The Jackson Laboratory

DIGITAL MEASURES IN AN ANIMAL MODEL OF NEUROMOTOR DISEASE

At a Glance

- The JAX Envision™ platform enhances sensitivity in measuring disease progression, facilitates earlier identification of end-stage disease phenotypes without disturbing animals or relying on manual scoring, and provides transformative insights for rare and neuromuscular disease research.
- Disruptions in inferred sleep in SOD1-G93A mice were detected before traditional clinical measures of disease onset and align with observations in ALS patients.
- Envision's average movement measure enabled identification of a movement breakpoint correlating with end-stage disease offering a more objective and sensitive measure of disease progression in the SOD1-G93A model.

Background

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord. Many of the current preclinical in vivo motor and movement assays, as well as endpoints, are time and resource consuming, laborious, and often subjective (e.g., rotarod, observational neuroscore, open field, voluntary running wheel, etc.). The Envision platform utilizes computer vision to continuously monitor mice in their home cage environment, across all phases of the light cycle. This study was conducted to understand the application of digital measures in a mouse model of neurodegeneration by collecting continuous, non-invasive, longitudinal monitoring of behavior and physiology from animals throughout their circadian cycle.

Methods

B6.Cg-Tg(SOD1*G93A)1Gur/J (Stock No. 004435) mice express a human transgene that carries the G93A mutant form of human SOD1 on a C57BL/6J congenic background. Thirty hemizygous and 30 wildtype (non-carriers, or NCAR) littermate males received at 4 weeks of age, housed 3 mice/cage, were monitored from acclimation to 28 weeks of age. Traditional measures, including rotarod performance, body weight, neuroscore, CMAP/RNS, and serum NfL (an ALS biomarker), were measured at 6, 12, and 16 weeks. The Envision platform was employed to generate computer vision derived continuous assessments of average movement (cm/s) using machine learning that processed raw video data in real time. Inferred sleep was computed using the criteria of Pack et al. (2007), which demonstrates that runs of inactivity of $\geq$ 40 seconds correlate with sleep. Activity breakpoints were computed with segmented line regression on circadian-detrended activity.

Results

Hemizygous SOD1-G93A mice showed a median survival of 23 weeks, with body weight decreasing from 15 weeks. Despite no significant differences in neuroscore or rotarod performance, the mice exhibited progressive muscle denervation and motor neuron degeneration, as indicated by declining compound muscle action potential (CMAP) and impaired neuromuscular transmission following repetitive nerve stimulation (RNS) at 12 and 16 weeks. Elevated serum neurofilament light chain (NfL) levels at these time points further confirmed neurodegeneration in SOD1-G93A mice (data not shown). Continuous monitoring detected disrupted patterns of inferred sleep in SOD1-G93A mice earlier (at 6 weeks) than traditional clinical disease onset measures (12 weeks) **(Figure 1)**. A distinctive breakpoint, marked by a sudden reduction in movement compared to control mice, correlated with the transition to an end-stage disease phenotype **(Figure 2)**. Tracking a digital measure of average movement provided a less subjective alternative to neuroscore assessments, which would enable a reduction of the number of animals required for adequately powered studies.

