

Automated detection of spike-wave discharges in WAG/Rij rats: age-progression and response to chronic valproate



John Huxter¹, Pabitra Patra¹, Lauren Giggins¹, Sandy Thevarkunnel², Guy Higgins²

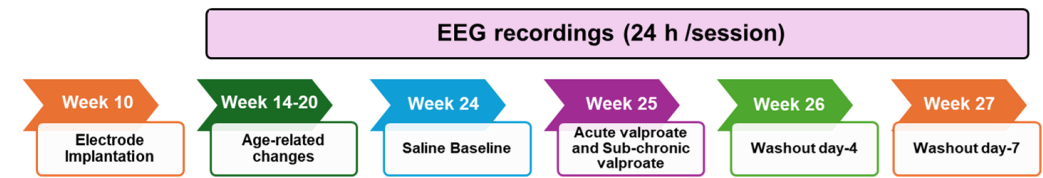
¹Transpharmation Ltd. UK. ²Transpharmation Canada.

INTRODUCTION

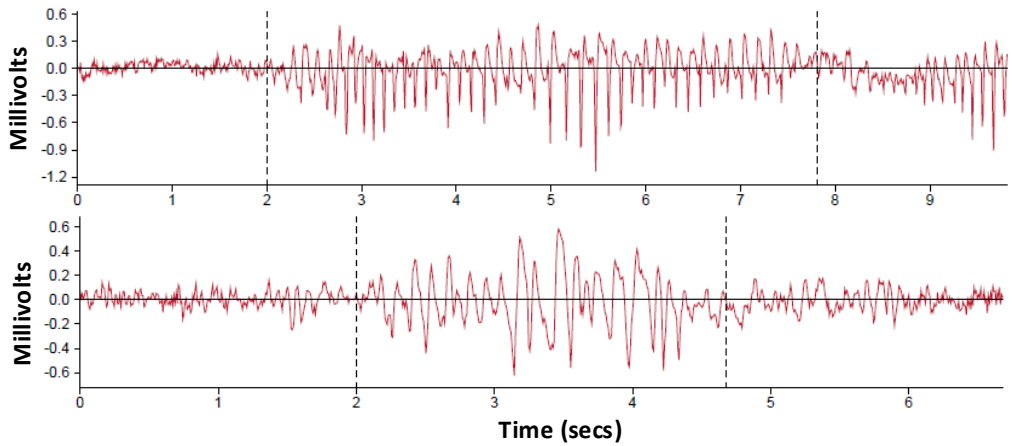
Absence seizures are characterised by sudden, frequent episodes of unconsciousness, often accompanied by automatic movements. Approximately 10% of childhood epilepsy cases involve typical absence seizures, with genetic factors believed to be the primary cause. It occurs at a rate of 6-8 per 100,000 children aged 0 to 15 years¹. To understand absence seizures, we employed the WAG/Rij rat model² coupled with EEG in 6 rats, using a new automated detection method to distinguish the spike-wave discharges (SWDs) associated with absence seizures from sleep-spindles.

METHODS

Six male WAG/Rij rats, ~11 weeks old, were implanted with epidural bipolar EEG (fronto-parietal) and EMG electrodes, and abdominal transmitters (DSI model HD-S02). From 14 to 20 weeks of age, fortnightly 24-hour recordings were used to monitor the emergence of SWDs, alongside locomotion, body temperature and wake/sleep architecture. Then, the effects of both acute and 5 days BID (“chronic”) dosing with 250 mg/kg i.p. of valproate were compared against a baseline recording, followed by a short (4-day) and long (7-day) washout. Timelines with **animal ages in weeks** were as follows:

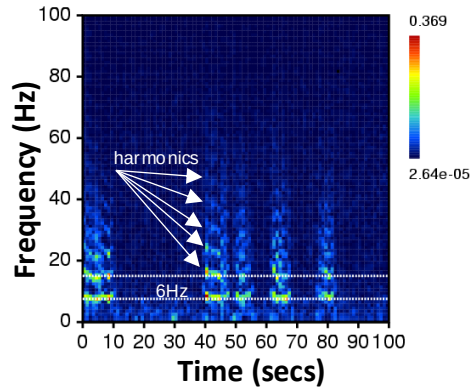


SWDs (below top) and sleep-spindles (below bottom) have a similar characteristic amplitude, duration and principal frequency (6-15Hz “sigma”), making distinguishing them a difficult, and typically manual task. Vertical dashed lines represent the start and end of the sigma-band events.



