Exploring corticostriatal dynamics associated with auditory driven action impairments in Neurexin1 alpha mutant mice

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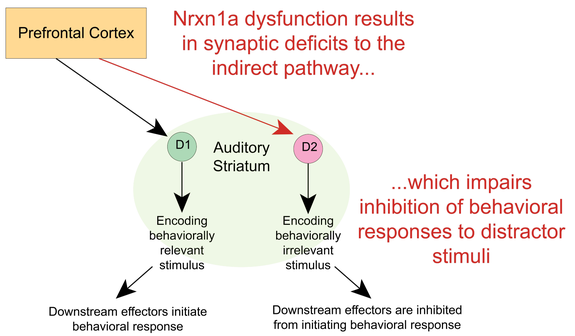
Introduction

While sensory processing impairments are associated with a variety of neurodevelopmental disorders including Autism Spectrum Disorder and Attention-Deficit Hyperactivity Disorder, the underlying neural mechanisms remain unclear. While basal ganglia have known involvement in sensorimotor processes including movement and action selection, recent work has also implicated this structure in mediating sensory-driven motor output. Prefrontal inputs to the tail of striatum are known to regulate multimodal sensory selection through inhibition of distinct sensory thalamic regions. Furthermore, direct stimulation of SPNs in the tail of striatum is sufficient to bias auditory discrimination. Taken together, these data suggest that disruption of corticostriatal inputs to the tail of striatum may contribute to some of the sensorimotor impairments commonly associated with these disorders.

Copy number variation of genes encoding synaptic adhesion molecules, such as Neurexin1α (Nrxn1α), have been shown to confer a significantly increased risk for these disorders, however, the underlying neural mechanisms are currently unknown. Recent findings in acute striatal slices have revealed that loss of Nrxn1α function results in decreased synaptic strength of medial prefrontal cortical inputs to the indirect pathway of the dorsal striatum. It remains to be determined whether corticostriatal deficits to the tail of striatum can drive aberrant sensorimotor function.

Hypothesis

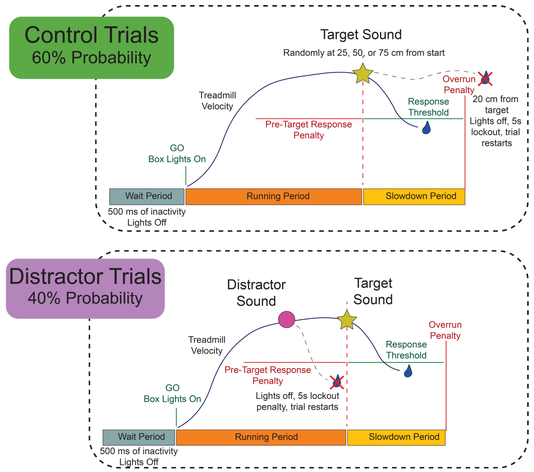


We hypothesize that the deficits in cortical-auditory striatum synapses from the Nrxn1α mutation will result in attentional deficits shown by an increase in distractor responding in response to an auditory distractor in a novel head fixed treadmill task.

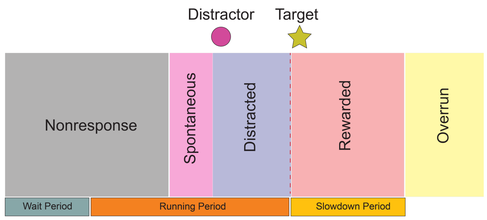
Behavioral Task

We used Nrxn1α$^{+/-}$ (Het) and Nrxn1α$^{+/+}$ (WT) mice (6-10 months). All mice have a metal headplate surgically attached for head fixation in the treadmill task. Mice were water restricted to ~85% of their initial bodyweight per our IACUC approved protocol to increase motivation for water rewards.

