Sensory Processing Deficits in a Rat Model of Fragile X Syndrome

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Abstract

Autism Spectrum Disorders (ASD) is a set of neurodevelopmental disorders characterized by impaired social skills and sensory deficits. One of the most common symptoms of ASD is sensory hypersensitivity, where everyday sensory stimuli are perceived as abnormally aversive. This hypersensitivity can cause a great amount of stress and decrease the quality of life for individuals with ASD. The neural mechanisms for this sensitivity are unknown. The goal of this project is to examine sensory processing deficits using a rat model of Fragile X Syndrome (FX), the leading inherited form of ASD.

A Sound Avoidance Paradigm (SAP) was utilized to assess sensory sensitivity in *Fmr1* KO and wild-type (WT) rats. This paradigm is based on a rat's innate preference to dark and closed areas and aversion to bright and open areas (Fig 1A). In different light conditions, the *Fmr1* KO group showed stronger preference to the dark than WT animals, indicative of light hypersensitivity. When sounds were introduced in the dark box, rats of both genotypes spent less time in the dark box and moved into the unfavorable light box, reflecting the aversive qualities of the sound. Despite their increased aversion to bright light, *Fmr1* KO rats spent less time in the dark box compared to WT group when noise was introduced. This suggests that FX animals also display auditory hypersensitivity. This paradigm and the use of animal models will provide opportunities to understand sensory processing deficits and evaluate drug targets for FX and ASD.

Materials and Methods

- *Fmr1* Knockout (KO) male rats were purchased from SAGE Labs
- Wild-type (WT) male rats were purchased from Charles Rivers Lab
- Both animal groups were subjected to the Sound Avoidance Paradigm – a behavioral assay that consists of a dark and bright environment, and a runway that animals could freely move between (Fig 1A)
- The animals were habituated and then subjected to three consecutive 600 seconds (10 minutes) trials per day.
- During Baseline testing, light/dark preference was examined under 3 light conditions on alternating days: Low (50 lux), Medium (250 lux), and High (350 lux) (Fig 1B).
- After Baseline, each rat was exposed to 3 noise (2-20 kHz) conditions (silence, 65 dB, and 90 dB SPL) along with 3 light conditions (Fig 1B).

