Per1 mutation enhances masking responses in mice

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Abstract

Light can restrict the activity of an animal to a diurnal or nocturnal niche by synchronizing its endogenous clock (entrainment) which controls the sleep wake cycle. Light can also directly change an animal's activity levels (masking). In mice, high illumination levels decrease activity, i.e. negative masking occurs. To investigate the role of core circadian clock genes *Per1* and *Per2* in masking, we used a 5-day behavioral masking protocol consisting of 3h pulses of light given in the night at various illuminances (4-5 lux, 20 lux and 200 lux). Mice lacking the *Per1* gene had decreased locomotion in the presence of a light pulse compared to wild-type, *Per2* and *Per1 Per2* double mutant mice. *Per2* single mutant and *Per1 Per2* double mutant mice did not show significantly different masking responses compared to wild-type controls. This suggests that *Per1* suppresses negative masking responses in mice.

Introduction

Light profoundly affects the physiology and behavior of all living beings. Light can set the timing of behavior, i.e. synchronize the timing of the animal's circadian activity pattern, a phenomenon called entrainment. Conversely, light can override the influence of the endogenous oscillator on behavior, a process called masking (Aschoff, 1960; Mrosovsky, 1999). The interrelationship between both of these processes is indispensable for the survival of nocturnal and diurnal animals in their natural conditions (reviewed in (Smale, Lee et al., 2003)). However, substantially less is known about the molecular mechanisms that regulate masking compared to entrainment (Mrosovsky, 1999; Pendergast & Yamazaki, 2011; Morin & Studholme, 2014).

Masking responses are mediated by classical photoreceptor input involving rods and cones (Thompson, Foster et al., 2008) and melanopsin (*Opn4*) positive, intrinsically photosensitive retinal ganglion cells (ipRGCs)(Mrosovsky & Hattar, 2003). IpRGCs project to the central clock in suprachiasmatic nuclei (SCN) and to other brain areas via retinal projections, including the retinohypothalamic tract (RHT) (Berson, Dunn et al., 2002). The RTH projections are necessary for masking responses (Li, Gilbert et al., 2005), but the role of the SCN is still debated (Redlin & Mrosovsky, 1999; Li, Gilbert et al., 2005). Other brain regions modulate masking responses such as the dorsal lateral geniculate nucleus (Edelstein & Mrosovsky, 2001), the visual cortex (Redlin, Cooper et al., 2003) and the intergeniculate leaflet (Redlin, Vrang et al., 1999; Langel, Yan et al., 2014) among others. The circadian system can, in turn, modulate masking responses in both diurnal and nocturnal species (Smale, Lee et al., 2003; Shuboni, Cramm et al., 2012). The neural underpinnings of this link are not well understood, but extensive work on the Nile grass rat revealed that many brain regions play important roles, such as: the ventral subparaventricular zone (Gall, Shuboni et al., 2016), the olivary pretectal area (Langel, Yan et al., 2014; Gall, Khacherian et al., 2017), the superior colliculus (Gall, Goodwin et al., 2020), among others (reviewed in detail by (Yan, Smale et al., 2020)).

Circadian rhythms are driven on a cellular and molecular level by a complex network of interlocking transcriptional and translational feedback loops, involving core clock genes *Bmal1* and *Clock*, with *Per1-3* and *Cry1-2* comprising the negative feedback loop (Cox & Takahashi, 2019). The molecular outputs of this network coordinate the timing of a plethora of physiological processes by clock-controlled genes. Circadian oscillations were reported in wide variety of tissues and organs (Mure, Le et al., 2018), including in the retina (Tosini & Menaker, 1996). Numerous processes are under the control of the circadian clock in the retina including: melatonin release (Besharse & Iuvone, 1983; Tosini & Menaker, 1996), rod-cone coupling (Ribelayga, Cao et

al., 2008), ion channel sensitivity (Ko, Ko et al., 2001) and light sensitivity (Barnard, Hattar et al., 2006; Gegnaw, Sandu et al., 2021)(reviewed by (McMahon, Iuvone et al., 2014; Felder-Schmittbuhl, Buhr et al., 2018)).

