Behaviour and sleep-EEG effects of psilocybin in the mouse, as measured with TaiNi ultra-light wireless telemetry

John Huxter[1], Ashley Bernardo[2], Nicole Carroll[2], Matt Brown[2], Lukasz Dlugosz[2], Mark Duxon[1], Sandy Thevarkunnel[2] & Guy A. Higgins[2]

[1]Transpharmation Ltd. UK [2]Transpharmation Canada

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Introduction

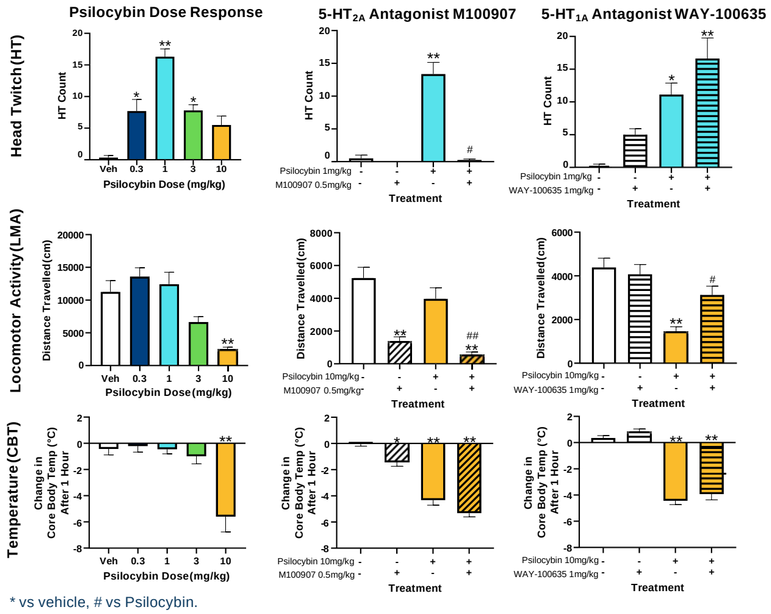
Sleep-electroencephalography (EEG) is a powerful, translational approach to probing disease-related changes in neural activity and sleep architecture. However, applying this to mice is challenging due to the bulk of tethers and implants. Here we demonstrate the application of **ultra-lightweight, head-mounted EEG** (Tainitec, London UK) for robust sleep-state classification and state-dependent qEEG. We avoid laborious human visual refinement by using **data-driven automated sleep stage classification.** Pharmacological validation is used to confirm the behavioural, REM-sleep, and qEEG effects of a **psilocybin dose-response**. Dose selection is based on head twitch (HT), core body temperature (CBT) and locomotor activity (LMA), which distinguish doses associated with **effects at the 5-HT$_{2A}$ receptor**, versus non-specific or off-target effects.

Methods: behavioural pharmacology

In male, C57BL/6J mice, we characterized psilocybin at 0.3mg/kg-10mg/kg s.c on measures of HT, CBT and LMA. Antagonist studies using the selective 5-HT$_{2A}$ antagonist M100907 (0.5 mg/kg IP) and selective 5-HT$_{1A}$ antagonist WAY100635 (1 mg/kg SC) were also conducted.

Results:

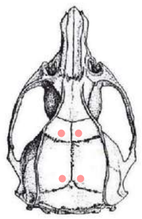
Psilocybin (0.3-1mg/kg) elicited a robust HT response blocked by M100907, thus consistent with 5-HT$_{2A}$R activity. At 3-10 mg/kg psilocybin, hypoLMA and hypothermia emerged. Neither effect was blocked by M100907. Rather, the hypoLMA response was attenuated by WAY100635, consistent with 5-HT$_{1A}$R agonist property of psilocybin.

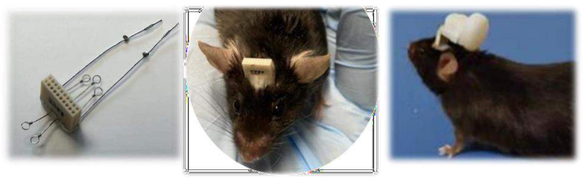


* vs vehicle, # vs Psilocybin.

Methods: TaiNi sleep-EEG

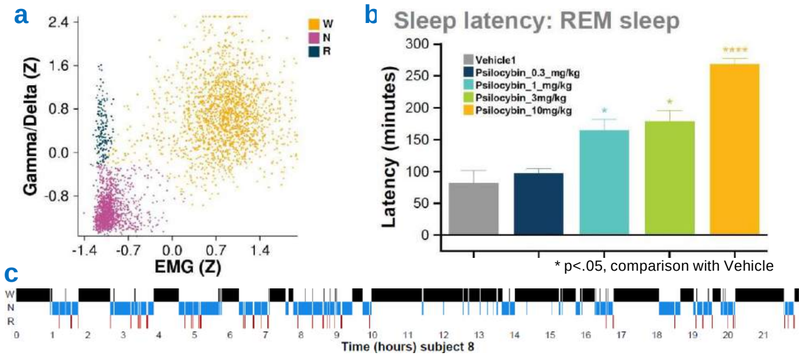
Male C57/BL6 mice were implanted with skull-screw electrodes over frontal and occipital/parietal cortices, EMG electrodes under the nuchal muscle, and a permanent Omnetics connector compatible with the TaiNi head-mounted transmitter (1.5g). In a Latin-square design, EEG was recorded during normal, unsupervised activity for 24h spanning a light and dark cycle. Data were aligned to dosing time (zero), 1 hour after lights-on.