Figure 1A

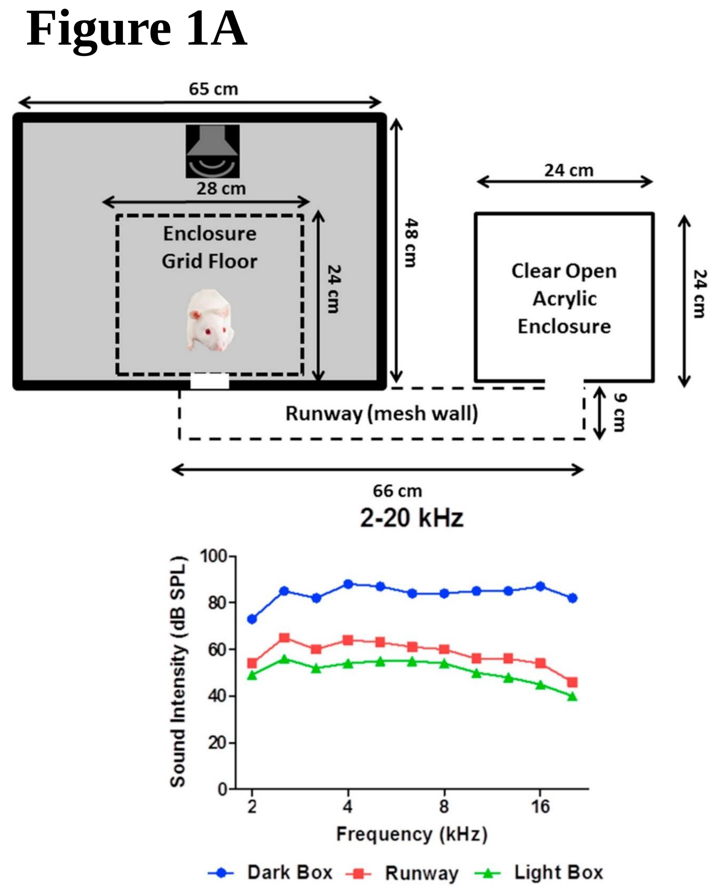
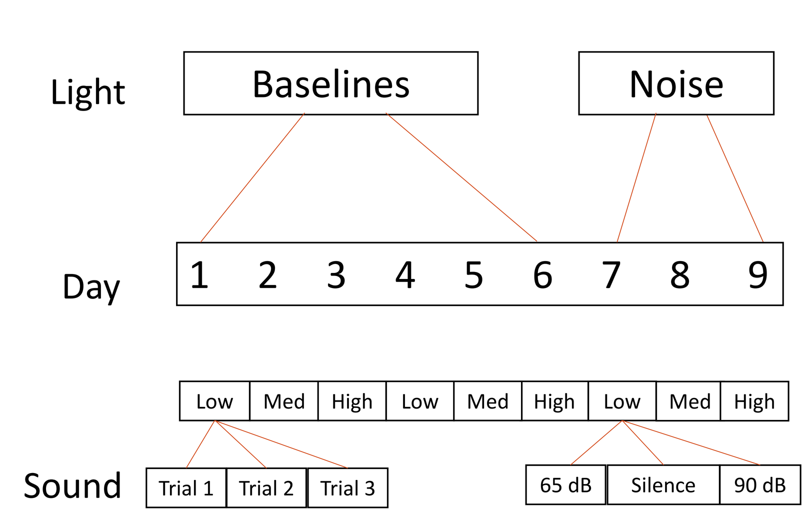
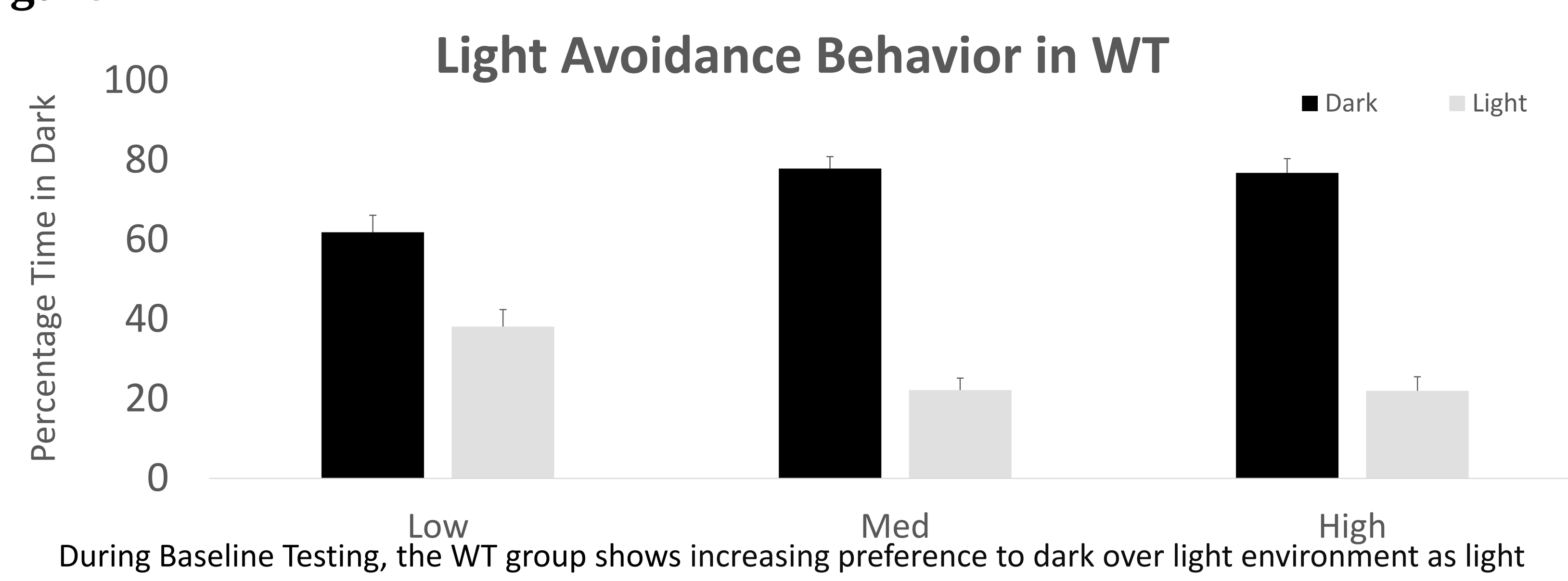