Clock genes also play a role in masking. *Clock* mutant mice have impaired masking (Redlin, Hattar et al., 2005). By contrast, deletion of the clock gene *Rev-Erbα* leads to increased light sensitivity and negative masking to dim light pulses (Ait-Hmyed Hakkari, Acar et al., 2016). *Per1* and *Per2* mutant mice show robust masking responses to bright light pulses (Pendergast & Yamazaki, 2011). However, it is unclear whether *Per1-2* mutation(s) show such responses to dim light. To address this question, we subjected $Per1^{-/-}$, $Per2^{Brdm1}$, and double mutant $Per1^{-/-}$ $Per2^{Brdm1}$ mice to a 5-day negative masking protocol using 3 light intensities (4-5 lux, 20 lux and 200 lux). Data suggests that *Per1* represses masking responses in mice.

Methods

Animals

Experiments were conducted using homozygote single and double mutant mice carrying the loss-of-function mutation of *Per1* gene ($Per1^{-/-}$; (Zheng, Albrecht et al., 2001)) and mutation of the *Per2* gene ($Per2^{Brdm1}$, (Zheng, Larkin et al., 1999); hereafter defined as $Per1^{-/-}$; $Per2^{Brdm1}$ and $Per1^{-/-}Per2^{Brdm1}$). Intercrosses between heterozygous (C57BL/6/J x 129 SvEvBrd) F1 offspring gave rise to F2 homozygous mutants. Mutant and wild-type (WT) animals on this mixed background were used in this study, maintained as described in (Albrecht, Zheng et al., 2001). Mice were maintained in our animal facilities (Chronobiotron, UMS3415) on a light–dark cycle (12L/12D, 300 lux during the light phase, < 5 lux during the dark phase), with an ambient temperature of 22 ±1 °C. The animals were given free access to food and water. We used 2-5 month old mice (14 male and 2 female, see Supplementary **Table S1** for details). Animals were acclimated to environmental conditions for at least 2 weeks before starting the experimental procedures. All experimental procedures were performed in accordance with the Association for Research in Vision and Ophthalmology Statement on Use of Animals in Ophthalmic and Vision Research, as well as the European Communities Council Directive (2010/63/EU).

Behavioral masking

Negative masking is the light-dependent inhibition of locomotor activity in nocturnal animals such as rodents (Mrosovsky, 1999). To assess the effect of genotype on light intensity-dependent masking responses, we subjected WT, single mutant $Per1^{-/-}$, $Per2^{Brdm1}$, and double mutant $Per1^{-/-}$ $Per2^{Brdm1}$ mice (N=4 / genotype) to a

5-day behavioral masking protocol. The mice were singly housed in cages and acclimated for 2 weeks prior to testing and received free access to food and water throughout the experiment. The cages were equipped with infrared detectors (CAMS, Circadian activity monitoring system, Lyon, France) and placed in a light-tight, ventilated compartment in 12 h L:12 h D. This custom-built chamber has a background illuminance of 0 lux and is equipped with automatically controlled lights. The mice received a 3h light pulse 2h after lights off (at ZT 14) on day 1 (4-5 lux), 3 (20 lux) and 5 (200 lux) as described by (Ait-Hmyed Hakkari, Acar et al., 2016). Locomotion was measured as infrared beam breaks / 5 min (counts/5min). Relative counts were calculated by dividing the mean value of beam breaks during the 3h light pulse on test days (1, 3 or 5) with the activity during the dark phase of the baseline day (ZT 14 – 24, day 0). Data was collected using ClockLab software (Actimetrics).

Genotyping

Mice were genotyped by polymerase chain reaction (PCR) amplification of tail DNA with four sets of primers specific either for the genomic regions that were deleted in mutants but present in WT (5′-GTCTTGGTCTCATTCTAGGACACC and 5′-AACATGAGAGCTTCCAGTCCTCTC for *Per1* gene; 5′-AGTAGGTCGTCTT CTTTATGCCCC and 5′-CTCTGCTTTCAACTCCTGT GTCTG for *Per2* gene), or for the recombinant alleles present in mutants only (5′-TCAGAGCAGGACAACCCATCTACC and 5′-ACTTCCATTTGTCACGTCCTGCAC for $Per1^{-/-}$, 5′-TTTGTTCTGTGAGCTCCTGAACGC and 5′-ACTTCCATTTGTCACGTCCTGCAC for $Per2^{Brdm1}$).

