Sleep and Orexinergic Pathway Alterations in Mice Models of Amyotrophic Lateral Sclerosis

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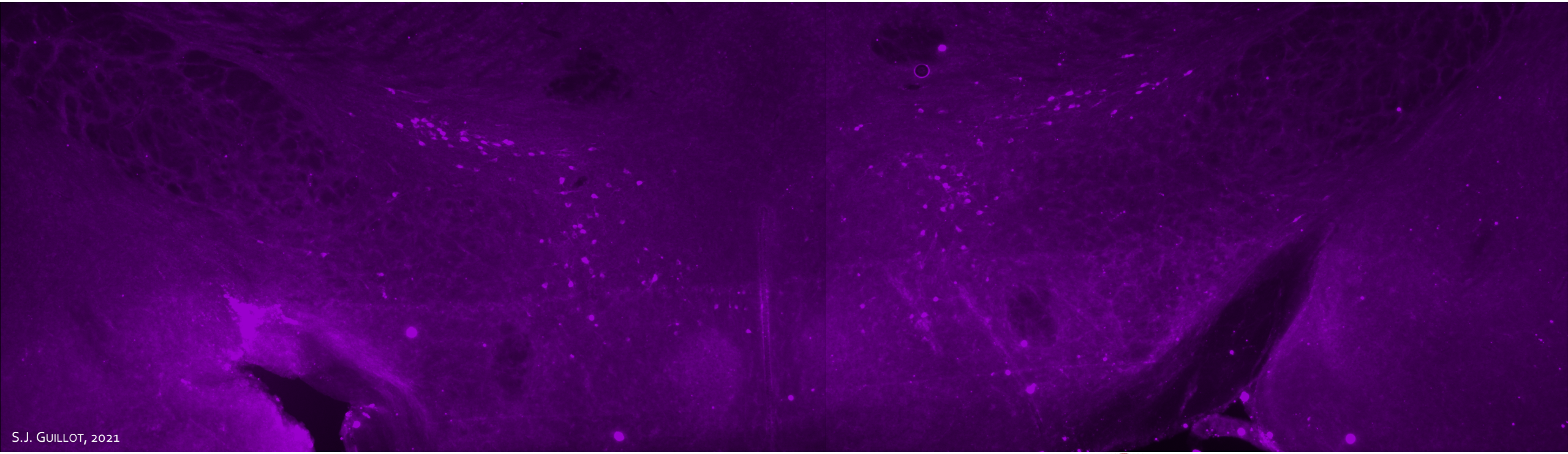

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Introduction

Amyotrophic lateral sclerosis (ALS) is a **progressive motor neuron disease** leading to an early death. We showed that in ALS mice models (SOD^{G86R} and FUS) and in patients' **melanin-concentrating hormone** (MCH) and **orexin** (Ox) neurons are lost. This depletion is correlated with an increase in **wakefulness**.

Sleep disturbances (increased wakefulness) have been described and appear at a later stage of the disease. Thus, investigating sleep disturbances are of utmost importance to understand the **pathomechanisms in ALS**.

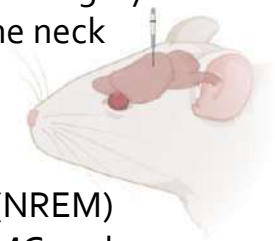
We **investigated the sleep pattern and performed a sleep rescue using Suvorexant®** (an anti insomniac drug acting on orexin receptors) before the onset of the symptoms. Wild-type (WT) and $SOD1^{G86R}$ mice electroencephalograms (EEG) and electromyograms (EMG) were recorded to assess the **impact on sleep in the** disease.

Experiments

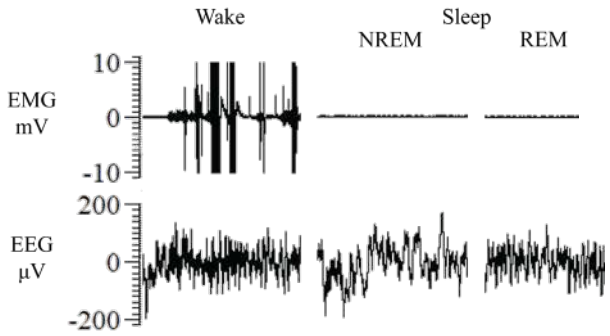
• EEG|EMG Electrodes Surgery

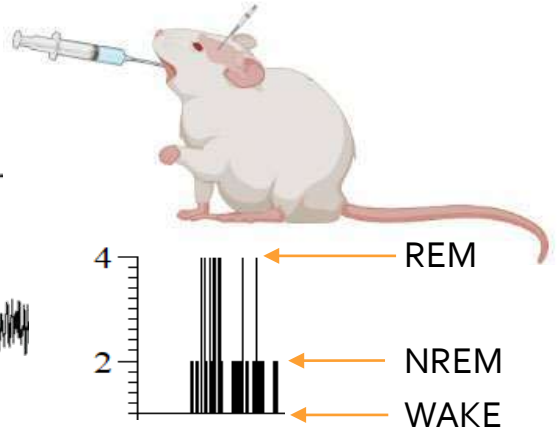
EEG and EMG electrodes were implanted using stereotaxic surgery

