Development and application of a machine learning-based digital biomarker to detect lateral position associated with spontaneous seizures in preclinical epilepsy models

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INTRODUCTION

This work describes the development of a computer vision-based algorithm to detect hallmarks of seizures in individual mice within socially-housed environments. This algorithm identifies **loss of upright posture (LoUP)**, a key indicator of tonic-clonic seizures. LoUP occurs when mice are in a lateral or supine position, signaling the inability to maintain an upright body posture, which correlates with loss of consciousness during seizures.

Two studies were conducted to develop and validate this algorithm:

1. **PTZ assay**: Mice were injected with pentylenetetrazol (PTZ) to induce seizures, generating a dataset for algorithm development.
2. **SCN1A natural history study**: The algorithm was applied and refined in a study that characterized two mouse models of Dravet syndrome.

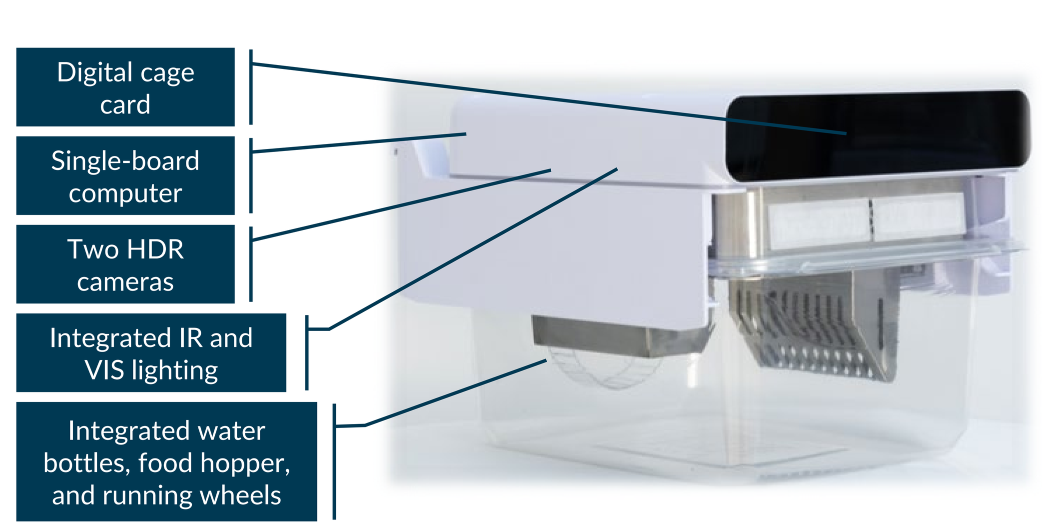
The use of continuous monitoring from the home cage offers several benefits:

- Noninvasive, real-time detection of spontaneous seizures.
- Simultaneous collection of multiple phenotypic metrics, enabling the analysis of the relationship between LoUP and other behaviors.
- Improved reproducibility in seizure detection across studies.

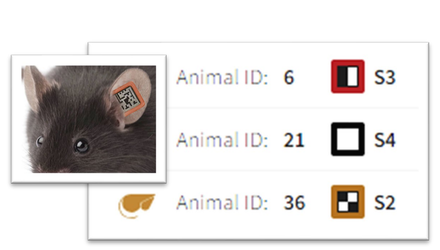
This system enhances the ability to assess seizure dynamics and other key metrics in preclinical epilepsy research.

ENABLING TECHNOLOGY

The digital measures were developed by collaborators within the Digital In Vivo Alliance (DIVA), using a novel home cage computer vision system developed by the Jackson Laboratory (JAX) that continuously captures rodent behavior through a cloud-based platform, enabling longitudinal studies spanning weeks or months.



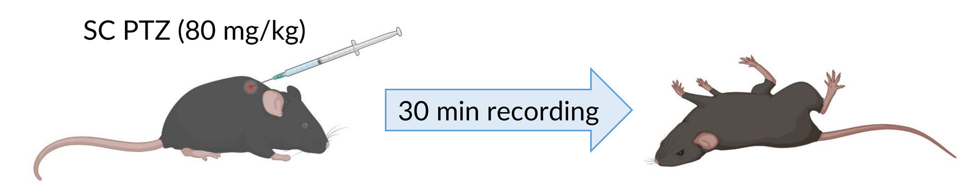
Custom ear tags enable the analysis of individual animal behavior.