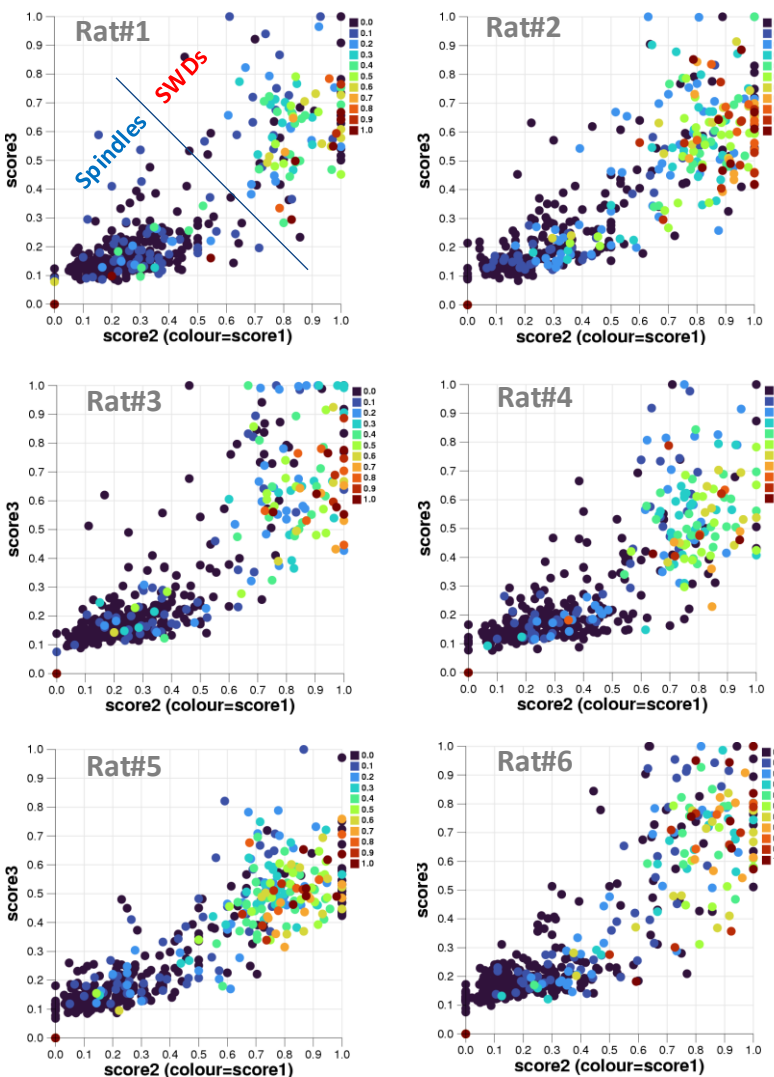
However, SWDs are characterised by asymmetry and the presence of a spiking component, producing harmonic responses in the power spectrum (below right).

We used these features of SWDs to generate **three novel scores** representing “spiking” in sigma-band oscillatory events. The distribution of scores in multi-dimensional space defined thresholds for separating events into sleep spindles and SWDs. Events were assigned to 10s epochs and analysed in 5-hour bins using 2-way repeated-measures ANOVA. Missing values were imputed and the Greenhouse-Geisser correction for sphericity was applied as necessary. For all figures, error bars are means ±SEM. *p<.05 **p<.01 ***p<.001.



