



Auditory Adaptation in ASD Mouse models



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Introduction

One of the core symptoms of Autism Spectrum Disorder (ASD) is altered adaptation or habituation. This impairment has been linked to challenges in forming predictions and integrating prior experiences. Behaviorally, reduced adaptation in ASD has been observed across diverse domains, including tactile processing and audiovisual asynchrony. One domain in which adaptation can be directly investigated at the neural level is the auditory system. The auditory cortex is highly sensitive to stimulus repetition and temporal regularities, making it an ideal structure for studying prediction and adaptation processes. Here, we use in vivo calcium imaging to examine how these processes are altered in the auditory cortex of different ASD mouse models.

Cntnap2 mice showed reduced rate of adaptation to a repeating auditory stimuli

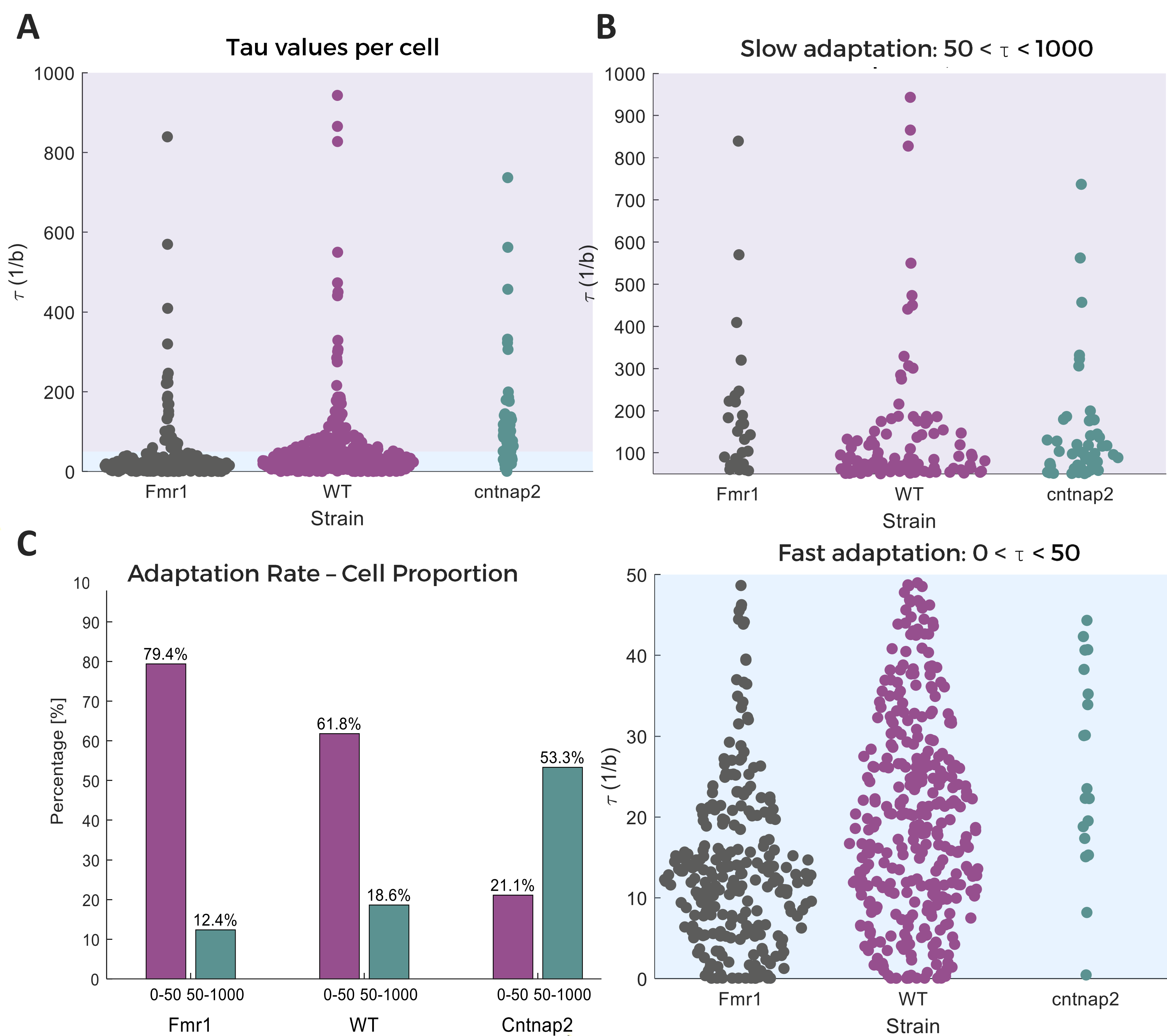


