

Characterisation of Spike-and-Wave Discharge Modulation by Ethosuximide in the GAERS Model of Absence Seizures With Extended Homecage EEG Monitoring

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Objective

- To evaluate the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) rat model of absence seizures in undisturbed conditions for longer durations, to determine whether it provides a more translational model of human absence epilepsy

Conclusions

- These measures of spike-and-wave discharges (SWDs) using telemetric electroencephalogram (EEG) highlight the importance of evaluating GAERS models in naturalistic conditions.
- The natural behaviour allows alternation between wake and sleep. The epileptic activity is notably different from evaluations in forced wakefulness, reflecting the state-dependent nature of SWDs in GAERS animals, similar to epileptic activity in humans
- Compared with the forced wakefulness method limited to ~2 hours, the assessment of pharmacological effects with telemetry over 24 hours allows a pharmacodynamic characterisation of anti-absence compounds in preclinical studies. These naturalistic conditions allow the detection of pharmacological effects, when these effects are long-lasting (ethosuximide) or lasting a few hours (compound X)
- Parallel tracking of the locomotor activity in these spontaneous conditions can provide a surrogate read-out, detecting possible side effects of test compounds such as sedation

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References: 1. Depaulis A, et al. *J Neurosci Methods*. 2016;260:159–174. 2. Polack PO, Charpier S. *Epilepsia*. 2009;50(7):1816–1820.
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Disclosures: NS and BB are employees of Jazz Pharmaceuticals, Inc., and hold stock and/or stock options in the company. AE and VD are employees of SynapCell SAS.



