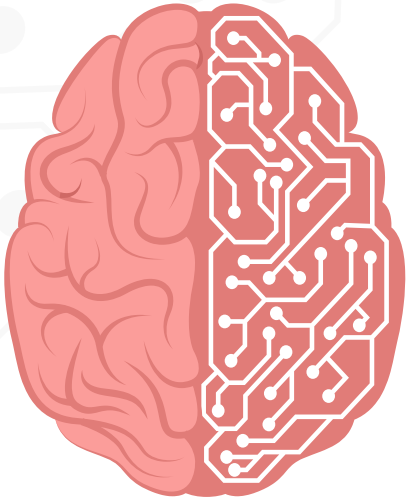


Cortical Circuitry Underlying Hyperfixation in ASD

Research Presentation by Aia Roshdi, Joanne Andre, Melanie Cruz and Morsaline Mozahid

Autism Spectrum Disorder

- Neurodevelopmental disorder that affects 1 in 59 American children, with boys diagnosed four times more often than girls. (CDC, 2020)

- Clinical areas in the Autism phenotype: deficits in social interaction, motor movements, and cognitive function

    - Hyperfixation - stereotyped behavior that involves persistent concentration

https://www.integrityinc.org/signs-symptoms-of-high-functioning-autism/

Hyperfixation

Sensory Cognitive Imbalance

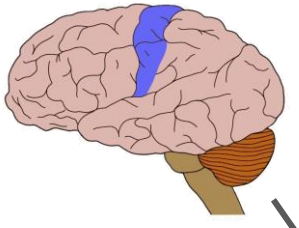
↓

Networks
Hyperconnectivity and Hypoconnectivity

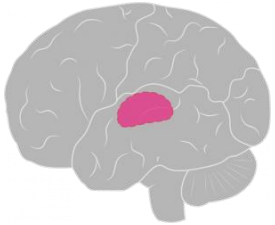
↓

Molecular/Cellular Mechanisms
Synaptic Pruning

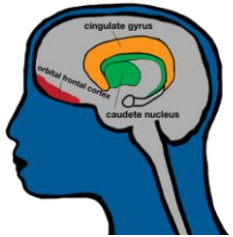
Primary Sensory Cortex



Thalamus

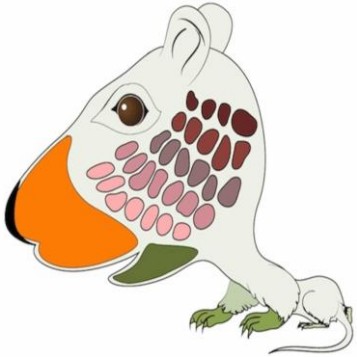


Associative Cortex



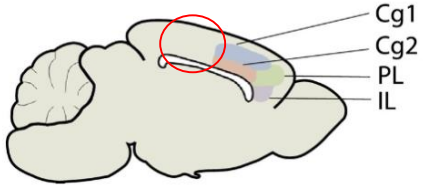
Somatosensory Barrel Field & Posterior Cingulate

- Barrel Field(S1BF): clusters of neurons in the whiskers
  - Most abundant area of sensory input in a mouse's body (Zembrzycki et al., 2013)



Zembrzycki et al.(2013). Nature Neuroscience
DOI:10.1038/NN.3454

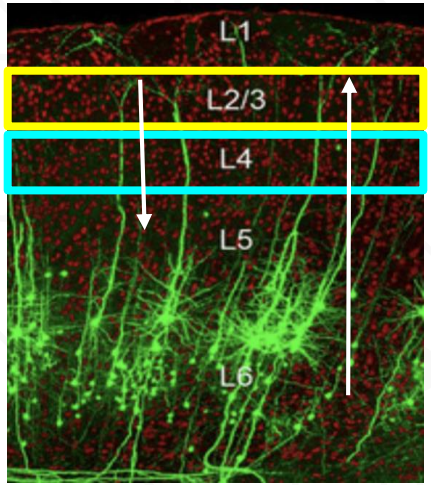
- Posterior Cingulate (PCC):
  - Plays a role in cognitive function
  - PCC plays a more direct role in regulating the focus of attention *(Gusnard and Raichle, 2001; Hampson et al., 2006; Hahn et al., 2007)(Leech et al., 2011).*