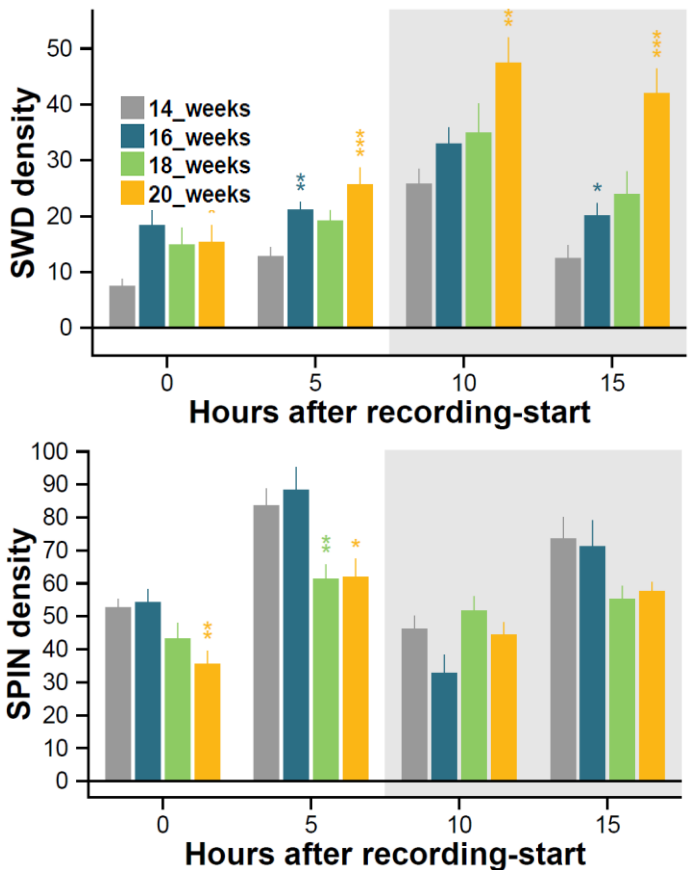
RESULTS: bimodal event-distribution

For all 6 animals, by 20 weeks of age there was clear evidence of a bimodal distribution of spindle-like and SWD-like events in all three score dimensions.



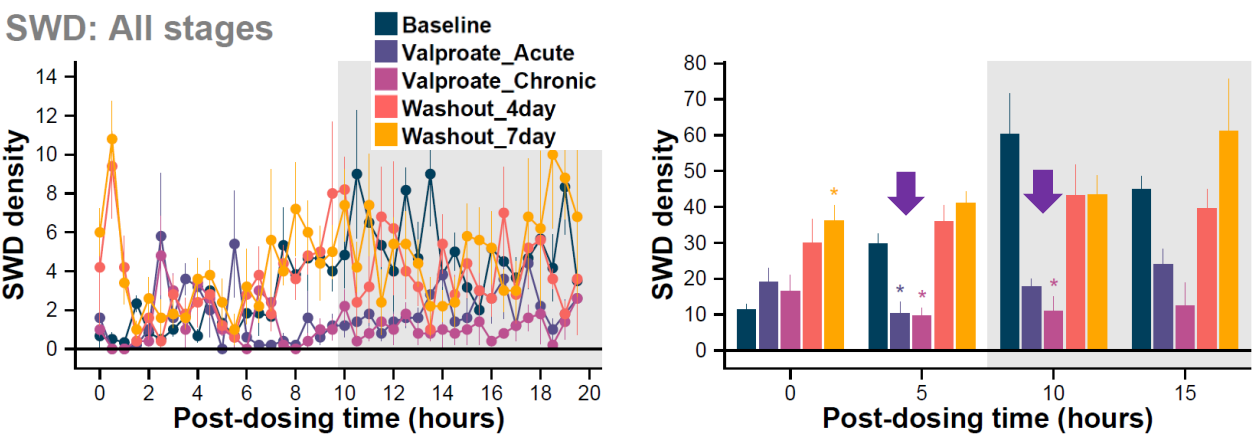
RESULTS: changes with age

SWD density increased with age (top), while sleep-spindle density decreased (bottom).