Figure 2 (A) Distribution of adaptation time constants (τ) for individual cells in Fmr1, WT, and Cntnap2 mice. Lower τ values reflect faster adaptation, whereas higher τ values reflect slower adaptation. Cntnap2 mice show a significantly different τ distribution compared with WT and Fmr1. **(B)** Expanded views highlight both the fast-adapting (bottom) and slow-adapting (top) neuronal populations. **(C)** Proportion of adapting cells across strains, revealing an increased fraction of slowly adapting neurons in Cntnap2 mice relative to WT and Fmr1.

Cntnap2 mice showed reduced initial response to repeating stimuli and a lower adaptation magnitude

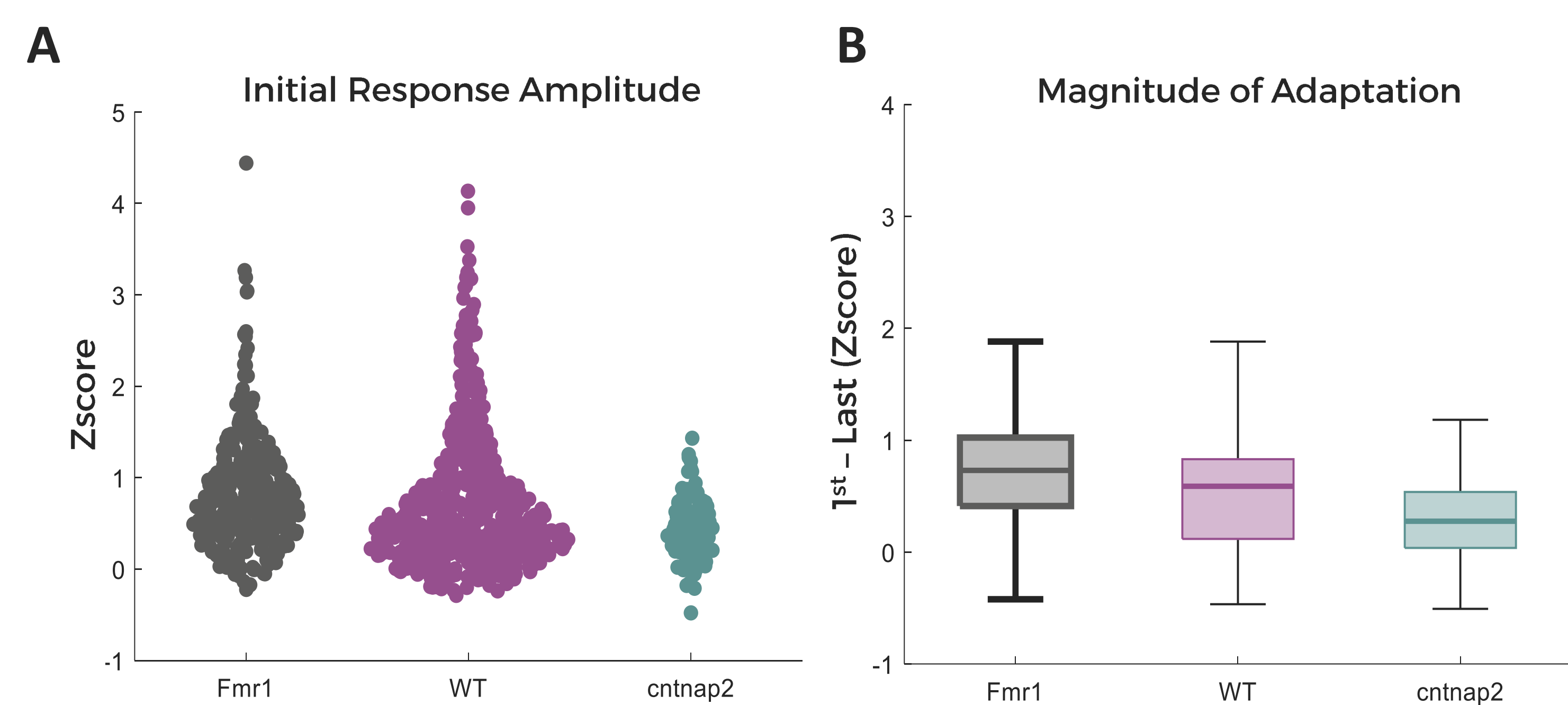


Figure 3 (A) The average response to the first block of repeated sounds was lower in Cntnap2 neurons compared with WT and Fmr1, suggesting an early difference in sound processing. **(B)** Comparison of the first block with the last three blocks showed distinct patterns of change across all three groups, reflecting strain-specific adaptation.