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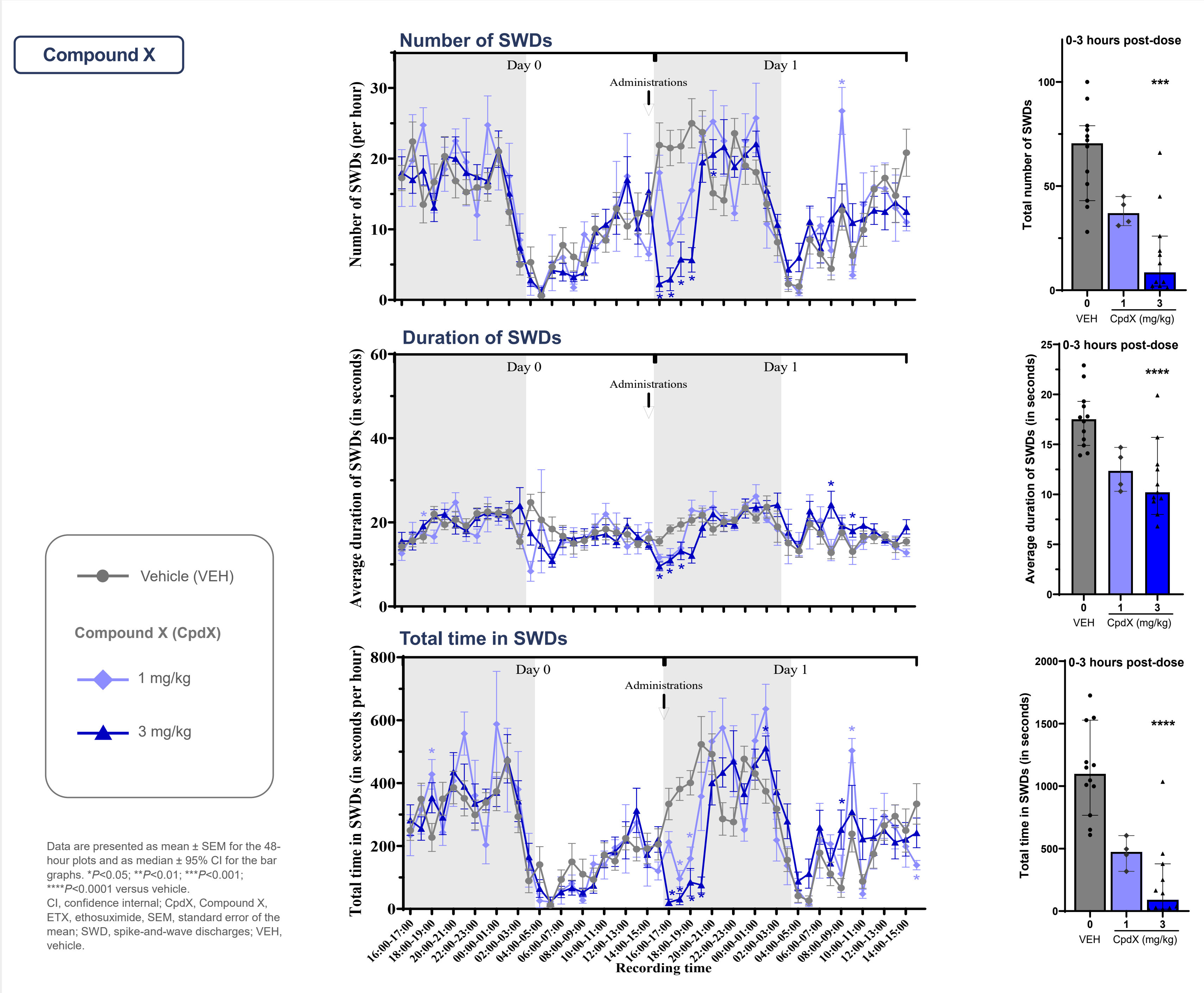
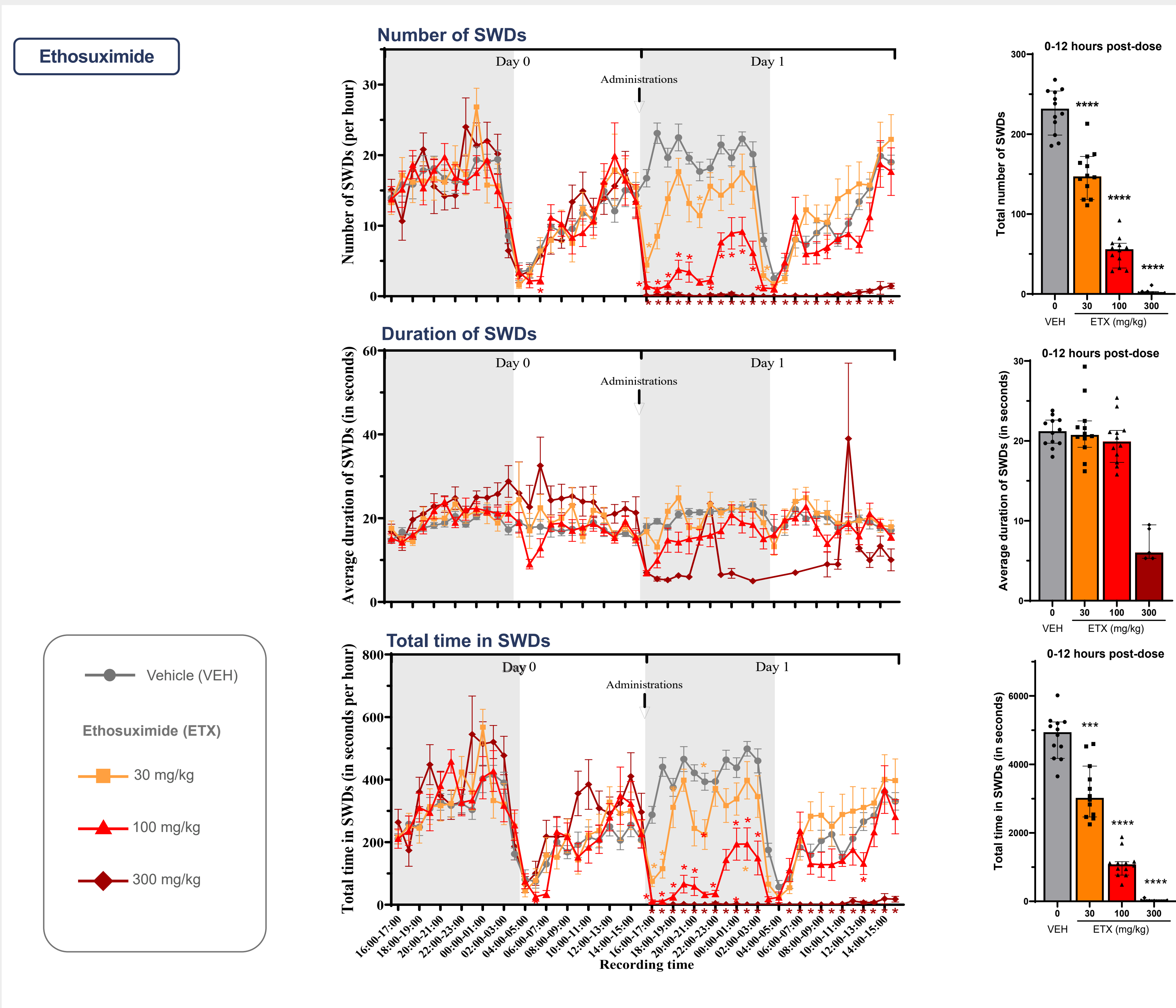
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Introduction