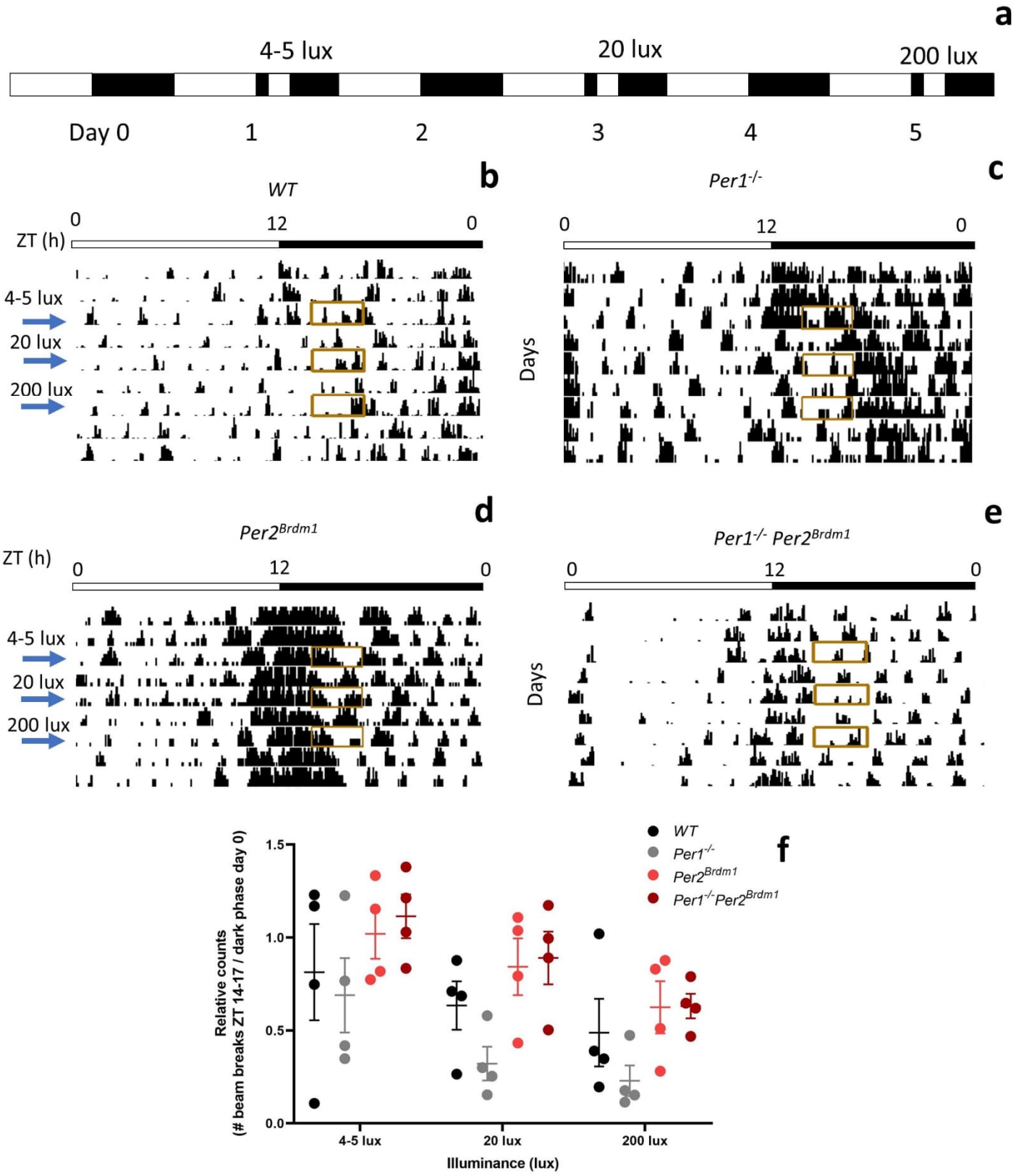
Statistics

GraphPad Prism software was used for generating the graph and performing statistics (version 8.3.0, La Jolla, CA, USA). Normality of distribution was tested by the Kolmogorov-Smirnov test. The effect of time (in days) and genotype on relative beam-break counts was assessed by a two-way ANOVA with repeated measures. Differences between groups were assessed by the two-stage step-up method of Benjamini, Krieger and Yekutieli (Benjamini, Krieger et al., 2006).

