Context Novelty Modulates Melanopsin-mediated Sleep-promoting *versus* Alerting Responses in Mice

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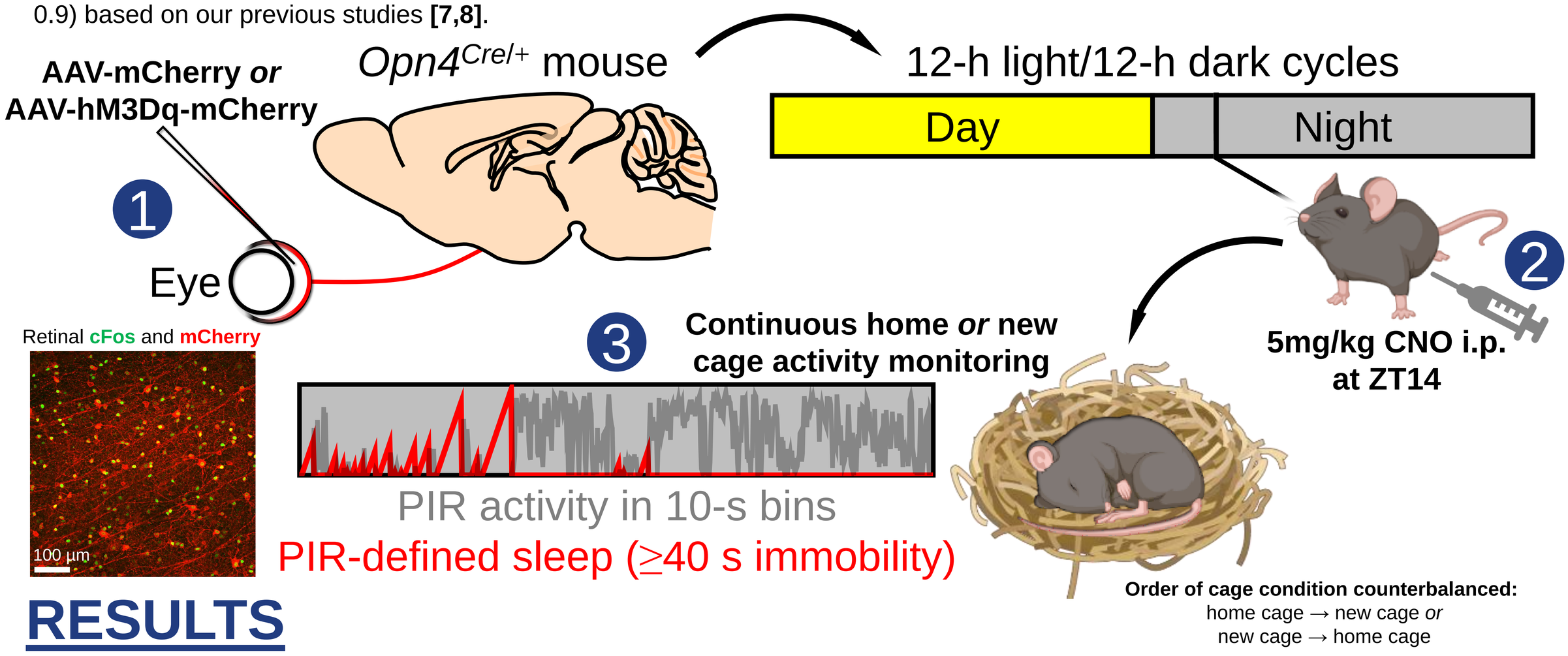
INTRODUCTION

Light directly modulates sleep and wakefulness in many species. In laboratory mice, nocturnal light induces sleep and reduces heart rate and body temperature **[1–3]**. But in certain unfamiliar situations nocturnal light can promote alertness, activating the hypothalamic–pituitary–adrenal axis and elevating glucocorticoid release from the adrenal gland, as well as enhancing fear responses to aversive stimuli **[4,5]**. Both sleep-promoting and alerting effects of light are known to be partially driven by melanopsin (OPN4)-expressing retinal ganglion cells (pRGCs) **[5,6]**. **What can account for such divergence in light responses? Here we examine the role of context novelty in modulating melanopsin-mediated sleep-promoting *versus* alerting responses.**