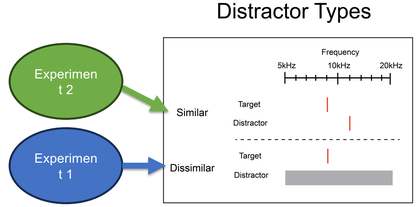
Treadmill Behavior Task Schematics: Control vs. Distractor Trials



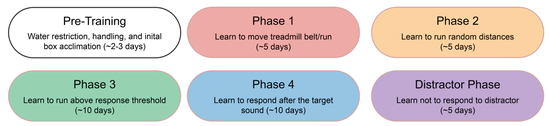
Trial types are classified based on when the animal responds during the run



Frequencies of target and distractor stimuli



Training Progression



Results

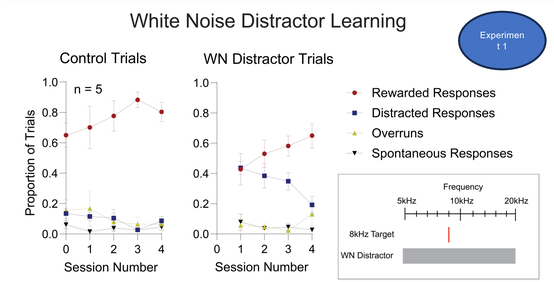


Figure 1. Comparison of 8kHz target trials to white noise distractor trials in wildtype mice showed that mice learned to filter out behaviorally irrelevant distractors (WN) within 4 training sessions as seen through decreasing distracted response proportions.

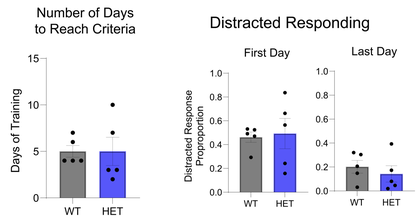


Figure 2. Nrxn1α$^{+/-}$ and Nrxn1α$^{+/+}$ mice both needed an average of five days to reach >2 RW/min and >50% RW/Trials (criteria) for 3 days in a row, however Nrxn1α$^{+/-}$ mice showed greater variability. When the distractor tone (WN) was **first** introduced, Nrxn1α$^{+/-}$ mice showed more variation in proportion of distracted response, although average proportion was similar to WT mice. By the final day, both showed decreased distracted response from day 1.

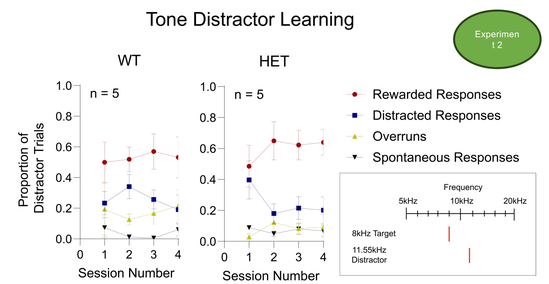


Figure 3. Comparison of 8kHz target trials and 11.55 kHz single tone distractor showed increased distracted response on day 1 in Nrxn1α$^{+/-}$ mice. Rewarded responses were similar across genotypes on day 1. Nrxn1α$^{+/-}$ mice also showed and maintained a greater increase in rewarded responses and decrease in distracted response after day 1.

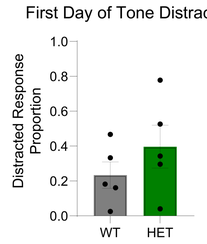


Figure 4. When the 11.55 kHz distractor tone was first introduced, Nrxn1α$^{+/-}$ mice showed an increase in distracted response proportion. This may suggest that Nrxn1α$^{+/-}$ mice have a reduced ability to filter out distracting sensory stimuli that is acoustically similar to the target sound.

Discussion

- To investigate sensory driven behavior and its underlying neural dynamics, we developed a novel treadmill-based operant task for head-fixed mice which assesses their responding to behaviorally relevant target sounds as well as behaviorally irrelevant distractor tones.
- Preliminary behavioral results suggest that mice with Nrxn1α mutation are more susceptible to distraction when distractor tones are closer to the target sound.
- We are currently gathering data in Nrxn1α$^{-/-}$ (knockout) mice to further investigate this phenotype.
- Future experiments aim to describe the striatal population recruitment related to task performance in both Nrxn1α WT and Nrxn1α KO mice using *in vivo* and slice electrophysiological techniques.
- Together, these findings will provide valuable insight into the neural pathology involved in neuropsychiatric and neurodevelopmental disorders while elucidating corticostriatal mechanisms involved in action control regulation.
- Further, we are currently conducting a project investigating the importance of auditory striatum behaviorally relevant sensory filtering using optogenetic inhibition or Muscimol inhibition techniques. We hope this can provide insight on the roles dSPNs and iSPNs play in attention.

Acknowledgements

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