Planned Behavioral Task

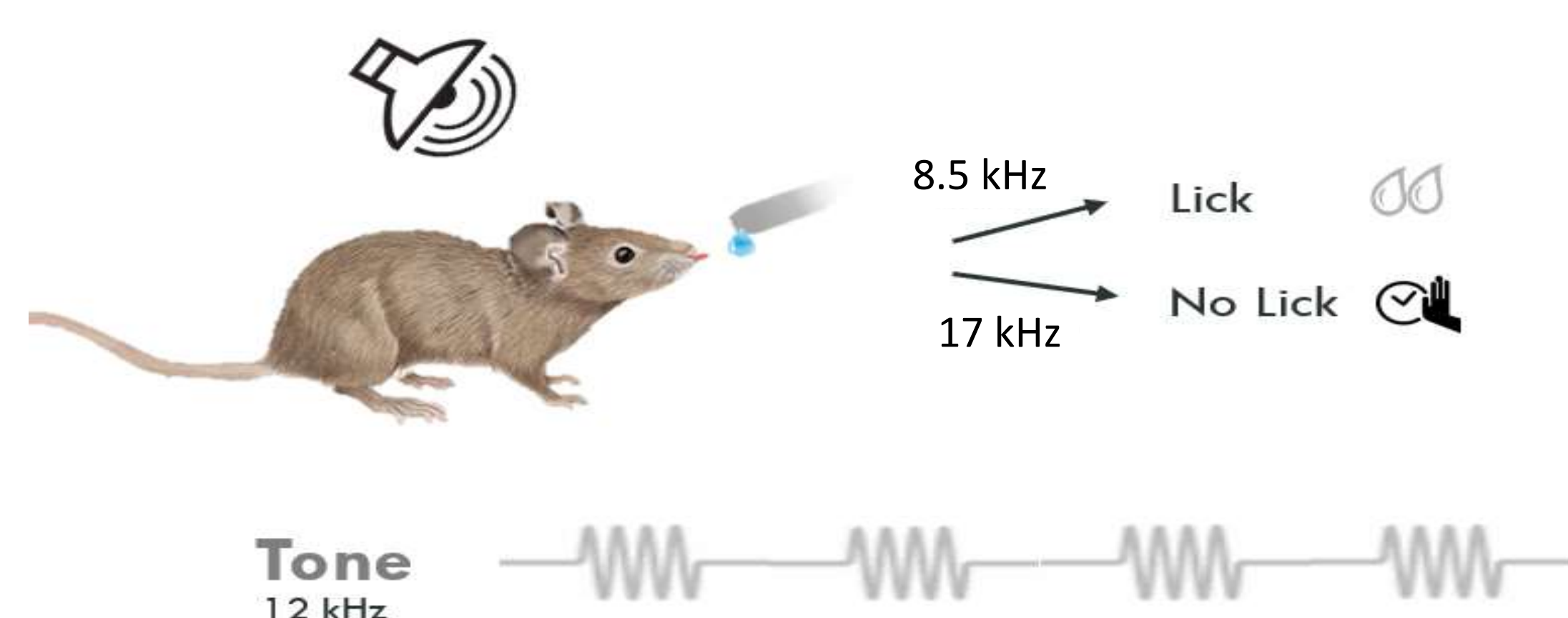


Figure 6 Mice will be trained on a go/no-go task to discriminate between two pure tones. After reaching stable performance (~90% accuracy), a third pure tone will be introduced as a background stimulus. This manipulation is expected to initially reduce performance, and the recovery time to high accuracy will be measured.