Cortical Layers

- Layer 2:
  - Cortico-cortical pathway - communication between nearby, associative cortices (Roland et al, 2014)

- Layer 4:
  - Thalamic-cortical pathway - communication between the thalamus and other cortices
  - Major receptive zone for excitatory stimuli (Chabrol et al., 2013)

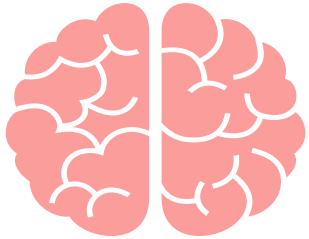


Known

- Hyperconnectivity in subcortical to cortical circuitry (Thalamus-->layer 4 S1BF) *(El-Boustani, 2020)*
- Hyperconnectivity in the local cortico-cortical circuitries (i.e layer 2) *(Courchesne, 2005)*
- Dopamine:
  - Relates to attention
  - Is a novelty input
  - Hyper focus is thought to be caused by low dopamine levels *(Nieoullon, 2002)*
  - Can be excitatory and inhibitory

Unknown

- Are the sensory/cognitive cortices uncoupled?
- Does hyper/hypoconnectivity underlie the sensory cognitive imbalance?
- How do the thalamic-cortical and cortico-cortical layers differ between autistic and neurotypical brains?
- How will dopamine impact cortical cortical and thalamic cortical connections?



General Hypothesis.

The functional connectivity within the somatosensory cortex and posterior cingulate cortex is uncoupled, which leads to hyperfixation.

Specific Aims

Specific Aim 1:

Measure cortical-cortical and thalamic- cortical neural activity in the S1BF in wild type and ASD animal model mice with and without dopamine.

Working Hypothesis: Dopamine will normalize cortical activity in the S1BF in the ASD animal model to wild type levels

Specific Aim 2:

Measure cortical-cortical and thalamic- cortical neural activity in the Cingulate in wild type and ASD animal model with and without dopamine

Working Hypothesis: Dopamine will normalize cortical activity in the Cg in the ASD animal model to wild type levels

Research Design: Wild Type, FMR1 KO, KO + MIA (n = 2)

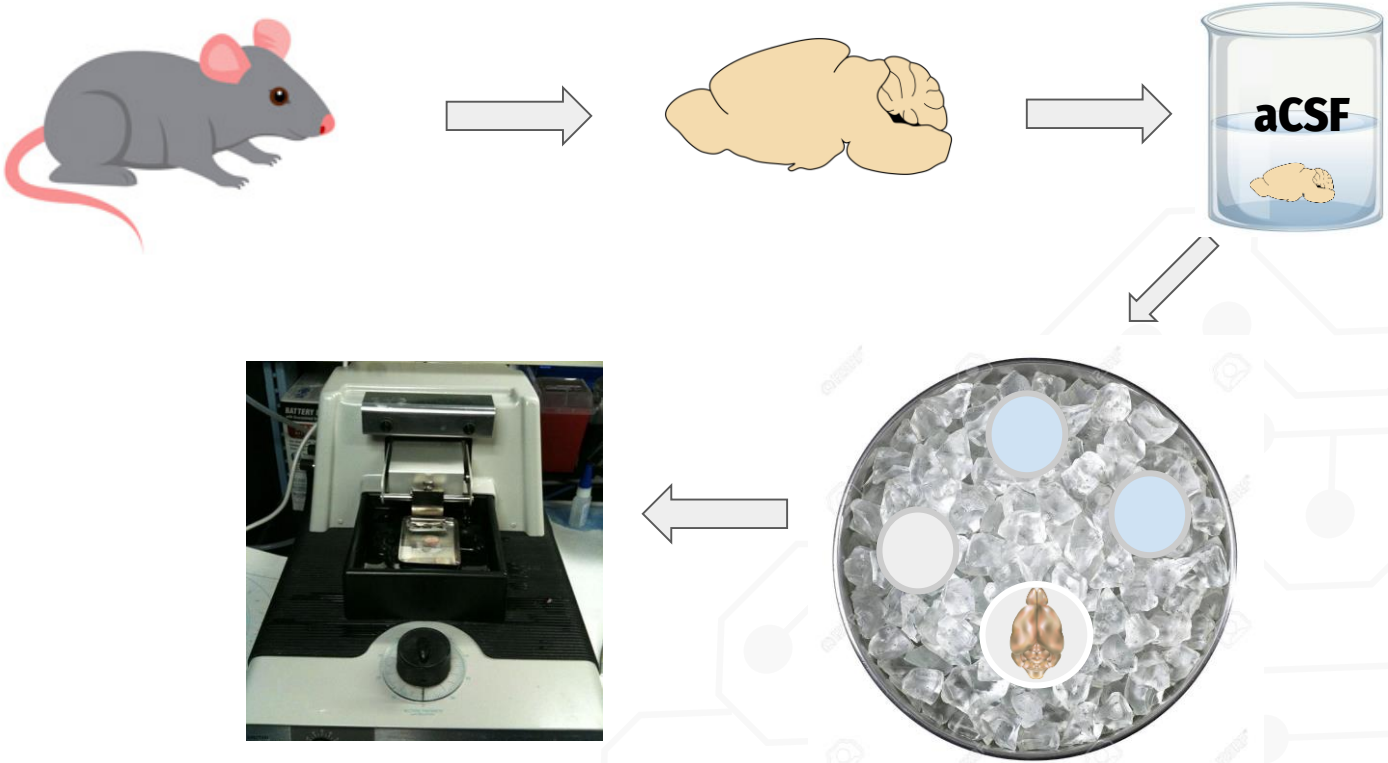
FMR1 Knockout (One Hit)

