2020

Striatal Dopamine and Norepinephrine Levels in Conjunction with OCD-like Behaviors in a Novel Animal Model of Obsessive-Compulsive Disorder

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Striatal Dopamine and Norepinephrine Levels in Conjunction with OCD-Like Behaviors in a Novel Animal Model of Obsessive-Compulsive Disorder

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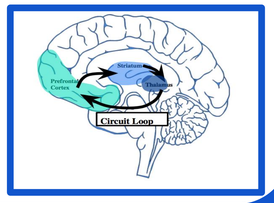
INTRODUCTION

- Approximately 7 million United States Americans suffer from Obsessive Compulsive Disorder (OCD)[1]
- Current pharmacological treatment, serotonin reuptake inhibitors (SRIs), have significant issues (effectiveness, onset, side effects).[2]
- Neonatal Clomipramine (NeoCLOM) Animal Model of OCD[3]:
  - New model that causes a permanent change in brain circuitry and may offer multiple strong validities as an animal model
  - Animal models are evaluated on face, predictive, and construct validity[4]
- Striatum
  - Major integration site of cortico-basal ganglia-thalamic loops
  - These circuit loops believed to be overactive in OCD patients[5]
- Serotonin (5-HT) - Low levels implicated in OCD[6]
- Norepinephrine (NE) - High levels implicated in anxiety disorders[7]
- Dopamine (DA) - High and Low levels implicated in OCD[6]



GOALS

1. **Evaluate the face validity of the neoCLOM model via behavioral assessment of male and female rats in the Hole-Board (HB) and Elevated Plus Maze**
2. **Evaluate the levels of DA and NE in the post mortem tissue homogenates of the ventral and dorsal striatum of male and female experimental neoCLOM and control neoSAL rats**

METHODS

Subjects
- Sprague-Dawley rats (n = 72)

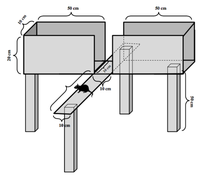
Neonatal Treatment
- Days 9-16
- 15 mg/kg clomipramine (n = 19 ♀, 17 ♂)
- 0.9 % saline (n = 17 ♀, 19 ♂)
- 2x daily

Behavioral Trials:
- Days 83 - 92
- 5 min each
- Elevated Plus Maze
- Hole Board

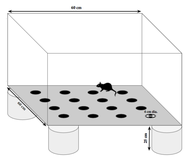
Tissue Extraction
- Rapid decapitation: Days 87-93
- Brain Extraction - punches from ventral striatum (2.4 mm ML; 6.0 mm DV; 10 mm interaural) and dorsal striatum (2.4 mm ML ; 4.2 mm DV; 10 mm interaural)[8]

Neurochemical Analysis
- Tissue homogenized and centrifuged
- NE and DA measured using HPLC

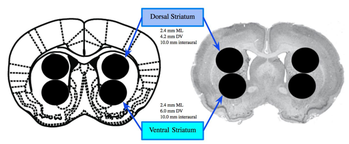
Data Analysis
- Data expressed as mean ± Standard Error of the Mean (SEM)
- 2 factor ANOVA tests were performed, followed by two-tailed Student's t-tests with $p < 0.05$



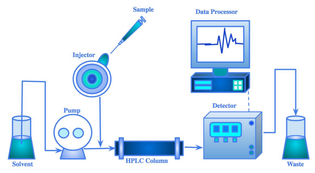
Elevated Plus Maze



Hole Board



Dorsal and Ventral Striatum Hole Punch Coordinates

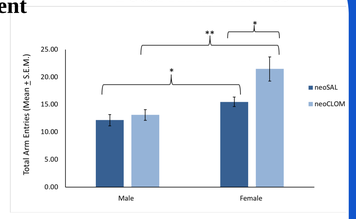


High Performance Liquid Chromatography

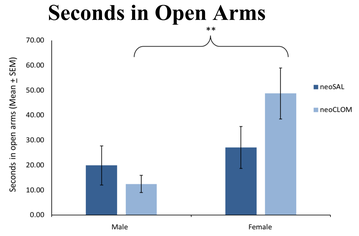
BEHAVIORAL RESULTS

Elevated Plus Maze (EPM) Effect of Sex, Interaction between Sex & Treatment
- Female neoCLOM had more total arm entries versus female neoSAL
- Female neoCLOM had more time in open arms, open arm entries, total arm entries versus male neoCLOM
- Female neoSAL has more total arm entries vs. male neoSAL

