Characterization of auditory physiology in FXS at critical developmental timepoints

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BACKGROUND

- Fragile X syndrome (FXS) is the most common monogenic form of ASD (Autism spectrum disorder). It is associated with heritable cognitive disability, and impaired sound processing and localization.

Various brain regions in FXS show reduced or delayed myelination

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Mutation in Fmr1 gene

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Targets mRNA, affects translation of proteins ← **Fragile X Messenger Ribonucleoprotein (FMRP)**

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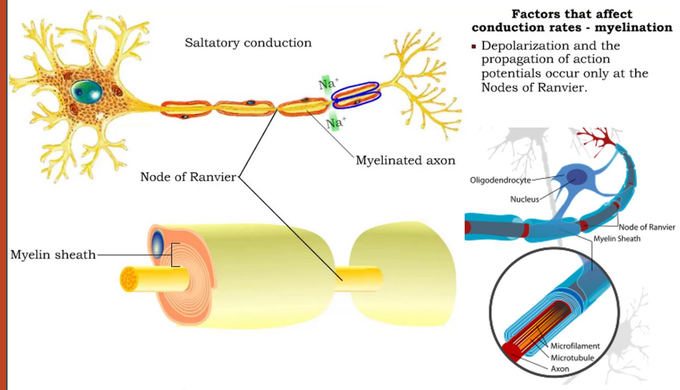
Previous studies FMRP targets myelin proteins



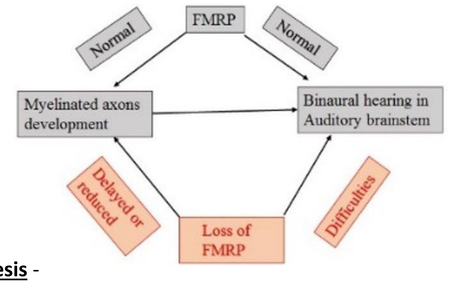
Factors that affect conduction rates - myelination

- Depolarization and the propagation of action potentials occur only at the Nodes of Ranvier.

Research Questions –

1. **When** during development does auditory hypersensitivity phenotype arise in FXS?
2. BROADER - Are these changes **myelin dependent**? If so, how?

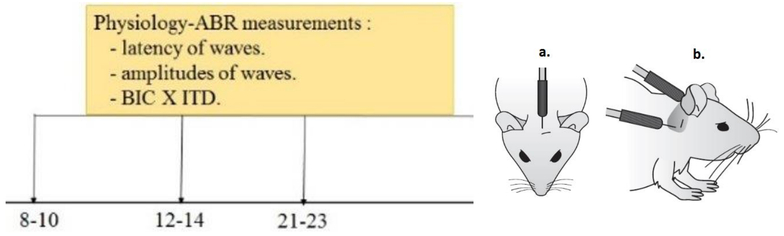
Rationale - FXS is a neurodevelopmental disorder, therefore characterizing when during development auditory dysfunction arises in addition to understanding if these changes are myelin dependent is critical to elucidating the full etiology of FXS.



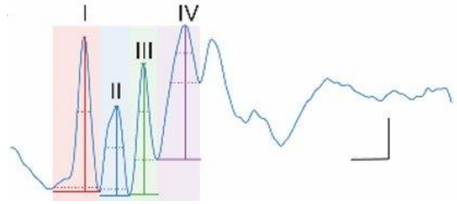
Hypothesis -

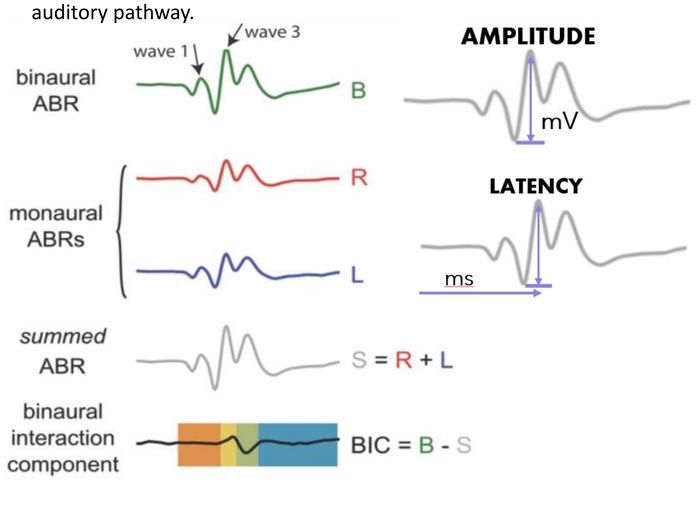
- The **sound localization circuit is altered** in FXS, specifically in the **C57BL6/J mouse strain**.
- Transgenic *Fmr1* mice will have **increased latencies** and **decreased amplitudes** in their Auditory Brainstem
  Responses waves compared to the wildtype most prominently **at P14 developmental time point.**

MATERIALS AND METHODS



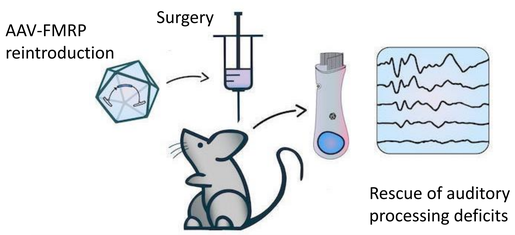
- Auditory brainstem responses (ABR) are a non-invasive representation of the synchronized electrical activity over time of the neurons in the auditory pathway and the eighth cranial nerve.
- In ABR measurements, click stimulation generates a signal consisting of 1-4 waves in rodents. Each wave represents the activity of different regions of the ascending auditory pathway.