Figure 1B



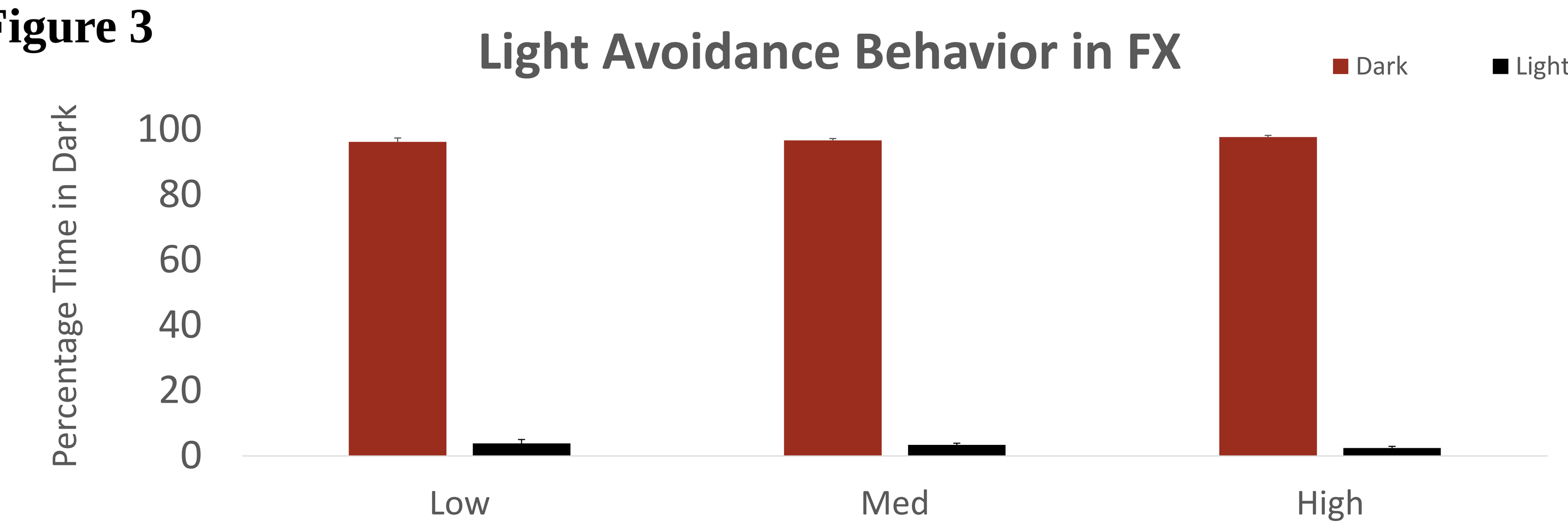
Results

Figure 2



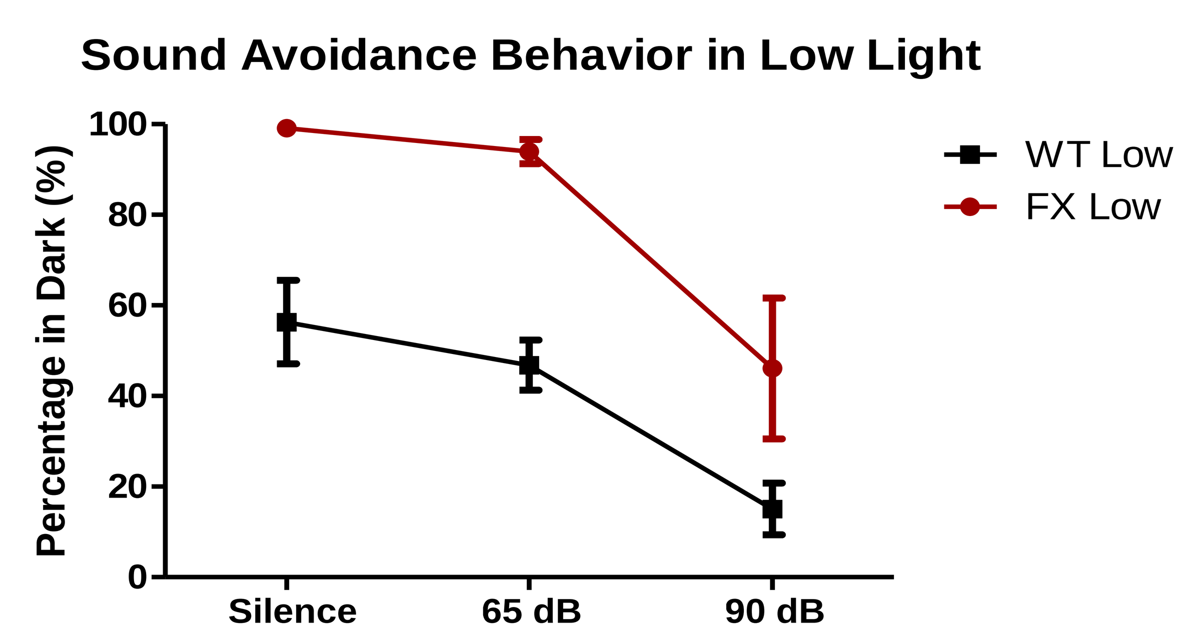
During Baseline Testing, the WT group shows increasing preference to dark over light environment as light intensity increases.