- Absence of FMR1 gene that produces FMRP
  - FMRP helps regulate the transport of mRNA and translation of synaptic proteins.
  - Leads to Fragile X Syndrome.
- Reliable model for studying ASD.

FMR1-KO + Maternal Immune Activation (Double Hit)

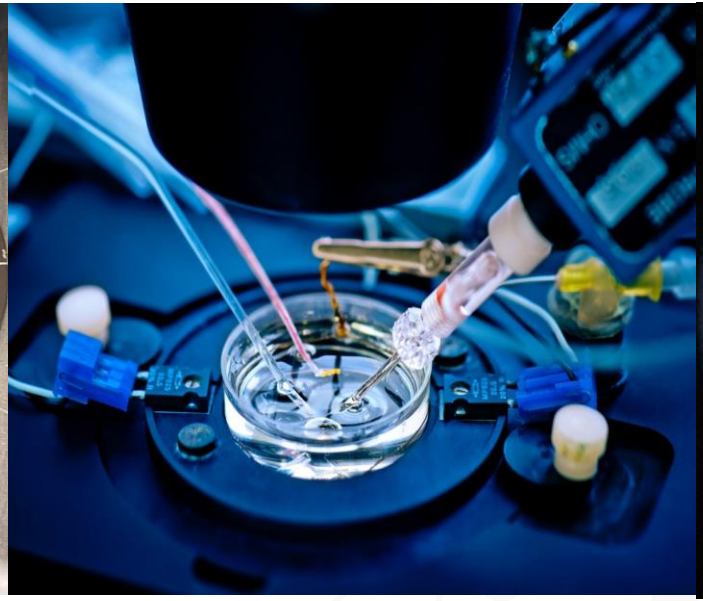
- Immune response to external stimuli (stress, infections, pollution, etc.)
- Rabbit IgG protein injection into pregnant mouse
- Immune responses travel through placenta, affecting the neurodevelopment of the fetus.