Methods

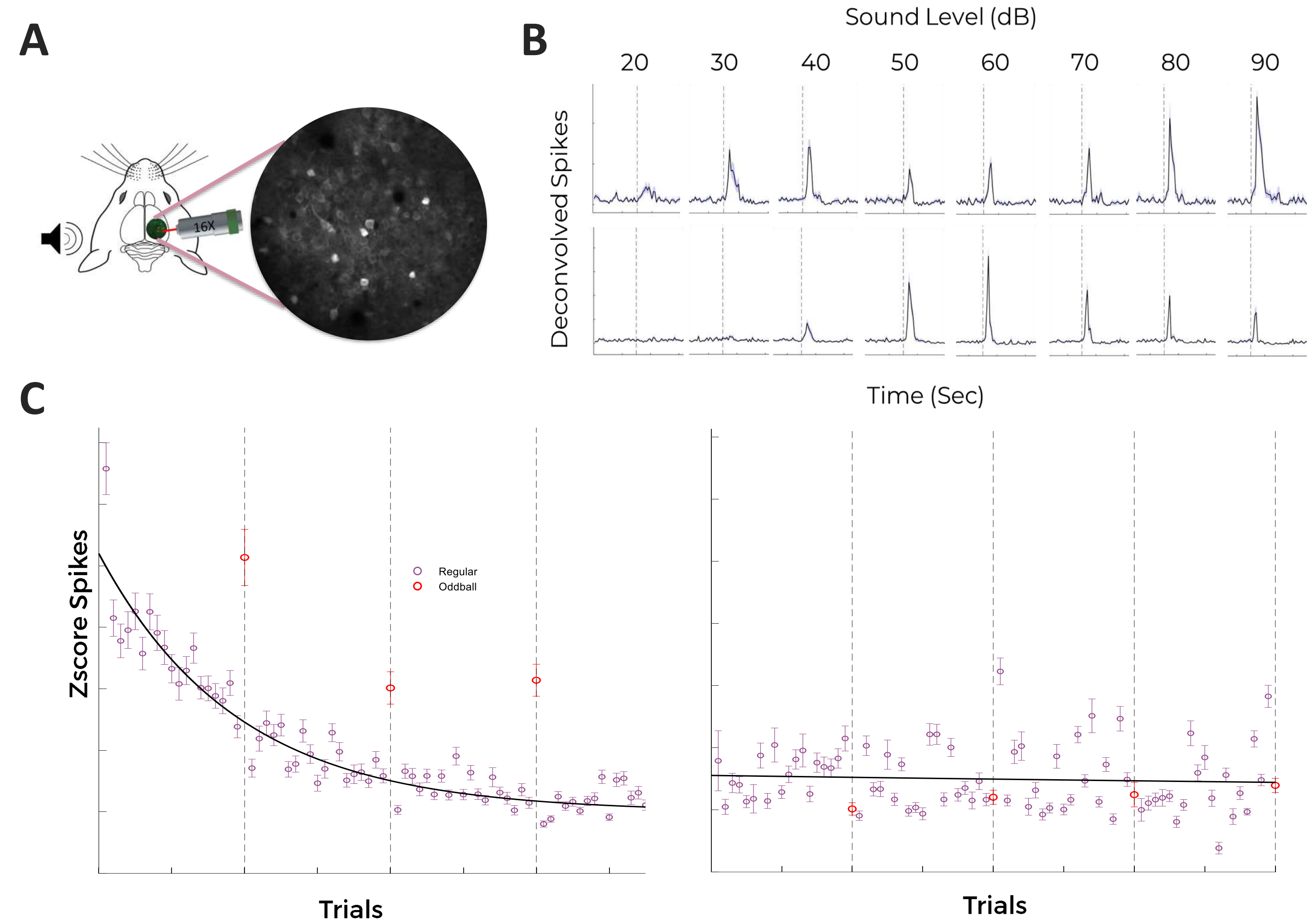


Figure 1 (A) Experimental scheme: ASD-model and WT Mice underwent craniotomy and viral injection to express GCaMP in the auditory cortex. Two weeks later, excitatory and inhibitory neuronal activity was recorded using two-photon imaging. **(B)** Schematic illustration of two-photon recordings from layer 2/3 neurons in A1 of awake, head-fixed mice expressing GCaMP6s. **(C)** Example of sound-evoked activity during a repeated pure-tone sequence. Tau values were derived from exponential fits to quantify response decay. Each tone was repeated 19 times before a deviant tone was presented. Representative traces: WT (left), ASD (right).