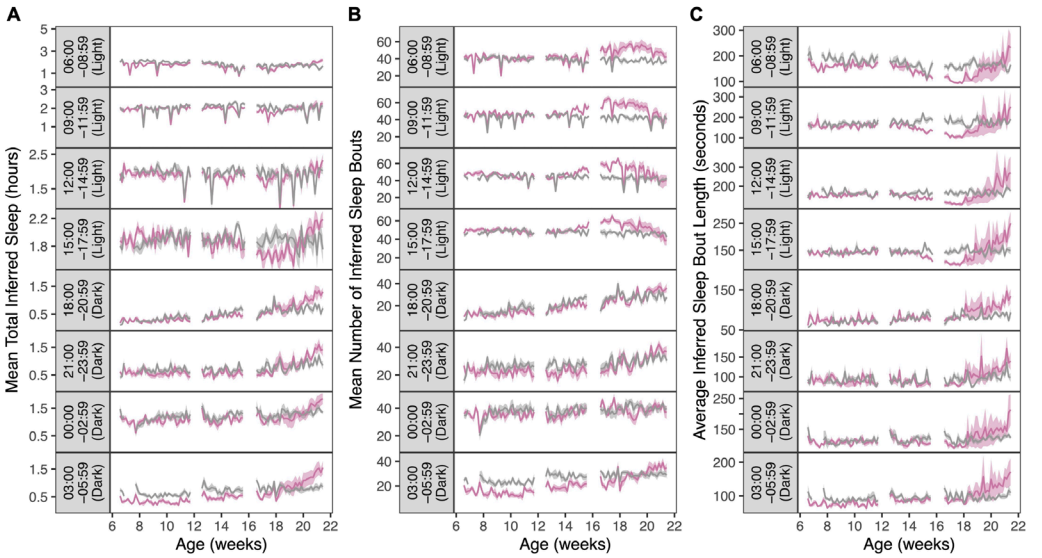

Figure 1
SOD1-G93A (Pink) inferred sleep disturbance relative to NCAR (Gray) controls presents at 6 weeks toward end of dark period (A). SOD1-G93A mice progress to more sleep bouts in the dark period (B) that are shorter (C) during the light period after 14 weeks of age, reflecting fragmented sleep. Lines = mean, ribbons = ±SEM.

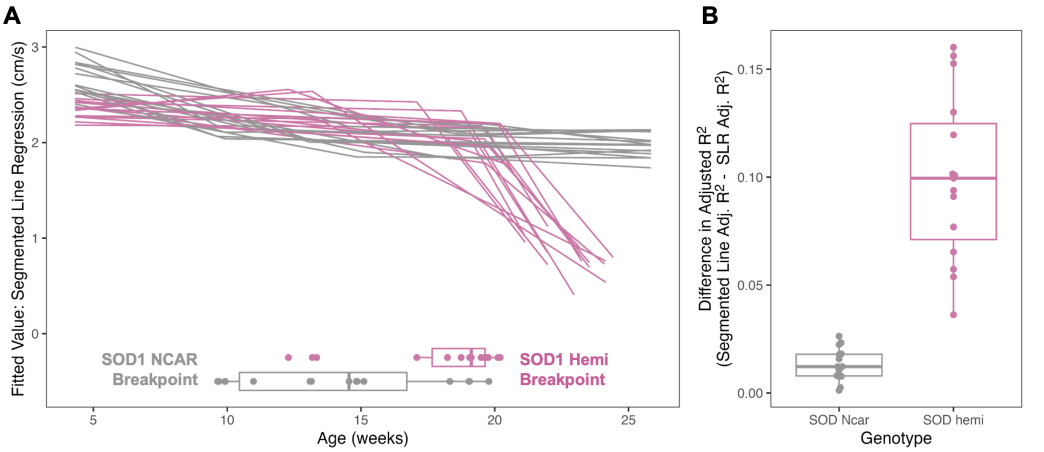

Figure 2
Average movement in SOD1-G93A mice drops near study endpoint and segmented line regressions have a median breakpoint of 19.1 weeks (A). SOD1 hemi segmented line model fits outperform straight line model fits relative to NCAR mice, evidence for change in slope (SOD1-G93A median adjusted R^2 increase: 0.0995; B).

In summary, leveraging Envision's average movement measure to computationally interrogate inferred sleep and identification of a movement breakpoint correlating with end-stage disease offers a more objective and sensitive measure than standard measures of disease progression in the SOD1-G93A model. These findings highlight the utility of non-invasive home cage monitoring for reducing variability and improving study efficiency by requiring fewer animals to achieve statistically significant results.

References

Pack AI, Galante RJ, Maislin G, Cater J, Metaxas D, Lu S, Zhang L, Von Smith R, Kay T, Lian J, Svenson K, Peters LL. Novel method for high-throughput phenotyping of sleep in mice. Physiol Genomics. 2007 Jan 17;28(2):232-8. doi: 10.1152/physiolgenomics.00139.2006. Epub 2006 Sep 19. PMID: 16985007.

This data was collaboratively generated and analyzed through the Digital In Vivo Alliance (DIVA). For more information about DIVA, visit **https://DIVA.bio**.

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