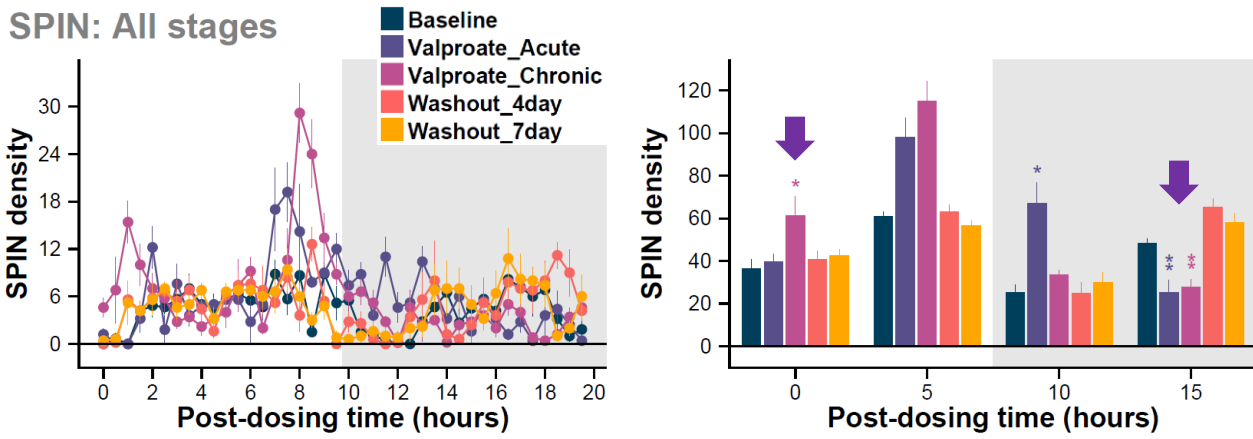


RESULTS : effects of valproate on WAG rats

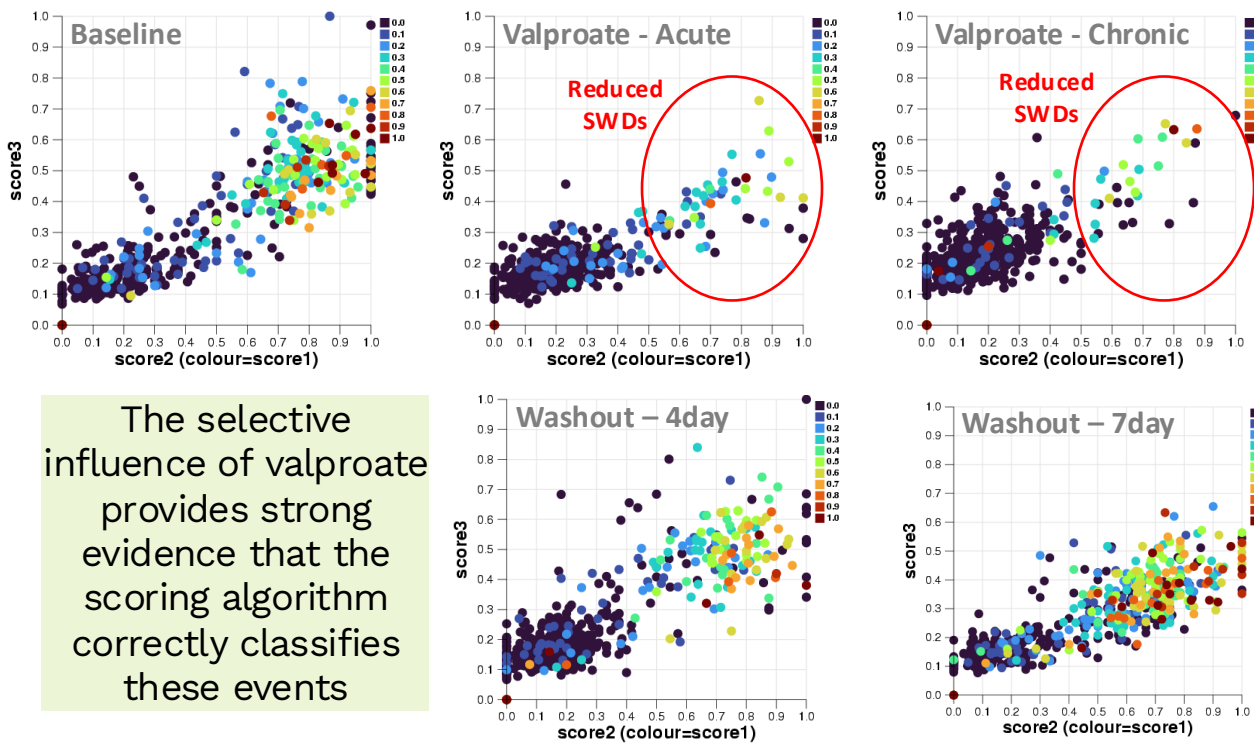
SWD density was significantly reduced after both acute and chronic valproate, in the period just before and after lights-off when SWD density is normally highest.



In contrast, sleep-spindle density increased significantly under valproate, particularly following chronic dosing. There was also an apparent homeostatic decrease in sleep-spindle density late in the dark cycle.