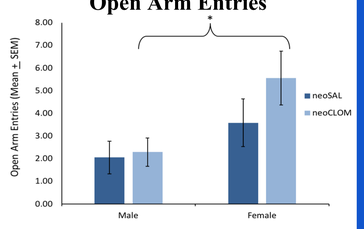
Total Arm Entries



Seconds in Open Arms

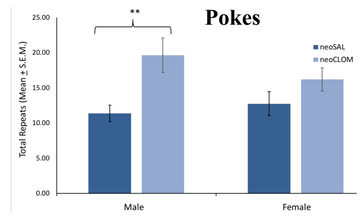


Open Arm Entries

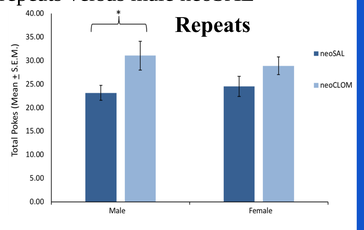


Hole Board (HB) Effect of Treatment, not Sex, for pokes and repeats
- Male neoCLOM had more pokes and repeats versus male neoSAL

Pokes



Repeats



Correlations of HB and EPM behaviors

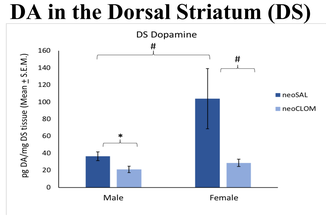
Positive correlation between total pokes and total repeats

No correlation between open arm activity and hole poking

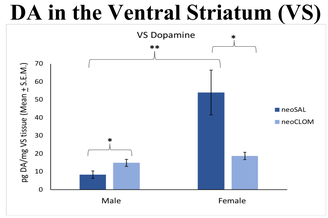
NEUROCHEMICAL RESULTS

Dopamine (DA): Effect of Treatment, Sex, and Interaction
- Female neoCLOM had lower DA in both the DS & VS versus female neoSAL
- Male neoCLOM had lower DA in the DS and higher DA in the VS versus male neoSAL
- Female neoSAL had higher DA in the both DS and VS versus male neoSAL

DA in the Dorsal Striatum (DS)

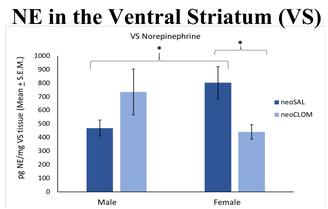


DA in the Ventral Striatum (VS)



Norepinephrine (NE): Effect of Interaction of Treatment and Sex
- Female neoCLOM had decreased NE levels in the VS vs. female neoSAL
- Female neoSAL rats had increased NE in the VS vs. male neoSAL

NE in the Ventral Striatum (VS)



CONCLUSIONS

The neoCLOM model has face validity in male rats for Hole Board Behaviors.

Hole poking is neither neophilic nor neophobic. Hole Board and Elevated Plus Maze represent different aspects of the animal's behavior.

Female expression of anxiety in the Elevated Plus Maze may be different than traditional interpretations based on males.

Treatment and Sex differences in dopamine and norepinephrine levels of the dorsal and ventral striatum suggest the neoCLOM model may offer additional validity.

FURTHER RESEARCH

Test predictive validity	Administer rats drugs proven effective in OCD patients: • serotonin reuptake inhibitors • glutamate antagonists • combination of SRIs and glutamate antagonists
Control for the female estrous cycle	Manage the estrous cycle: • pharmacologically • via an ovariectomy • daily monitorization
Further evaluation of face validity	Examine other apparati and methods for behavioral trials: • spontaneous alternation • open field test • lever pressing test
Obtain supplemental neurochemical data	Utilize alternative *in vivo* methods to measure other neurotranmitters: • glutamate • serotonin • acetylcholine
Additional review of construct validity	Analyze other brain structures theorized to be implicsted in OCD: • thalamus • anterior cingulate cortex • orbitofrontal cortex

ACKNOWLEDGEMENTS

We would like to thank Jason Howard, Mia Cruceta, and Kaitie Forbes for their guidance; the BU Laboratory Animal Resources staff for their husbandry; the First-year Research Immersion Program and the fifth Neuroscience Stream cohort; Trevor Tower and Kim Papastrat for their help in the decapping process; and May Vititow and Gina Rizzo for their help in obtaining brain punches.

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