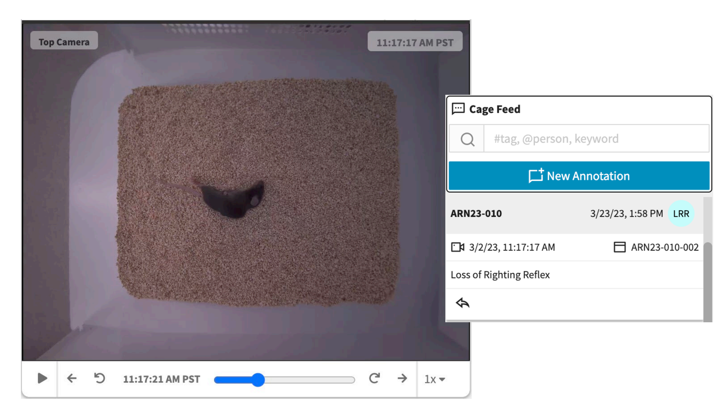
PTZ ASSAY

Methods

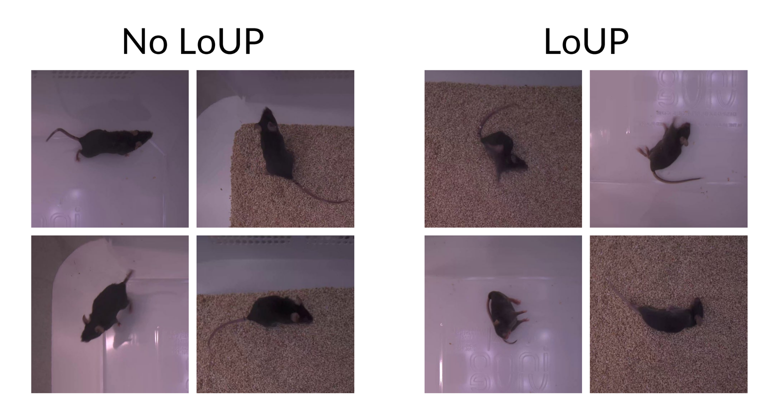
1. Subcutaneous injection with pentylenetetrazol (PTZ) to induce seizures