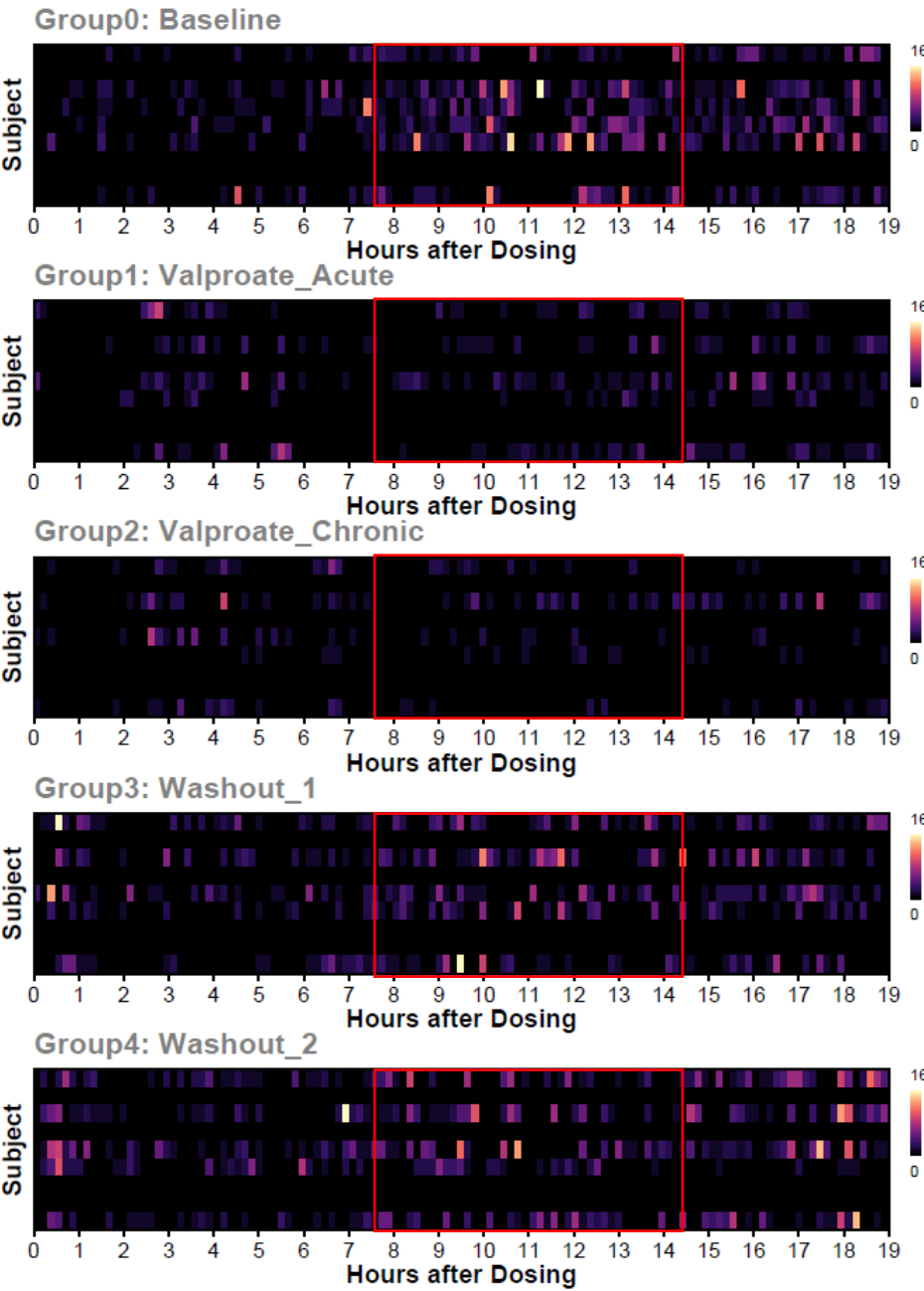
Score plots below for a single representative animal (#5) show that, at baseline, there is an even mix of sleep-spindles and SWDs. Acute and chronic valproate **selectively reduces events classed as SWDs** (red circles). On washout trials, SWDs clearly returned. An apparent increase above baseline in SWDs on washout day 7 is likely due to the continued age-related increase expected in this strain.



The selective influence of valproate provides strong evidence that the scoring algorithm correctly classifies these events

RESULTS: individual responses to valproate

Increased SWD density 8-14 hours post-dosing (red boxes) was **absent** under valproate, and returned after washout. Data below is averaged in 30-minute bins.



CONCLUSIONS

- Both acute and chronic valproate significantly mitigated spike-wave discharges in WAG/Rij rats.
- Sleep-spindle density was reduced with age and increased under valproate, in contrast with SWDs.
- We validated **automated SWD-detection** using the known efficacy of valproate in this model.
- Separation of SWDs from sleep-spindles** by responses to age and valproate further validated the detection methods.
- These findings contribute to our understanding of absence seizures and enable **higher-throughput screening** of novel treatments for epilepsy.

REFERENCES

- Guilhoto, LM. Absence epilepsy: *Continuum of clinical presentation and epigenetics?* Seizure, 44, 53 - 57.
- van Luijckelaar EL, Coenen AM. *Two types of electrocortical paroxysms in an inbred strain of rats.* Neurosci Lett. 1986, 70(3):393-7.