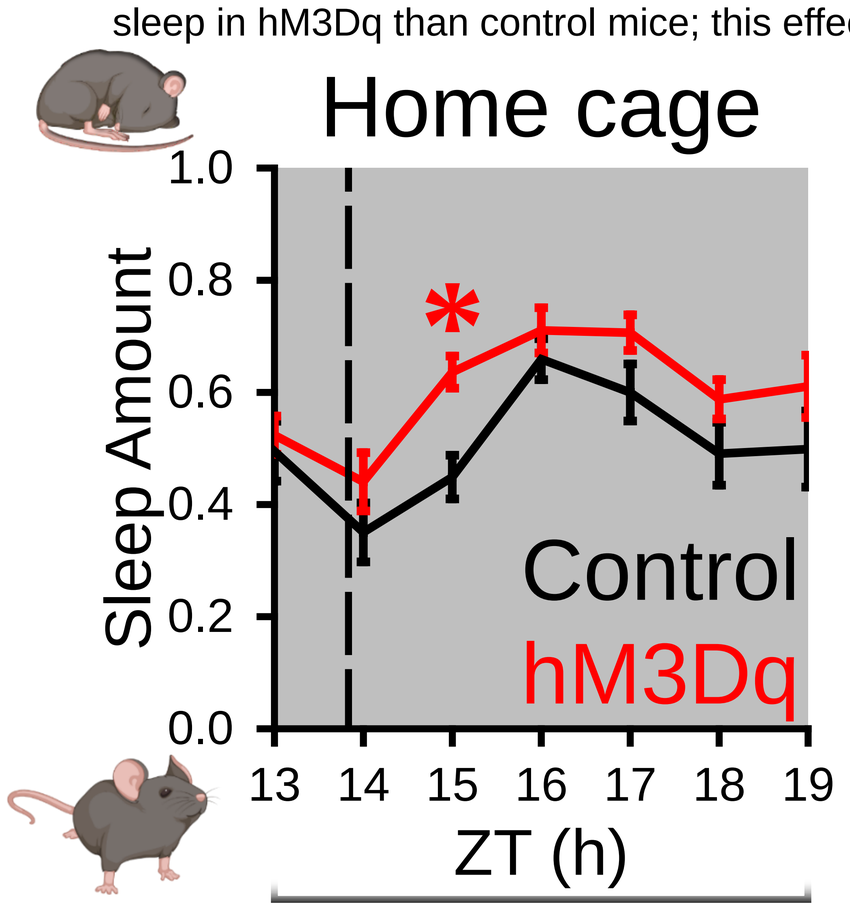
METHODS

Melanopsin-*Cre* (*Opn4*$^{Cre/+}$) mice received intravitreal injection of AAV2-hSyn-DIO-mCherry (13 mice) or AAV2-hSyn-DIO-hM3Dq-mCherry (15 mice) as in a previous study **[6]**. Five weeks after viral transduction, mice received one intraperitoneal injection of 5 mg/kg clozapine N-oxide (CNO) per week to **chemogenetically activate OPN4-expressing pRGCs during the biological night at Zeitgeber time (ZT) 14**. After CNO administration, mice were either returned to home cages or placed in identical cages containing clean bedding and new nesting materials; the order of cage condition was counterbalanced. Sleep was assessed non-invasively using passive-infrared (PIR) sensors and was defined as periods with ≥40 s of behavioural immobility—which is known to correlate with EEG-defined sleep ($r \geq 0.9$) based on our previous studies **[7,8]**.



RESULTS

- **Home cage:** hM3Dq *Opn4*$^{Cre/+}$ mice showed 18% (~11 min) more sleep than control *Opn4*$^{Cre/+}$ mice during the 1st hour post-CNO administration (ZT15, **left panel**), indicating that pRGC activation briefly promoted sleep.
- **New cage:** No group difference during the 1st hour, as both groups were ≥99% of the time awake at ZT15 (**right panel**). Context novelty delayed the onset of the sleep-promoting effect, and hM3Dq mice started to show more sleep than control mice by the 2nd hour (ZT16, **right panel**). The size of the sleep-promoting effect in new cages was stronger than that in home cages: 29% or ~18 min more sleep in hM3Dq than control mice; this effect persisted until the 3rd hour post-CNO administration (ZT17, **right panel**).



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CONCLUSIONS

1. **Context novelty alters the dynamics and strength of *Opn4*-mediated sleep-promoting effect**
2. **The environment in which responses are assessed and the corresponding motivational state can account for the divergence in light responses**

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