Machine Learning-Informed Digital Measures Improve the Sensitivity and Translational Relevance of In Vivo Neurodegenerative Disease Models

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BACKGROUND

- **Digital measures offer transformative insights** for neuromuscular disease research.
- Traditional endpoints are episodic, labor-intensive, can be disruptive to the animals, and may miss subtle changes associated with disease and/or therapeutic effects.
- We compared **digital *measures* to traditional measures** in a mouse model of Amyotrophic Lateral Sclerosis (ALS).

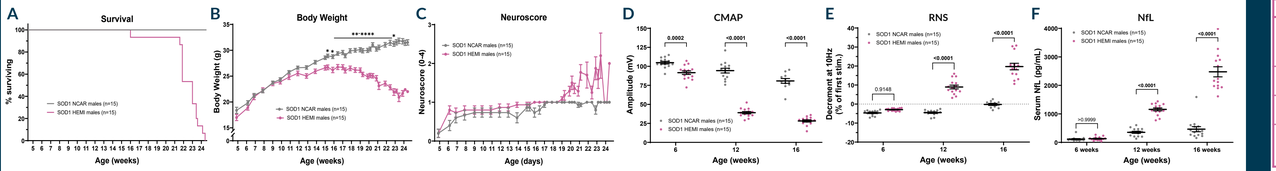
METHODS

- Animals: Male B6.Cg-Tg(SOD1*G93A)1Gur/J (SOD1, JAX Strain #004435) and non-carrier controls; housed 3 mice per cage
- Traditional measures were collected at 6, 12 and 16 weeks: rotarod performance, body weight, Neuroscore, CMAP/RNS and serum NfL
- Digital measures were collected 24/7 from the home cage from 5 to 25 weeks of age.
- Advanced machine learning from a beta version of the JAX Envision™ platform was used to generate the outcome measures of cage-level and individual animal activity.

JAX Envision™ collects video and sends the results through a set of machine learning algorithms that are reported through a cloud-based user interface.

- Inferred sleep was computed using the criteria of Pack et al. (2007), which demonstrates that runs of inactivity of ≥40 seconds correlate with sleep.
- Activity breakpoints, when activity patterns change drastically, were computed with segmented line regression on circadian-detrended activity.

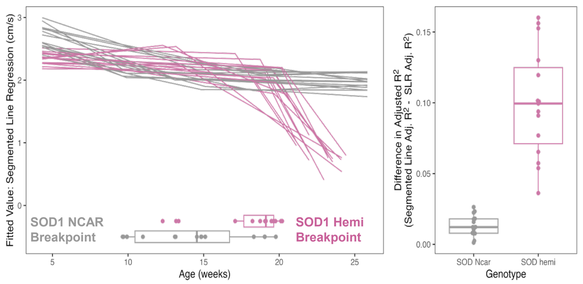
RESULTS: TRADITIONAL MEASURES



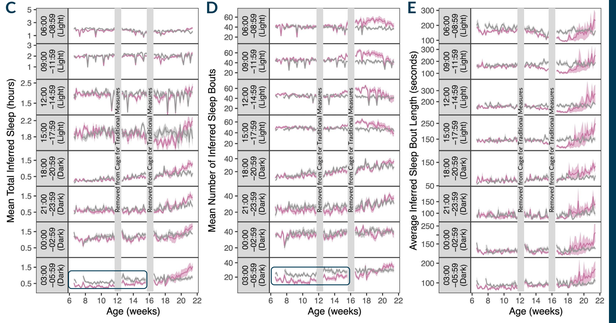
- SOD1 hemi mice had a median survival of 23 weeks (**A**), body weight loss from 15 weeks (**B**), and a nonsignificant increase in Neuroscore at 19 weeks.
- Declining motor neuron function was evident in SOD1 hemi mice in compound muscle action potential (CMAP) at 6 weeks with further decline at 12 and 16 weeks (**D**).
- Reduced neuromuscular transmission was observed via greater signal loss in repetitive nerve stimulation (RNS) was seen in SOD1 hemi mice at 12 and 16 weeks (**E**).
- Serum neurofilament light chain (NfL) levels were elevated in SOD1 hemi mice relative to NCAR mice at 12 and 16 weeks (**F**).
- No differences were found in rotarod performance at 6, 12, or 16 weeks (data not shown).

RESULTS: DIGITAL MEASURES

Longitudinal Average Movement



Inferred Sleep



- Average movement in SOD1 hemi mice declined near study endpoint, with a median segmented regression breakpoint at 19.1 weeks (**A**). Segmented models fit SOD1 data better than linear models (SOD1 hemi median adjusted R^2 increase: 0.0995; **B**).
- Sleep disturbance in SOD1 hemi mice emerged at 6 weeks (late dark period) (**C**) and progressed to more frequent (**D**), shorter bouts (**E**) by 14 weeks, indicating fragmented sleep. Lines = mean; ribbons = ±SEM

SUMMARY

Amyotrophic Lateral Sclerosis (ALS)					
Readout	Preclinical Measures				Clinical Measures
	Traditional		Digital		
	Measures	Age 1st Detected	Measures	Age 1st Detected	
Activity & Coord.	Rotarod	Not by 16 WOA	Activity	7-8 WOA	Activity (Actigraphy) 6 min walk test
General Neuro.	Neuroscore	First score of 3+: 20 WOA	Combinatorial algorithms	*Digital Neuroscore (not yet developed)*	ALS Functional Rating Scale-Revised (ALSFRS-R)
Sleep	Piezo sleep assay	N/A	Sleep/Wake time	7-8 WOA	Self-report Tracker (Fitbit) Sleep study

- Disrupted sleep patterns in SOD1 mice:
  - Detected prior to traditional measures of clinical disease onset.
  - Sleep disruptions occur in patients with ALS.
- Identified unique breakpoint in SOD1 mice (sudden decrease in average movement) correlated with a transition to end-stage disease phenotype:
  - Less subjective and less variability than traditional Neurocore → fewer mice for adequately powered studies.
  - Potential for continuous, non-invasive, longitudinal monitoring of disease progression → intervention at earlier timepoints, specific disease stages.

CONCLUSIONS

Longitudinal activity measurement and inferred sleep disruption detected using the JAX Envision™ platform enabled earlier identification of disease phenotypes with less animal disturbance and greater efficiency. This highlights the broader potential of digital measures to offer improved sensitivity and uncover novel insights into clinically relevant outcomes.

ACKNOWLEDGEMENTS

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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 validation and application of AI-enabled in vivo digital measures. For more information, visit DIVA.bio.