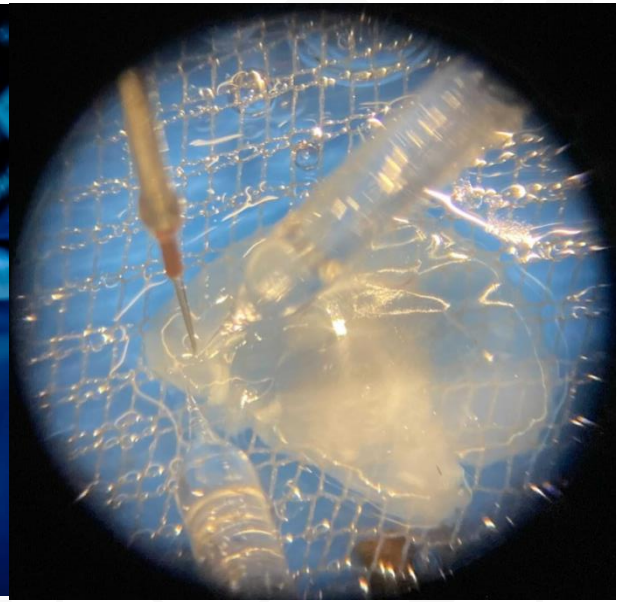
Method Electrophysiology of Brain Slices



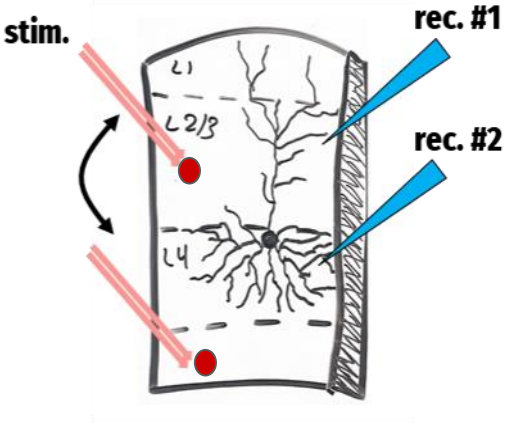
Method (cont.)

Brain Slicing and Recording Synaptic Potentials

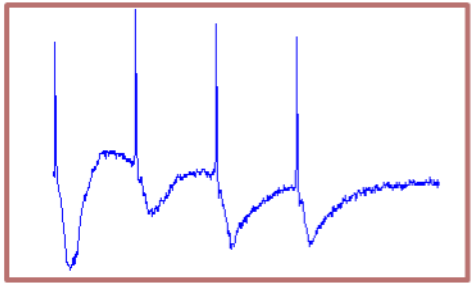


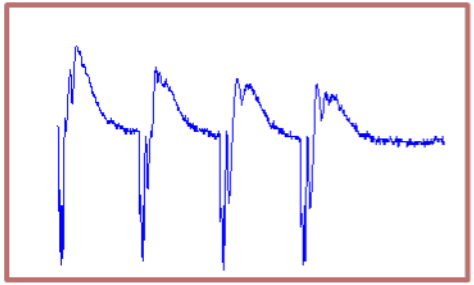


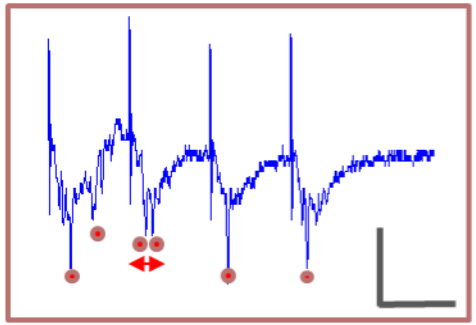
Method: Recordings



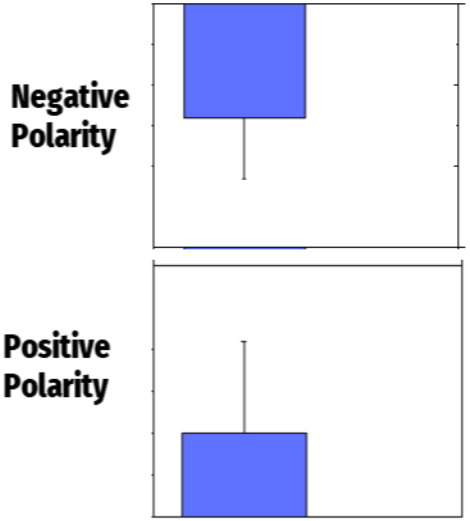
Input Stimulation~ 40 Hz
0-50 Volts (10 volt increments)