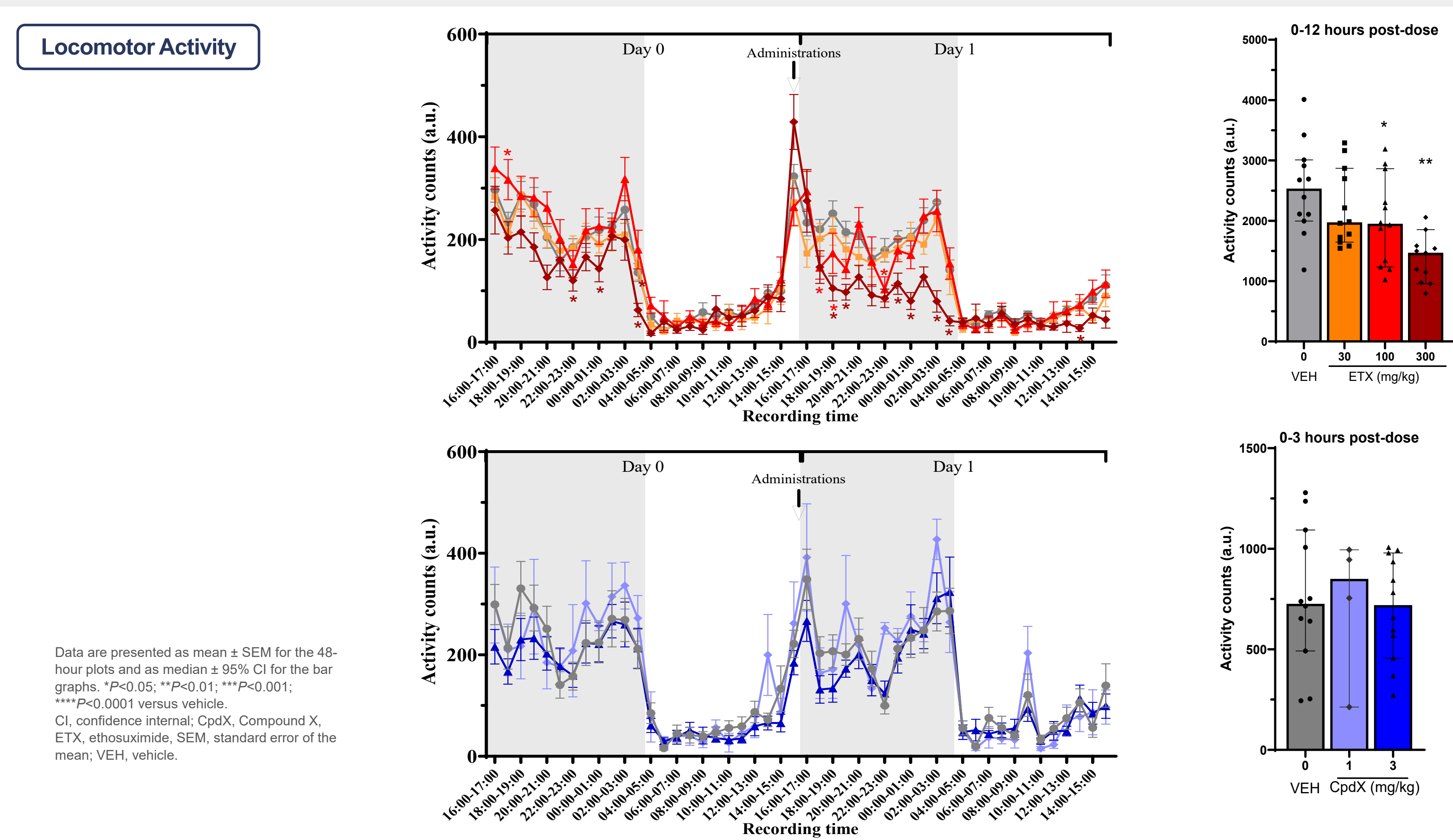
- Absence epilepsy** is characterised by brief episodes of impaired awareness and interruption of ongoing activity. Typical absence seizures are associated with generalised, synchronous spike-and-wave discharges (SWDs).
- The **Genetic Absence Epilepsy Rat from Strasbourg (GAERS)** is an inbred Wistar rat strain selected for spontaneous SWDs. It is a well-established model of absence epilepsy, reproducing key behavioral, electrophysiological, and pharmacological features of the disorder, including typical SWDs.¹ Cortical electroencephalogram (EEG) recordings show SWDs lasting 17–25 seconds, occurring 45–60 times per hour during wakefulness.
- Compound efficacy** in GAERS is typically assessed over a short period (~2 hours) while animals are kept in forced quiet wakefulness, which alters their natural behaviour. Evaluating compounds under undisturbed conditions and over longer periods may provide a more translational, clinically relevant model of human absence epilepsy.
- Two pharmacological compounds with different pharmacodynamic (PD) and pharmacokinetic (PK) characteristics were evaluated in these naturalistic conditions: the standard anti-absence medication **Ethosuximide² (T-type Ca²⁺ channel blocker)** and **Compound X from Jazz Pharmaceuticals** (undisclosed mechanism of action)