- 2 EMG electrodes were implanted on both sides of the neck
- 4 EEG electrodes were set on both sides of the brain



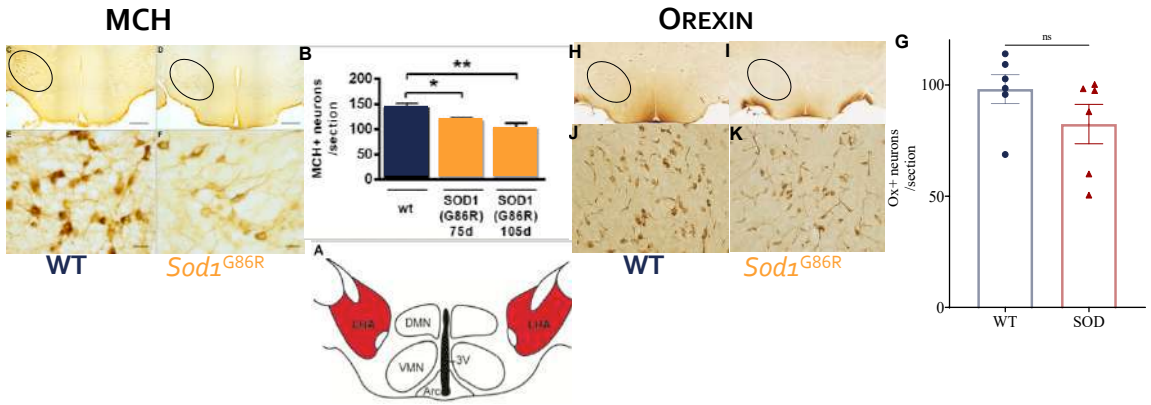
Characterisation of wake, non-rapid eye movement (NREM) and rapid-eye movement (REM) episodes using EEG|EMG and its corresponding hypnogram.





Results

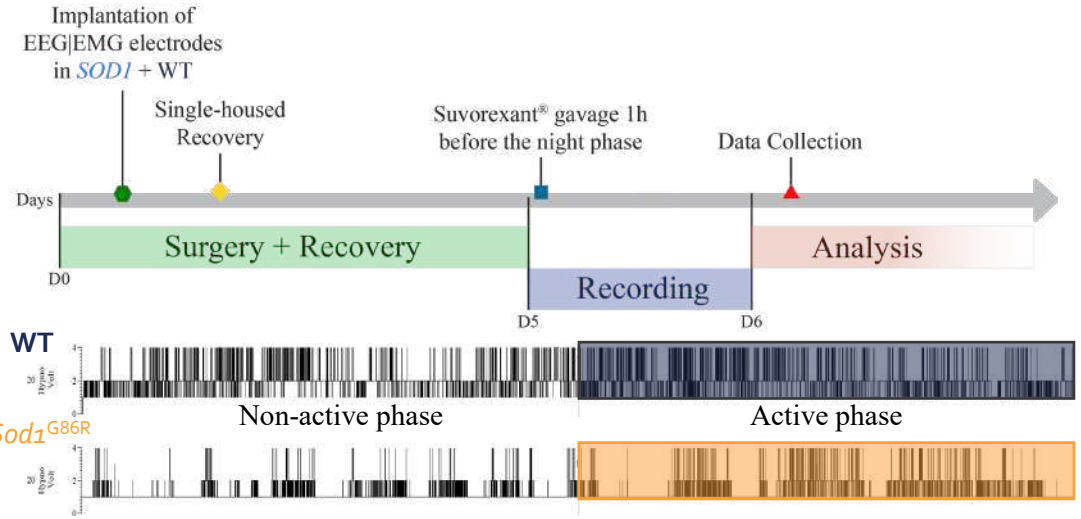
• IMMUNOSTAINING OF MCH AND OX NEURONS



A. Sagittal view of a mouse brain, in red the lateral hypothalamus (LH) where MCH and Ox neurons are known to be present; **C-F** & **H-K**. Immunostainings using DAB of, respectively, MCH and Ox neurons in the LH; **B-G**. Quantification of both MCH and Ox neurons in the LH.

Sod1^{G86R} mice exhibit a **significant decrease** in the **number** of **MCH+** neurons while **no impact** was observed in **Ox+** neurons compared to WT. The **decrease** of **MCH+ neurons** in *Sod1*^{G86R} mice seemed to **worsen with age**.