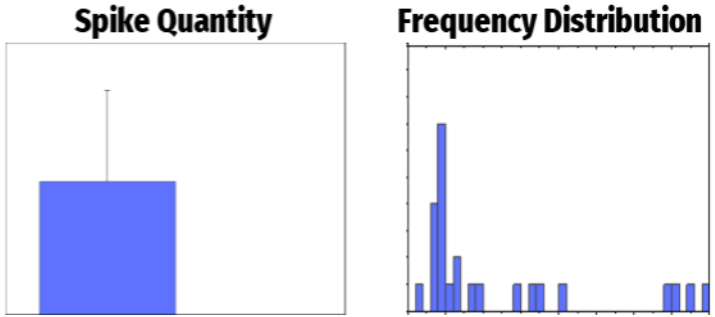




Envelope of Depolarization

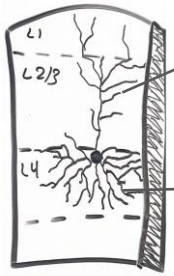


Spike Events

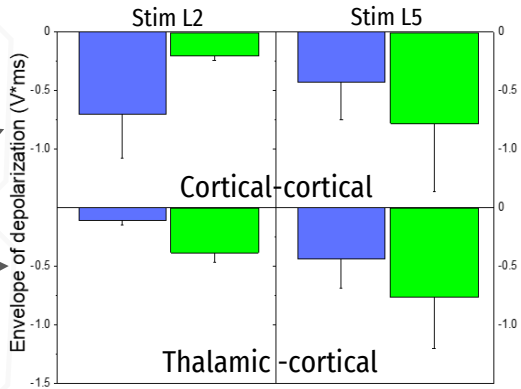


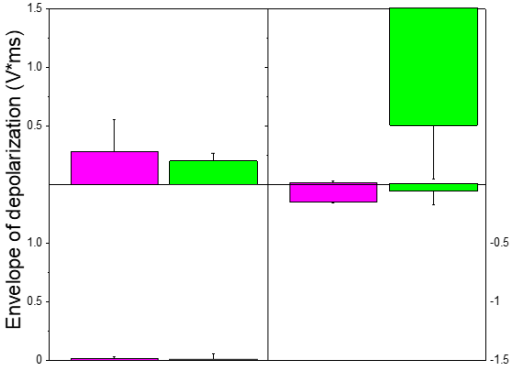
Disrupted cortical transfer in ASD models is partially rescued by dopamine