Methods

- Animals:** 12 male adult GAERS were obtained from Dr Antoine Depaulis (INSERM, Grenoble Institute of Neurosciences, Grenoble, France). Animals were 3 months of age at electrode implantation, and between 4 and 11 months of age at data collection. All animal procedures were conducted in accordance with applicable national and institutional guidelines for the care and use of laboratory animals, and were approved by the relevant ethics committee and regulatory authorities
- Housing conditions:** Animals were housed in single cages, with free access to food and water, and some enrichment. Homecages were maintained under artificial lighting between 4:00 am and 16:00 (4:00 pm) in a controlled ambient temperature (22 ± 2°C) and relative humidity
- Electrode implantations:** Under isoflurane anaesthesia, a telemetry transmitter (Data Sciences International, USA) was implanted in the abdomen, and its connections were channelled under the skin, up to the skull. Four electrodes (Protech Int., USA) were placed through the skull, over four locations of the cortex (frontal: anteroposterior (AP): +2 mm, mediolateral (ML): ±3; parietal: AP: -7, ML: ±3). After a week of recovery, EEG signals were validated during a test recording (see below), confirming the occurrence of SWD in the 12 rats, and a sufficient signal-to-noise ratio for SWD detection
- Recording conditions:** Animals were left undisturbed in their homecage to evaluate spontaneous SWDs during full light/dark cycles. The cortical EEG signals and the locomotor activity were continuously recorded for 48 hours, starting from the beginning of a dark phase. After a full cycle of baseline, animals were administered a test compound (see right) between 15:30 and 16:00, before the beginning of a second dark phase. Then the recording was continued for another full cycle, until the end of the second light phase. The same 12 animals were tested across doses after washout
- Test compounds:** Ethosuximide (Thermo Fisher Scientific) was formulated in 0.5% methylcellulose 4000 cps (w/v in water), and it was administered at the doses of 30, 100, and 300 mg/kg. Compound X (Jazz Pharmaceuticals) was formulated in 10% polysorbate 80 and 0.5% methylcellulose 4000 cps (w/v in water), and was administered *per os* at doses of 1 and 3 mg/kg
- Analysis:** EEG signals were analysed to identify SWDs. An initial automatic detection was secondarily validated by an analyst, blinded to the pharmacological conditions. SWD boundaries were verified, and artefacts were excluded. SWDs were then quantified following three metrics: the number of SWDs, the duration of each SWD, and the total time spent in SWDs, per given units of time (1, 3, or 12 hours). Locomotor activity was also extracted, and activity counts were summed following the same time units. Data are expressed as mean ± standard error of the mean (SEM; 48-hour data) or median ± 95% confidence interval (CI; bar graphs) of n=12 animals (except n=11 for ethosuximide at 300 mg/kg and n=4 for compound X at 1 mg/kg)
- Statistics:** Data were analysed using Prism v10 (GraphPad). Data were analysed using a mixed model with repeated measures, followed with Dunnett's *post hoc* test. On graphs: *, **, ***, ****: *P*<0.05, 0.01, 0.001, and 0.0001, respectively, as compared with vehicle



- SWDs followed a characteristic circadian variation, with higher frequency of events toward the end of the dark phase, and lower frequency at the beginning of the light phase, when animals were mostly asleep
- Ethosuximide and compound X produced a dose-dependent inhibition of SWDs, with different durations matching their PD and PK characteristics



- Ethosuximide produced a dose-dependent hypolocomotor effect, with a long-lasting reduction of activity counts over the 12 hours after administration
- Compound X had no significant effect on locomotion