Linking Sensory Processing and Sleep in Neurodevelopmental Disorders

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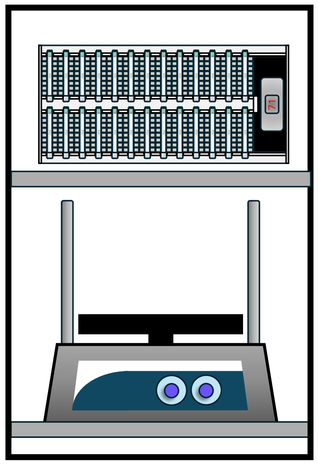
Introduction

- Many neurodevelopmental disorders are associated with altered sensory processing and disrupted sleep.
- To fall asleep and stay asleep, individuals must filter out sensations from the environment, indicating that sensory processing is ongoing throughout quiescence.
- Is altered sensory processing related to disrupted sleep in neurodevelopmental disorders?
- We have used the genetic accessibility of Drosophila to pose this question in models of multiple monogenic neurodevelopmental disorders:
  - Neurofibromatosis Type 1 (NF1)
  - Fragile X Syndrome (FMR)
  - Mutation of the Autism-associated gene Neurexin (NRX).
- Here, we focus on mutations of the autism-associated gene Shank, which encodes a synaptic protein critical for normal synaptic function.

Methods

- Adult female flies
- 25°C
- Activity was measured using Multi-Beam Drosophila Activity Monitors placed 40cm above the vortexer.
- Vibration generated by vortexer on bottom rack.
- 24 hours baseline sleep followed by 24 hours vibration sleep.



Results

Vibration-Induced Sleep (VIS) not observed in mutant flies

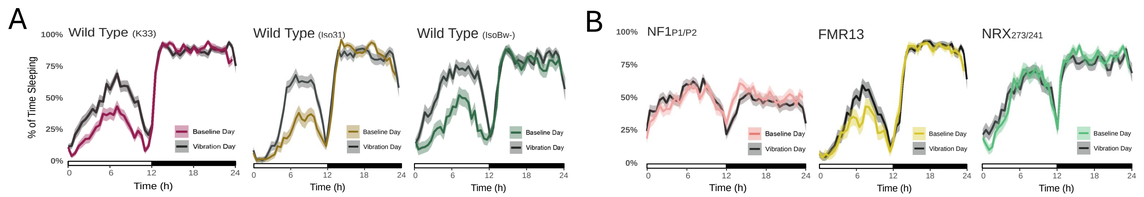


Figure 1.
A) Continuous vibration significantly increases daytime sleep in multiple control fly lines.
B) In contrast, NF1, NRX, and FMR mutant flies show very little or no increase in sleep in response to vibration.

Vibration-Induced Sleep observed in SHANK mutant flies

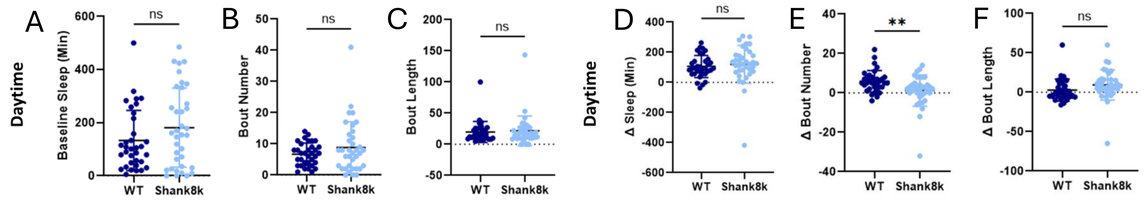
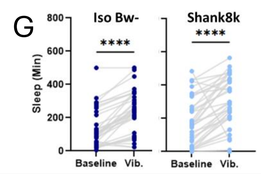
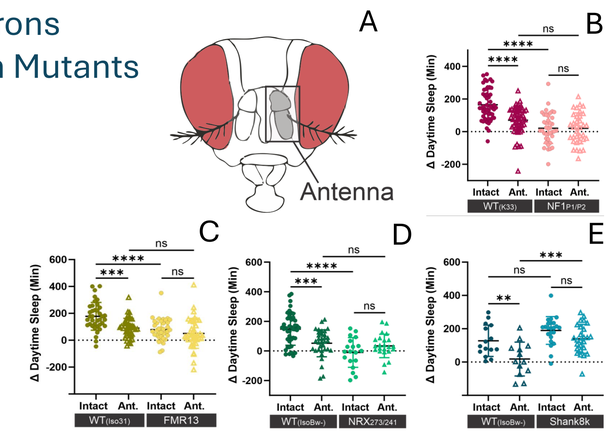


Figure 2.
A-C) Shank mutation has minimal effect on daytime sleep at baseline, with Shank-mutants displaying similar total sleep, bout number, and bout length.
D-E) The vibration-induced change in total sleep, sleep bouts, and bout length, are not significantly different between Shank mutants and controls.
G) Both Shank mutants and genetic controls show a significant increase in daytime sleep when exposed to vibration.



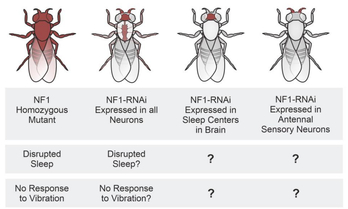
Removing mechanosensory neurons reduces VIS in controls but not in Mutants

Figure 3.
A) Previous work has shown that VIS is mediated in part by mechanosensory neurons in the antenna (Öztürk-Çolak et al., 2020). Here, we surgically removed all three antennal segments from adult female flies. After 3 days of recovery, we performed sleep assays on flies that received the antennectomy (Ant.) and intact controls (Intact).
B-E) Intact wild-type (WT) flies show increased sleep with vibration, as found in earlier experiments. This change is significantly reduced in WT flies that received antennectomies. Mutant flies, in contrast, show no change in VIS following antennectomy. This was independent of whether they show VIS as intacts (E, Shank mutants), or not (B-D, NF1, FMR, and NRX mutants).



Future Directions

- Use RNAi lines to identify which body parts are affected by the mutations and influence VIS.



NF1 Homozygous Mutant	NF1-RNAi Expressed in all Neurons	NF1-RNAi Expressed in Sleep Centers in Brain	NF1-RNAi Expressed in Antennal Sensory Neurons
Disrupted Sleep	Disrupted Sleep?	?	?
No Response to Vibration	No Response to Vibration?	?	?

- Experiment with different intensities of vibrations to determine if mutations cause flies to be hypersensitive or hyposensitive to sensory stimuli.

Conclusions

- Our work on NF1, FMR, and NRX mutant flies suggests that sensory input may influence sleep differently in these neurodevelopmental disorders.
- Results observed with Shank mutant flies contrasts with those observed in NF1, FMR, and NRX mutant flies, suggesting that different neurodevelopmental disorders have varying effects on sensory processing during sleep.
- Our Antennectomy results demonstrate that the VIS observed in wild-type controls relies substantially on mechanosensory neurons in the antenna, as reported previously (Öztürk-Çolak et al., 2020). Reducing mechanosensory input in mutant flies had little effect on their response to vibration. Results suggest that NF1, FMR and NRX mutant flies may be hyposensitive to mechanosensory stimuli, whereas Shank mutants may be hypersensitive.

Acknowledgements

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References:

1. Öztürk-Çolak et al. "Sleep Induction by Mechanosensory Stimulation in *Drosophila*." Cell Reports (108462) 33 (2020)
2. Medina E et al. "Shank3 influences mammalian sleep development." J Neurosci Res. (36056598) 100(12):2174-2186 (2022)