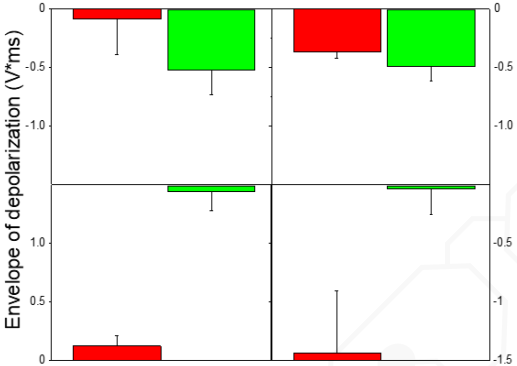
Barrel



Blue~ Wild Type
Magenta~ FMR1-KO
Red~ Double Hit
Green~ Dopamine

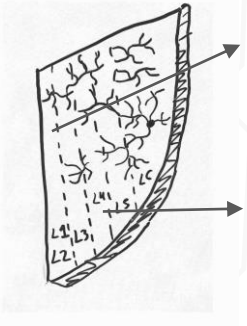


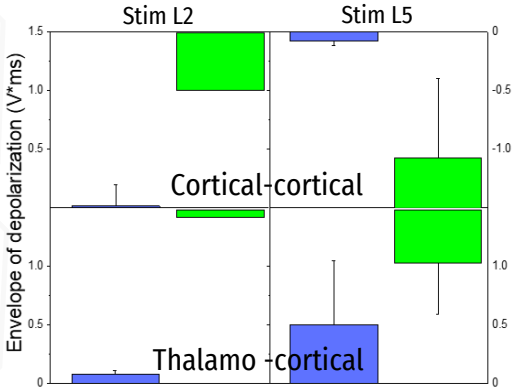


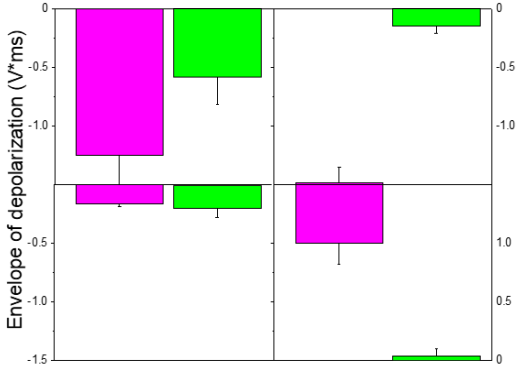


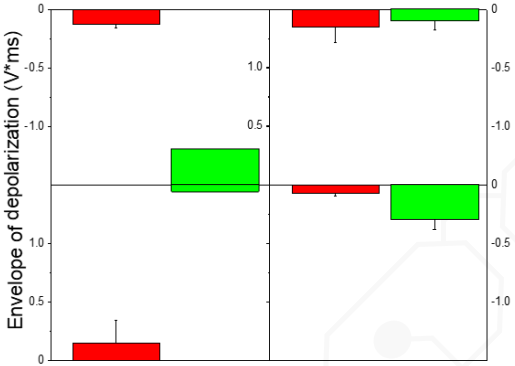
Altered cortical transfer in ASD models is partially reversed by dopamine

Cingulate



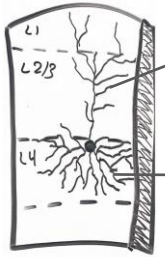




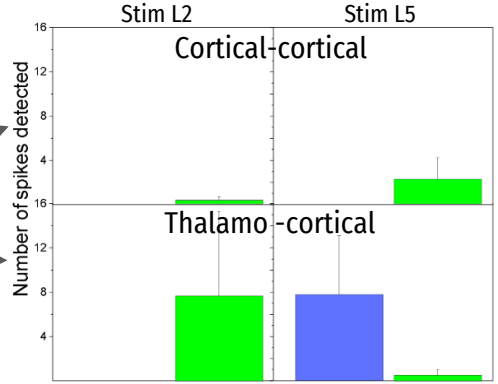


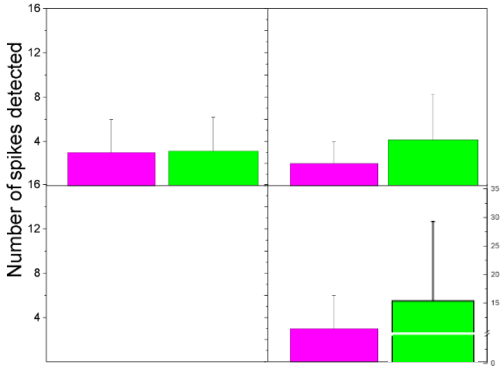
Increased spiking activity but decreased frequency range in ASD models is partially normalized by dopamine

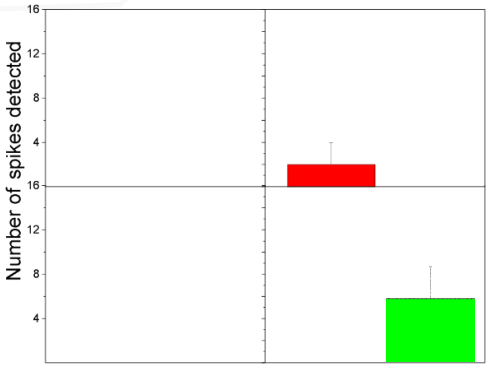
Barrel



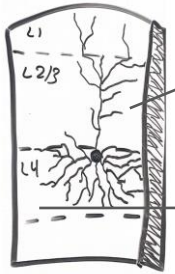
Blue~ Wildtype
Magenta~ FMR1-KO
Red~ Double Hit
Green~ Dopamine