Cntnap2 mice showed higher variance of sound-evoked activity

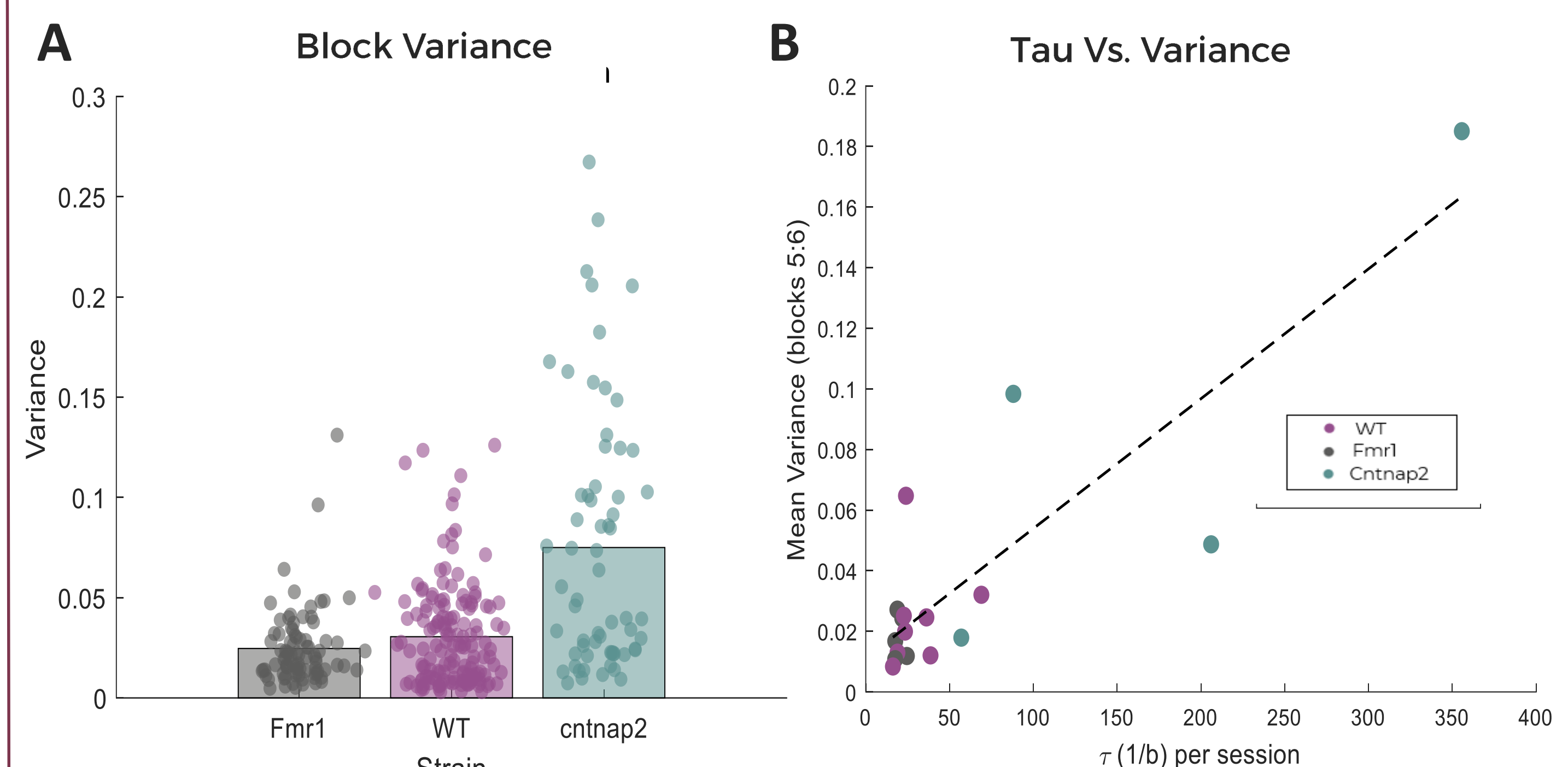


Figure 4 (A) Variance of sound-evoked responses was calculated across blocks for each session. Cntnap2 mice exhibited significantly higher variance compared with WT and Fmr1. **(B)** Correlation between adaptation rate (τ) and response variance, showing a strong positive relationship ($r = 0.86$).

