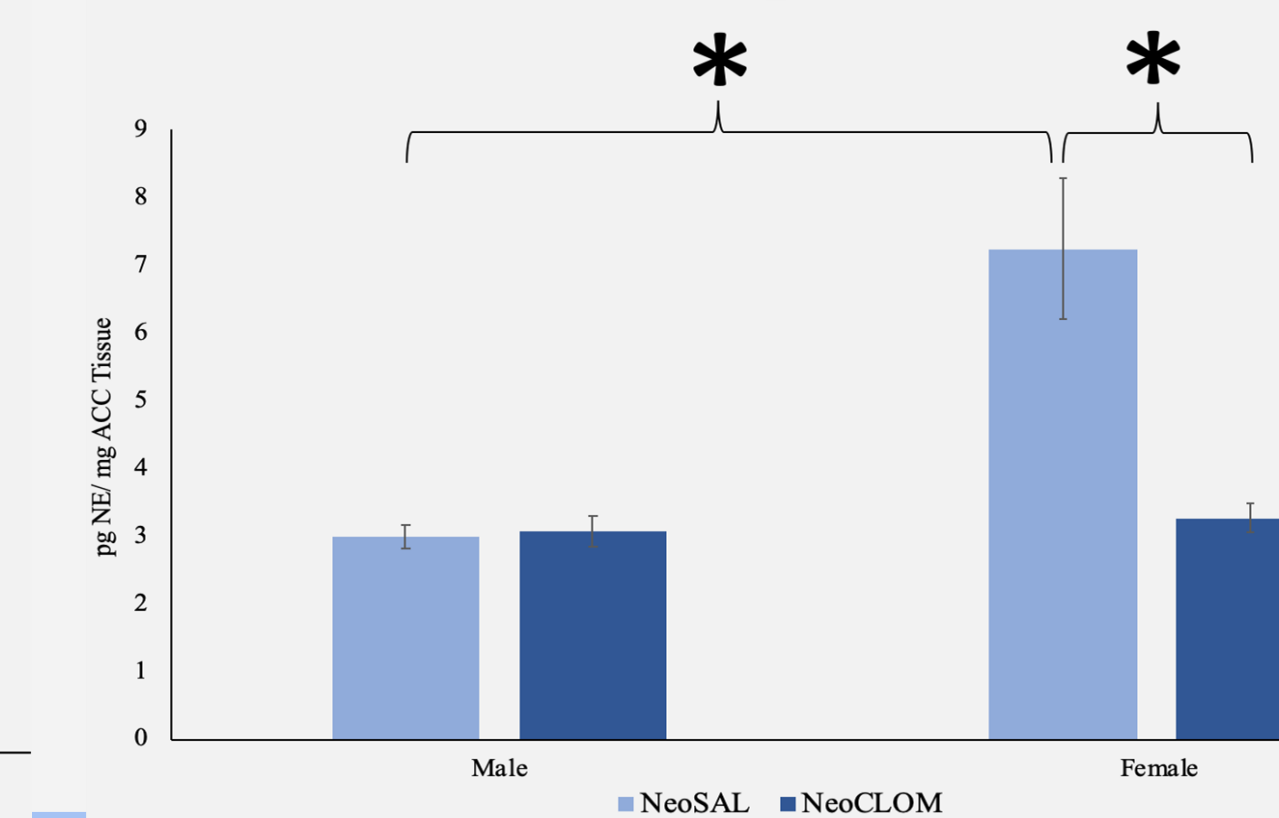
Lateral Thalamus



Ventral Striatum



Ant. Cingulate Cortex



Discussion

Levels of corticosterone (CORT) and norepinephrine (NE) did not correlate.

Sex affected both CORT and NE

- Females had higher levels of CORT, in accordance with previous studies.⁹
- Females had higher levels of NE in the prefrontal cortex, motor cortex, lateral thalamus, ventral striatum, and anterior cingulate cortex.
- Males had higher levels of NE in the hypothalamus.

Treatment affected NE, but not CORT

- NeoCLOM groups had higher levels of NE in the motor cortex, orbitofrontal cortex, amygdala, hypothalamus, and lateral thalamus.
- NeoCLOM groups had lower NE in the ventral striatum and anterior cingulate cortex.
- NeoCLOM groups did not have altered CORT.

Both neonatal Treatment and Sex influences the regulation of NE in the neoCLOM model of OCD.

Acknowledgments

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