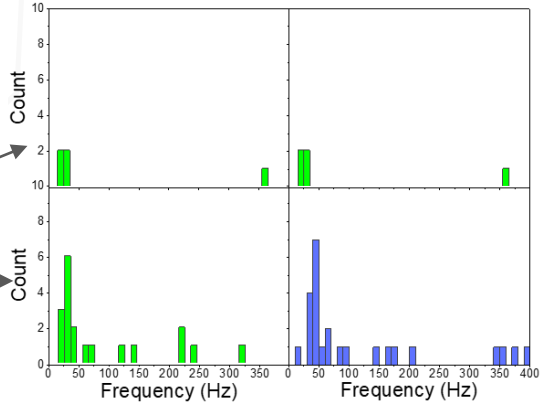


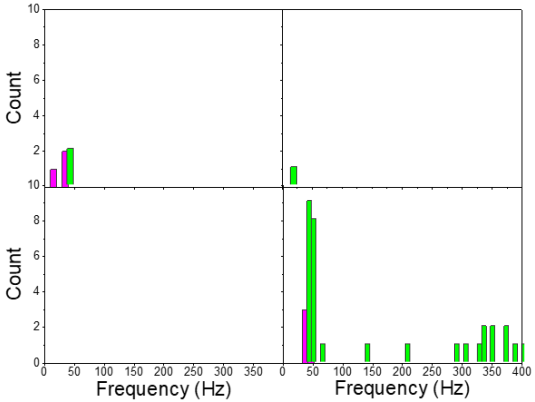


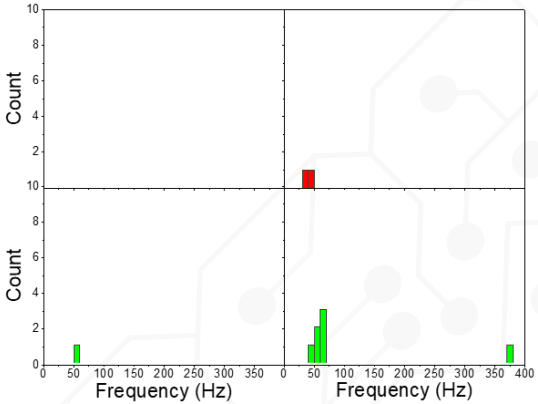


Barrel



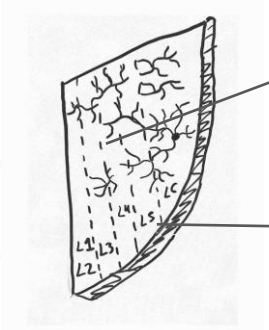


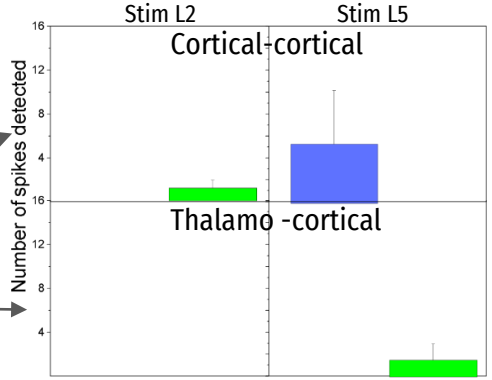


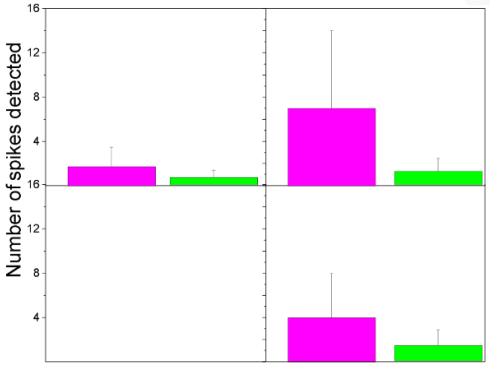


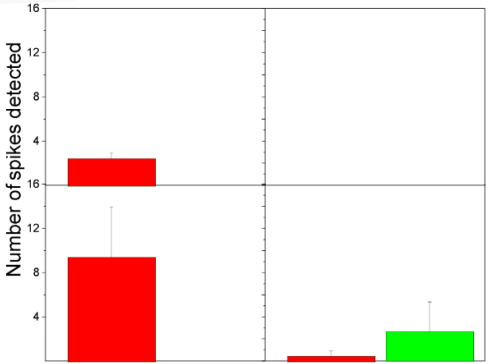
Increased spiking activity with divergent frequency range in ASD models is decreased by dopamine