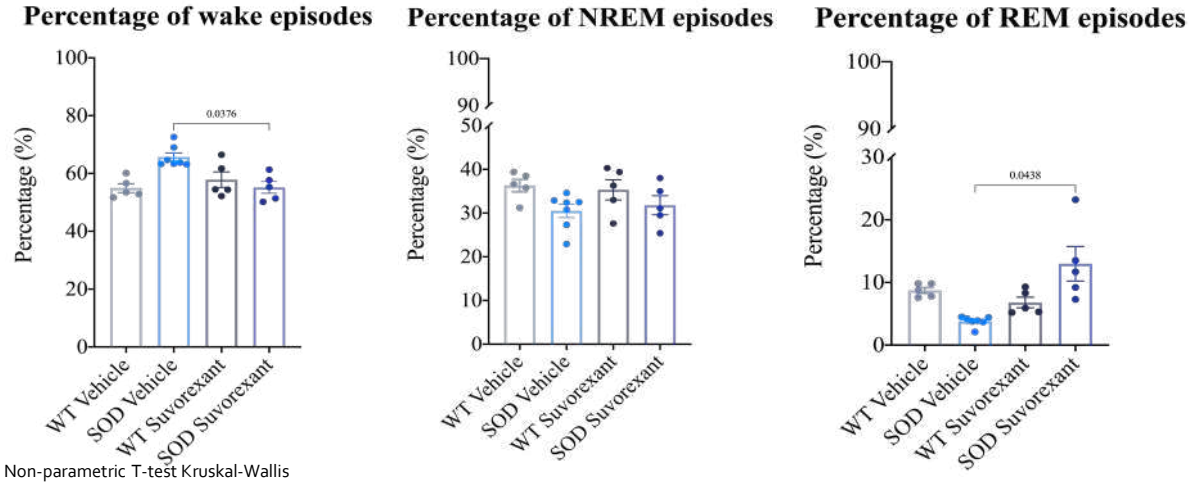
• RECORDING OF CEREBRAL ACTIVITY



Hypnograms of WT and *Sod1*^{G86R} mice over a 24-hour period administered with vehicle. *Sod1*^{G86R} mice present **lack of REM episodes** and **increased wakefulness** compared to the WT.

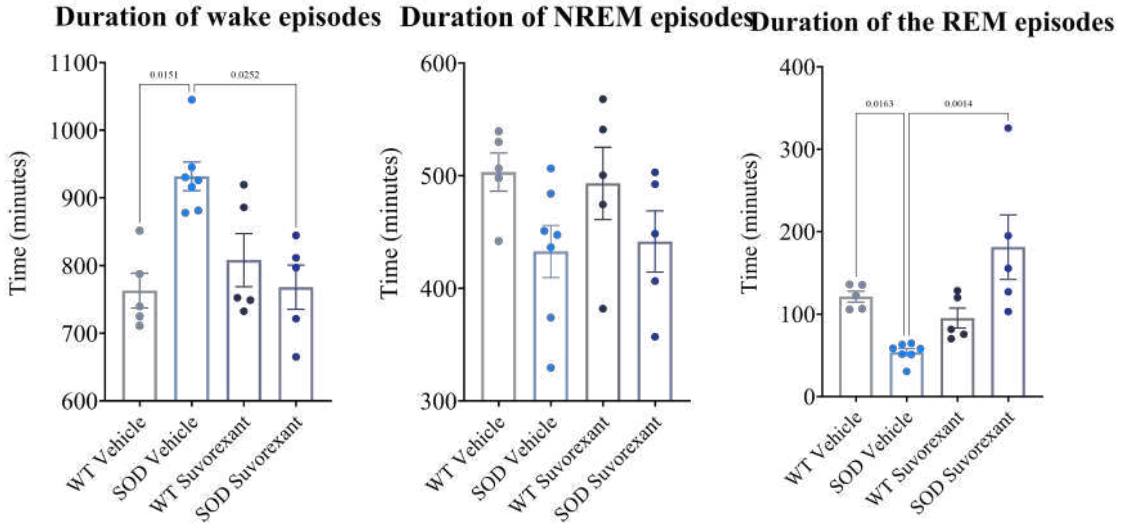
Results

- **SLEEP RESCUE USING SUVOREXANT®**



Non-parametric T-test Kruskal-Wallis

Suvorexant® gavage **decrease wakefulness** and **increase REM** episodes in *Sod1*^{G86R} mice.
No effect on NREM episodes.



Non-parametric T-test Kruskal-Wallis

Suvorexant® gavage **decrease the duration of wake** episodes and **increase the duration of REM** episodes in *Sod1*^{G86R} mice.
No effect on NREM episodes.

Discussion

We showed that *Sod1*^{G86R} mice maintained increased wakefulness and lowered NREM episodes compared to WT.
Suvorexant® had a significantly **decreased the percentage** and **duration of wakefulness** and its **episodes' duration** and **increased the percentage** as well as **the duration of REM** episodes in *Sod1*^{G86R} mice.