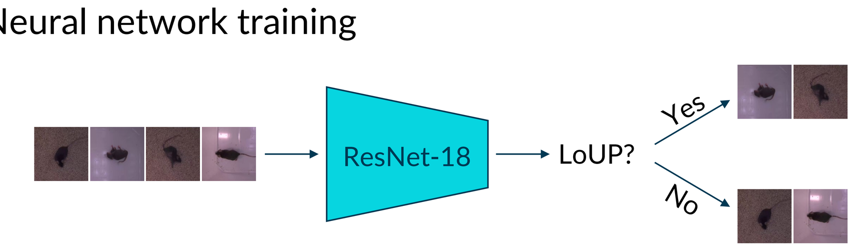
2. Manual annotation of LoUP from video



3. Manual selection of labeled frames



4. Neural network training



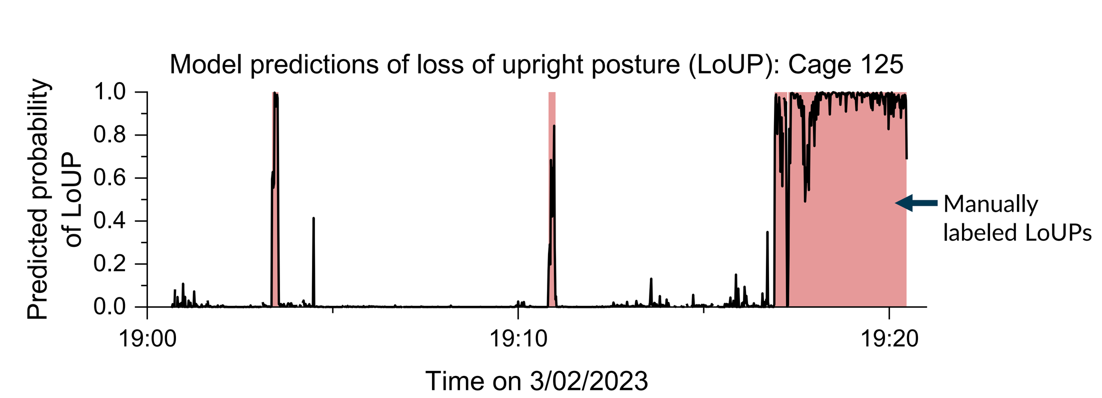
Results

5-fold cross-validation results

	Predicted non-LoUP	Predicted LoUP
True non-LoUP	188	9
True LoUP	7	172

96% LoUP samples are identified by the model
5% of LoUP detections are false positives

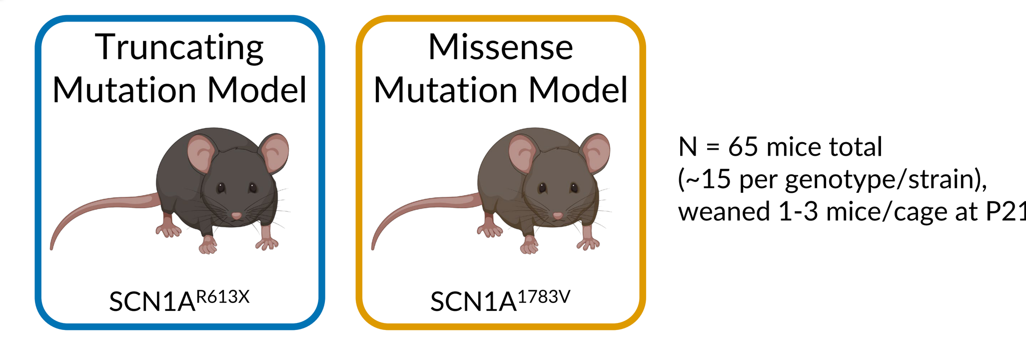
Model predictions on stretches of video align with manually labeled LoUPs.