Cntnap2 mice showed reduced response to an RLF stimuli while Fmr1 showed enhanced response

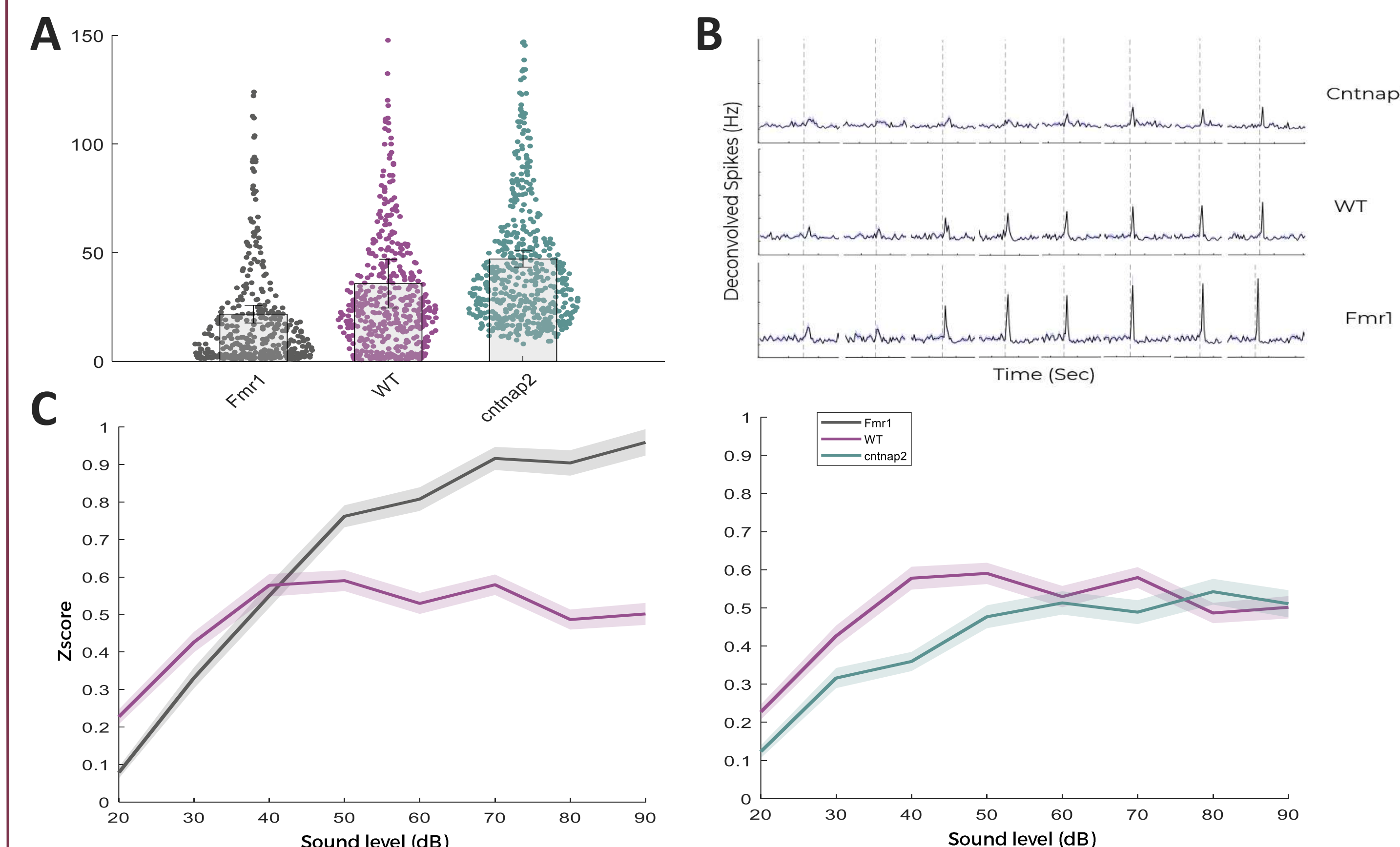


Figure 5 (A) Spontaneous activity of sound-responsive neurons, showing elevated activity in Cntnap2 mice and reduced activity in Fmr1 mice compared with WT. **(B)** Representative single-cell activity traces from the three strains. **(C)** Sound-evoked responses to a rate-level function (RLF) stimulus with white noise ranging from 20-90 dB. Fmr1 mice displayed enhanced responses, whereas Cntnap2 mice showed reduced responses relative to WT.

conclusions

- Cntnap2 mice show reduced neural adaptation to repeated sounds in A1 compared with WT and Fmr1.
- Higher trial-to-trial response variabilities in Cntnap2 neurons correlates with weaker adaptation.
- Fmr1 mice show enhanced initial sound responses relative to WT, while Cntnap2 responses are reduced, for both SSA and RLF.