Cingulate



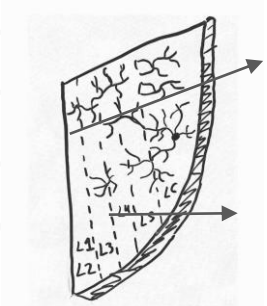


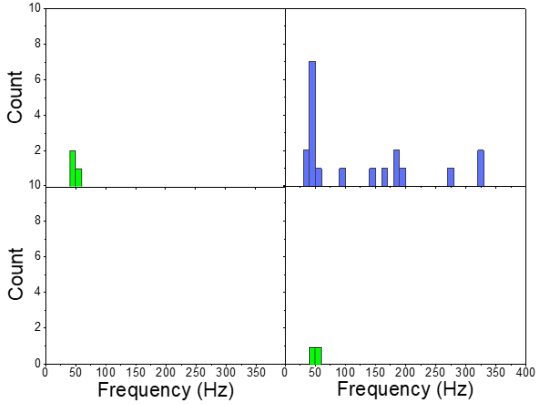


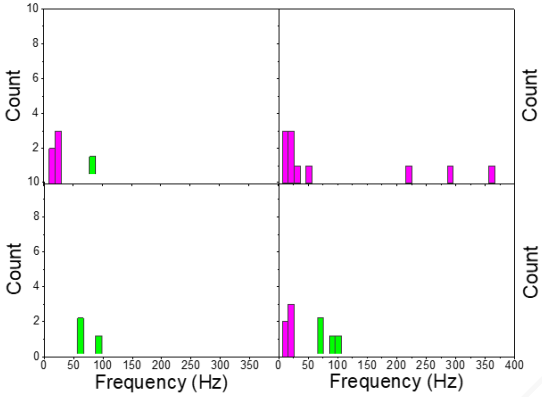


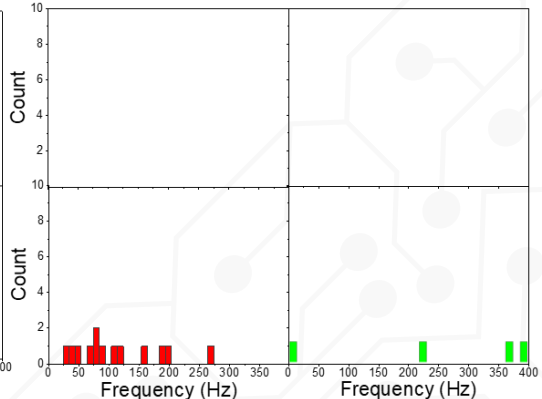
Blue~ Wild Type
Magenta~ FMR1-KO
Red~ Double Hit
Green~ Dopamine

Cingulate









Conclusions

- Barrel Field:
  - Disrupted cortical transfer in ASD models partially rescued by dopamine.
  - Increased spiking activity, but decreased frequency range in ASD models is partially normalized by dopamine.
- Posterior Cingulate:
  - Altered cortical transfer in ASD models is partially reversed by dopamine.
  - Increased spiking activity with divergent frequency range in ASD model is decreased by dopamine.

Limitations

- Sample size
- Technical Difficulties
- Allocation of D1 and D2 receptors
- Length of time during experiments

Interpretation

- The transfers of cortical activity show the differences among the animal types
- The sensory cortex should have higher connectivity than the cingulate cortex

Future Plans

- Experiments with different:
  - Dopamine concentrations
  - Time intervals
- Further investigate the Cingulate cortex

Acknowledgments.

A special thanks to the REACH Program for giving us the opportunity to inquire, discover, and create at such a young age and for giving us a community and freedom to learn.

Thank you to all of the mentors: Lindsay, Jenessa, Isaac, Natasha, Juan Marcos, and Daniel.

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Thank You!