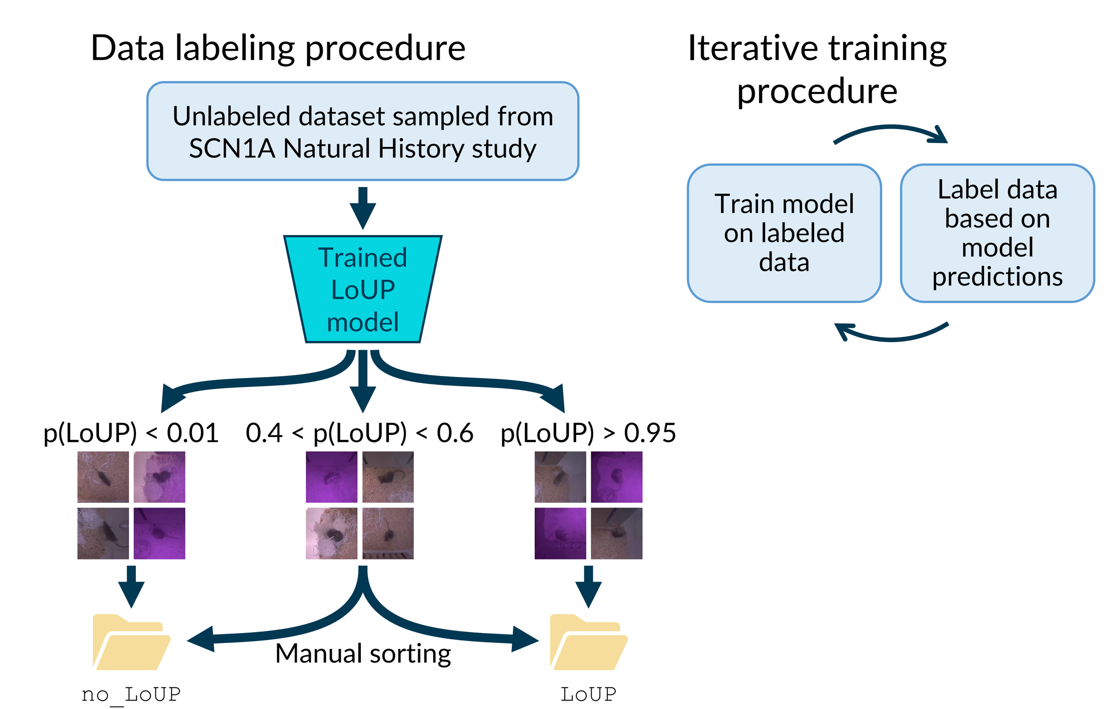
SCN1A NATURAL HISTORY STUDY

Methods

1. Natural history recording from P21 to P50



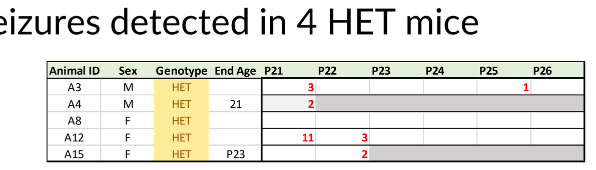
2. Semi-automatic data labeling, iterative model training



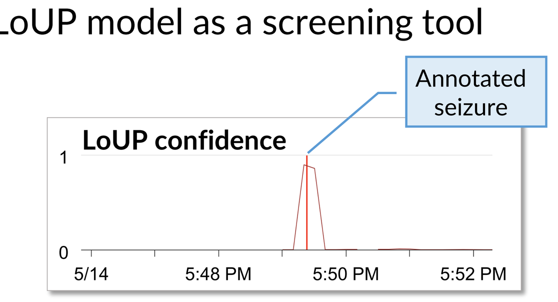
3. Documentation of spontaneous seizures in video dataset

↳ Manual video review

- 288 hours of video reviewed at 8x speed (36 human hours)
- 28 seizures detected in 4 HET mice



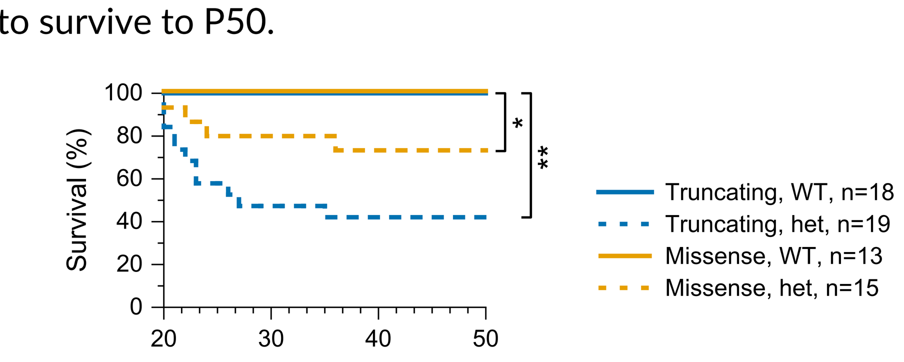
↳ Using LoUP model as a screening tool



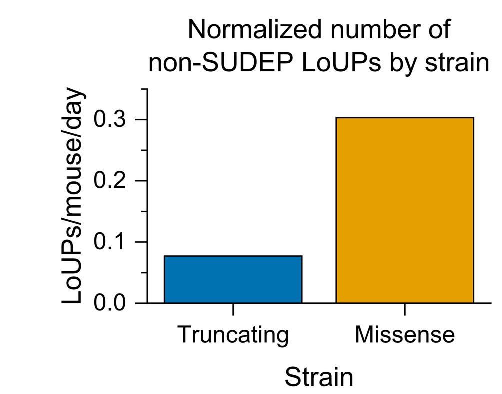
- 150+ spontaneous tonic-clonic seizures detected
- 89% of manually detected seizures are also detected by model

