The best of two worlds: Invasive and non-invasive approaches to unveil narcolepsy Type I in mouse models of narcolepsy

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Narcolepsy type 1 (NT1) is a neurological disorder caused by disruption of hypocretin (HCRT; or orexin) neurotransmission leading to fragmented sleep/wake states, excessive daytime sleepiness, and cataplexy (abrupt muscle atonia during wakefulness). Electroencephalography and electromyography (EEG/EMG) monitoring is the gold standard to assess NT1 phenotypical features in both humans and mice. Here, we evaluated the digital ventilated home-cage (DVC®) activity system as an alternative to detect NT1 features in two NT1 mouse models: the genetic HCRT-knockout (-KO) model, and the inducible HCRT neuron-ablation hcrt-tTA;TetO-DTA (DTA) model, including both sexes. NT1 mice exhibited an altered dark phase activity profile and increased state transitions, compared to the wild-type (WT) phenotype. An inability to sustain activity periods >40 min represented a robust activity-based NT1 biomarker. These features were observable within the first weeks of HCRT neuron degeneration in DTA mice. We also created a nest-identification algorithm to differentiate between inactivity and activity, inside and outside the nest as a sleep and wake proxy, respectively, showing significant correlations with EEG/EMG-assessed sleep/wake behavior. Lastly, we tested the sensitivity of the activity system to detect behavioral changes in response to interventions such as repeated saline injection, chocolate, and a wake-promoting compound. We conclude that the DVC® system provides a useful tool for non-invasive monitoring of NT1 phenotypical features and has the potential to monitor drug effects in NT1 mice.