Figure 3



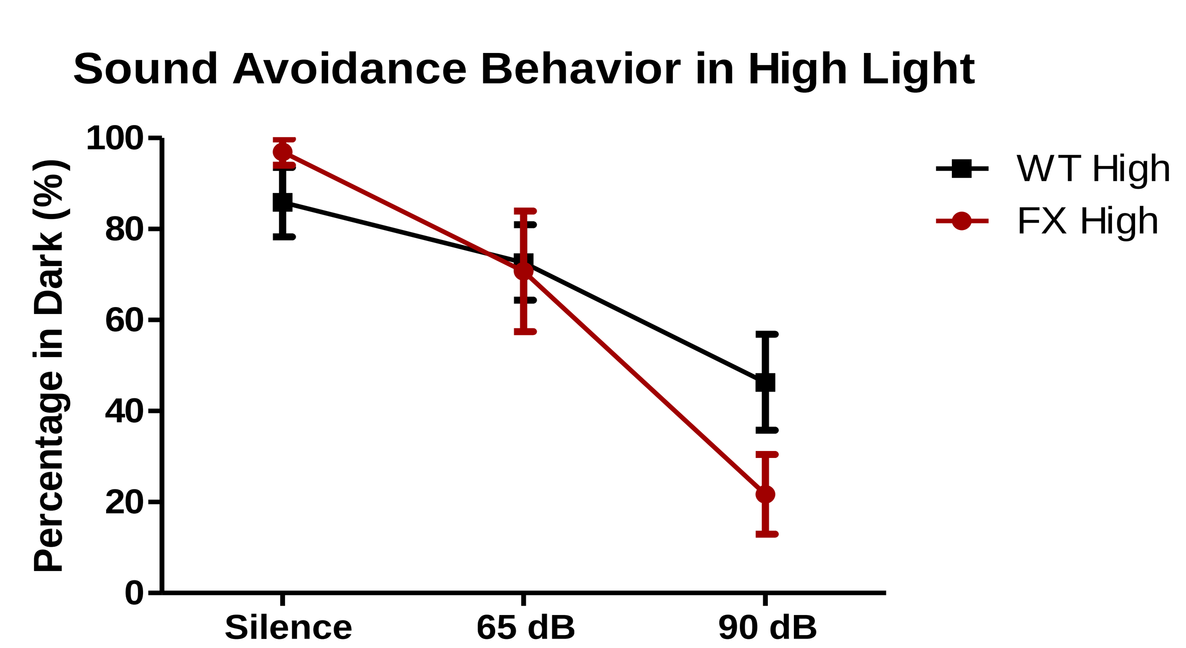
During Baseline Testing, the FX group shows a significantly greater preference to the dark versus the light even under low light conditions, indicating light hypersensitivity. 2-way ANOVA found a significant main effect of Light Intensity ($p < 0.0001$; $F = 2728$) and Genotype ($p < 0.0001$; $F = 2766$).

Figure 4



After Baseline testing, both WT and FX groups were exposed to noise in low level light. FX group shows greater preference to the dark than WT group across sound conditions. A 2-way ANOVA test shows a significant main effect of Sound Intensity (P value = < 0.001; F = 18.24) and Genotype (P value = < 0.001; F = 34.57).

Figure 5



After Baseline testing, both WT and FX groups were exposed to noises in high level light. FX group spent less time in the dark than WT group with 90 dB, but this difference did not reach statistical significance. A 2-way ANOVA test shows that a significant effect of Sound Intensity ($P = <0.0001$; $F = 16.60$), but not Genotype ($P = 0.2208$; $F = 1.59$).

Conclusion

- The Sound-Avoidance Paradigm is a model for assessing sensory processing deficits in FX and ASD
- FX group has a greater light sensitivity than the WT group
- FX group exhibits more avoidance behavior compared to WT group in presence of high light and loud sound, which may indicate auditory hypersensitivity
- FX group displays increased sensitivity to light and possibly sound, which indicates altered sensory processing across multiple modalities.

Future Works

- Use WT and *Fmr1* KO littermates to remove confounding variables that may affect rat's behavior
- Conduct more tests with the SAP to screen drug targets and treatments for sensory disruptions in FX and ASD.
- Design other behavioral experiments to further evaluate possible light and auditory hypersensitivity in FX animals
- Assess non-sensory processing deficits such as anxiety or stress (e.g. elevated plus maze and open field) that may influence avoidance behavior
- Evaluate areas in the brain involved in sensory processing using electrophysiological recordings

References

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