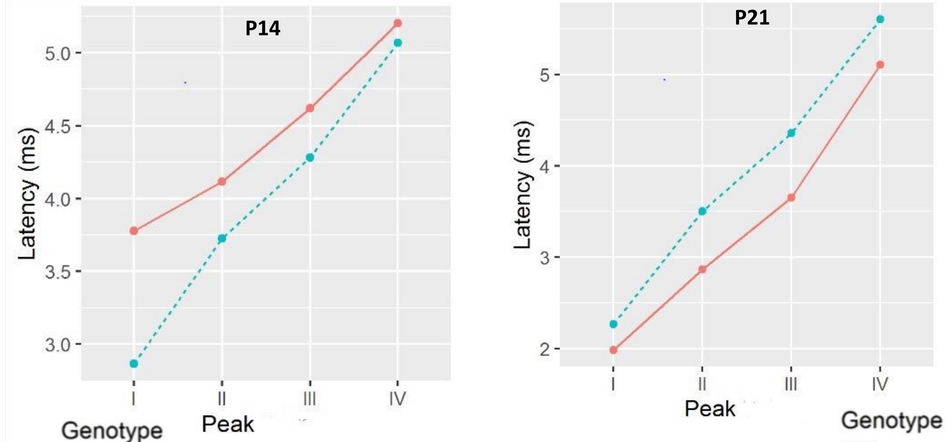
FUTURE DIRECTIONS

- Establish the utility of ABR as a tool to study FXS.
- Quantify myelination development and proliferation at critical timepoints using immunohistochemical experiments
- AAV (adeno associated viral) FMRP reintroduction via surgery on P1 mice
- Collection of ABR measurements with young mice post-surgery at the established developmental time points (P8, P14, and P21).



RESULTS

MONOAURAL ABR



EXPECTATION – increased latencies in FXS

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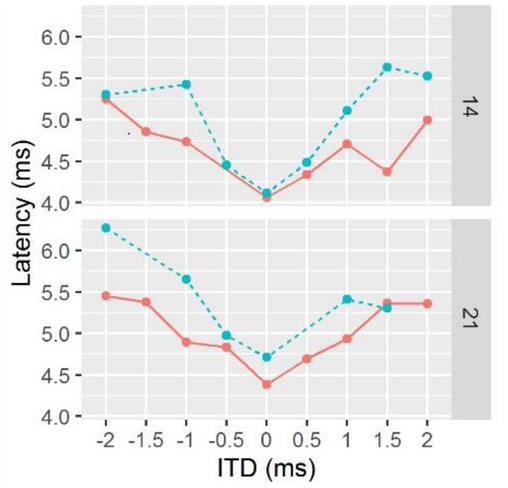

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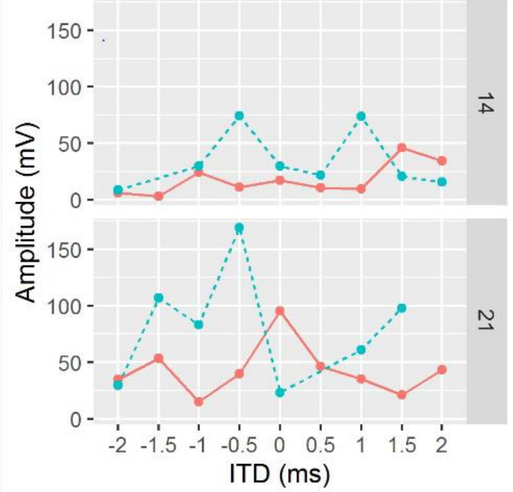
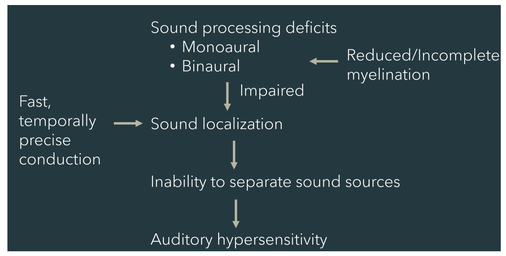


EXPECTATION – decreased amplitude in FXS



CONCLUSIONS

- Binaural sound processing and localization could be related to myelination development in the auditory brainstem.
- P14 seems to be the most critical timepoint where monoaural and binaural processing deficits manifest
- Interesting differences observed between P14 and P21 which could provide more information on how FXS manifests developmentally

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