Results

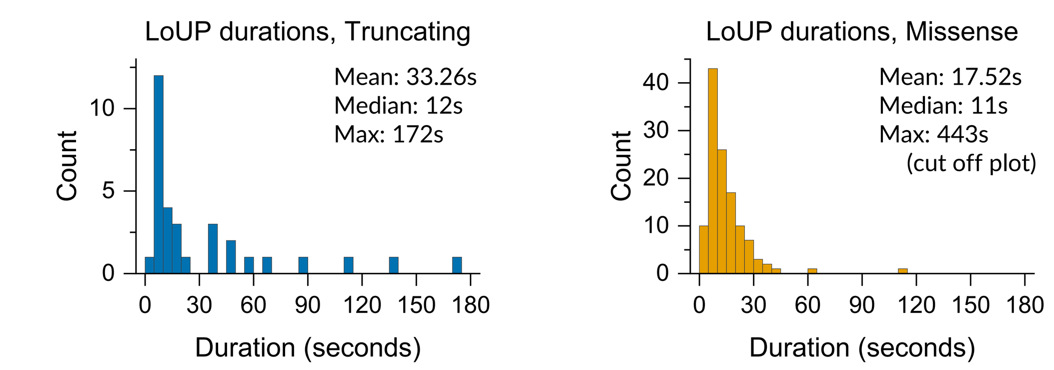
Heterozygous mice of both strains were significantly less likely to survive to P50.



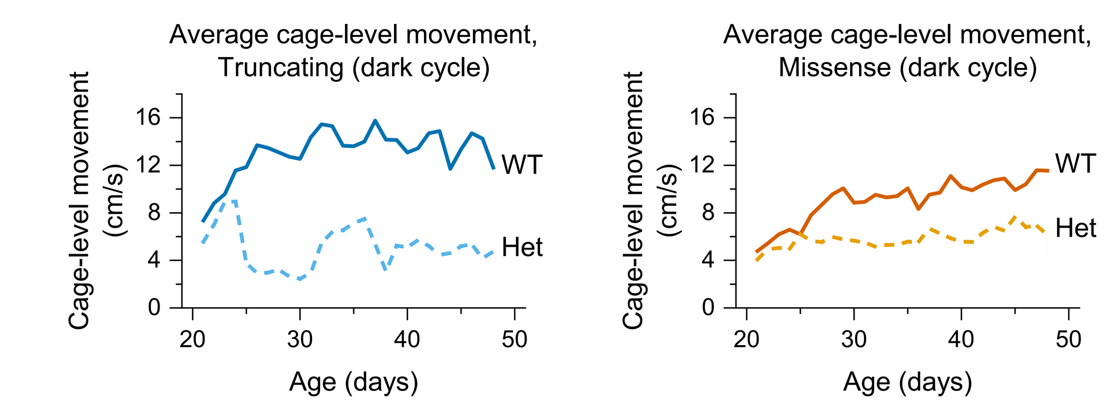
Missense mice had a greater frequency of LoUPs that were not associated with SUDEP compared to truncating mice.



Both strains had similar median LoUP duration, but truncating mice had a greater mean duration.



Heterozygous mice of both strains were less active than wildtypes during the dark cycle.



CONCLUSIONS AND NEXT STEPS

- Noninvasive continuous monitoring of rodent behavior during longitudinal studies using a computer-vision based platform enables the evaluation of spontaneous seizures in mouse models of Dravet syndrome.
- A neural network-based algorithm can detect losses of upright posture (LoUPs) associated with spontaneous seizures.
- Screening data with the LoUP detector greatly reduces the amount of time spent on manual data evaluation.
- Continuous monitoring revealed patterns that are not visible without 24/7 data collection, such as greater LoUP frequency in missense mice and reduced nighttime locomotion in heterozygous mice compared to wildtypes.
- Future algorithms may combine LoUP with other seizure-related measures, such as wild running, to produce a more robust seizure detector.

DIGITAL IN VIVO ALLIANCE (DIVA)

The Digital In Vivo Alliance (DIVA) is a collaboration of pharmaceutical industry and academic scientists with a shared interested in the discovery, development, validation, and application of AI-enabled in vivo digital measures of animal behavior and physiology in their home cage environment. For more information, visit DIVA.bio.