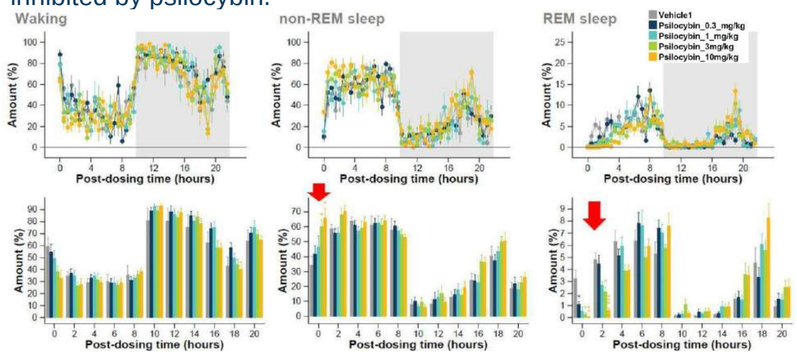
Results: sleep staging

a. Differential EMG and EEG (Frontal:L – Occipital:L) yielded robust separation of data into Wake (W), non-REM sleep (N), and REM sleep (R). **b**. REM sleep latency was selectively increased by psilocybin. **c**. Representative hypnogram (vehicle).

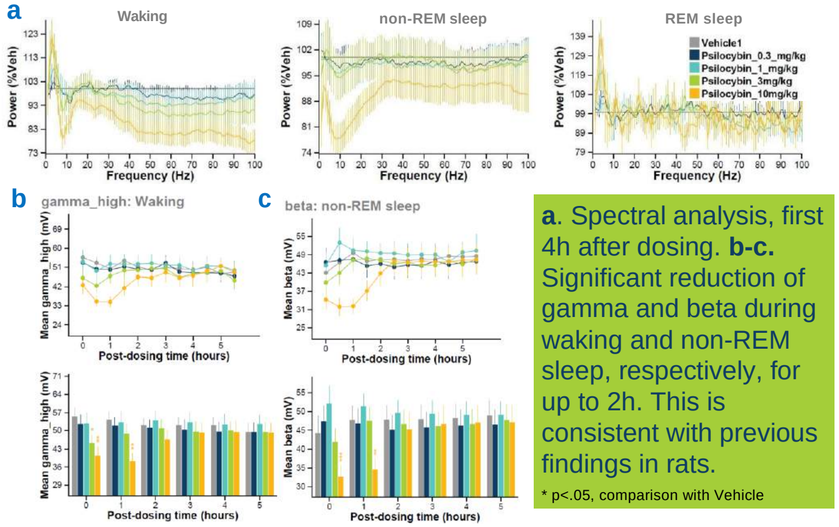


* p<.05, comparison with Vehicle

Mice exhibited a typical 24h distribution of vigilance states, and spent up to 10-15% of time in REM sleep. Only REM sleep was inhibited by psilocybin.



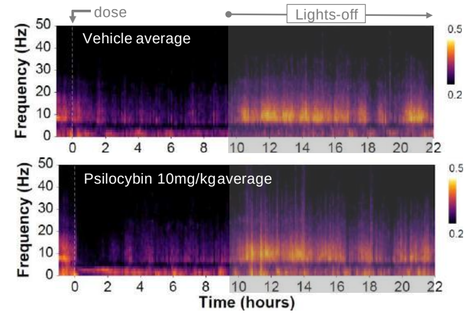
Results: qEEG analysis



a. Spectral analysis, first 4h after dosing. **b-c.** Significant reduction of gamma and beta during waking and non-REM sleep, respectively, for up to 2h. This is consistent with previous findings in rats.

* p<.05, comparison with Vehicle

Spectral coherence between the Frontal:L and Occipital:R electrodes is transiently suppressed in the 5-30Hz band after dosing (time-zero). Coherence increases again 10h later at lights-off.



Conclusions

- Psilocybin (0.3-1mg/kg) selectively elicited HT via 5-HT$_{2A}$R, at 3-10 mg/kg hypoLMA emerged at least in part via 5-HT$_{1A}$R activation.
- The lightweight TaiNi EEG system allows reliable 24h sleep-stage and qEEG recordings in mice, with virtually no behavioural burden.
- The use of multiple single-ended electrodes allows both conventional differential sleep staging, and site-specific analyses such as spectral coherence. This EEG system enabled the effect of a wide dose range of psilocybin (0.3-10 mg/kg) to be evaluated.

References

- Jiang, Z. et al. Sci. Rep. 7, 8086 (2017).
- Kao, et al., Sci. Rep. 11, 24331 (2021).
- Silvani et. al, Sleep, 40, 4, (2017) .

Contact

John.Huxter@transpharmation.co.uk
Denvor.Oorloff@transpharmation.co.uk