Results

Behavioral masking

A dim light pulse (0.1 lux) significantly suppressed the activity of *Rev-Erbα*$^{-/-}$ mice compared to WT mice (Ait-Hmyed Hakkari, Acar et al., 2016). Considering that negative masking responses are robust in mice carrying mutations in *Per* genes (Pendergast & Yamazaki, 2011), we hypothesized that *Per* mutant mice might have enhanced negative masking responses to dim light. To test this hypothesis, we subjected WT, single mutant *Per1*$^{-/-}$, *Per2*^{Brdm1}, and double mutant *Per1*$^{-/-}$ *Per2*^{Brdm1} mice to a 5-day behavioral masking protocol in which mice received a 3h light pulse at ZT14 (2h after lights off) (**Fig. 1a**) as described by (Ait-Hmyed Hakkari, Acar et al., 2016). The activity of mice was plotted as actograms (**Fig. 1b, c, d, e**). We compared relative beam breaks by repeated measures two-way ANOVA (**Fig. 1f**). We found that light intensity ($F(1.86, 22.36) = 8.47$; $p = 0.0022$) and genotype ($F(3, 12) = 4.97$; $p = 0.018$) significantly affected the activity of mice. The interaction of genotype x light intensity was not significant ($F(6, 24) = 0.15$; $p = 0.99$). Post-hoc testing for the effect of genotype revealed that the activity of *Per1*$^{-/-}$ mice was significantly lower compared to *WT* ($q = 0.043$; $p = 0.12$), *Per2*^{Brdm1} ($q = 0.002$; $p = 0.0039$) and *Per1*$^{-/-}$ *Per2*^{Brdm1} ($q = 0.0013$; $p = 0.0012$) (**Table S2**). Post-hoc tests performed for the effect of genotype within each light intensity suggest that a 20-lux pulse might suppress the activity of *Per1*$^{-/-}$ compared to *Per2*^{Brdm1} ($q = 0.053$; $p = 0.019$) and *Per1*$^{-/-}$ *Per2*^{Brdm1} ($q = 0.053$; $p = 0.0033$) mice (**Table S2**). We provide raw uncorrected beam breaks and statistics in the supplementary material (**Fig. S1** and **Table S2-3**). These results suggest that *Per1* might be involved in suppressing masking responses in mice.


a
4-5 lux
20 lux
200 lux
Day 0
1
2
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4
5
b
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0
12
0
4-5 lux
20 lux
200 lux
c
Per1-/-
Days
d
Per2Brdm1
e
Per1-/- Per2Brdm1
f
WT
Per1-/-
Per2Brdm1
Per1-/-Per2Brdm1
Relative counts
(# beam breaks ZT 14-17 / dark phase day 0)
1.5
1.0
0.5
0.0
4-5 lux
20 lux
200 lux
Illuminance (lux)

138

Figure 1. Behavioral masking responses of wild type (WT), single mutant *Per1*$^{-/-}$, *Per2*^{Brdm1} and double mutant *Per1*$^{-/-}$ *Per2*^{Brdm1} mice. (a) The masking protocol consisted of 3h light pulses administered 2h after lights-off (ZT14-17) on days 1, 3 and 5. (b) WT; (c) *Per1*$^{-/-}$, (d) *Per2*^{Brdm1} and (e) double mutant *Per1*$^{-/-}$ *Per2*^{Brdm1} locomotor activity was plotted as actograms. Actogram recordings during which the light pulses were administered are shown in brown rectangles. (f) Repeated measures ANOVA showed that light intensity ($p<0.01$) and genotype ($p<0.05$) significantly affected mouse activity. N = 4/genotype. Graphs show mean ± SEM and values from individual samples are shown as dots.

Discussion

The present study describes a distinct phenotype of *Per1*$^{-/-}$ compared to *WT*, *Per2*^{Brdm1} and *Per1*$^{-/-}$ *Per2*^{Brdm1} mice in response to light, with *Per1*$^{-/-}$ mice exhibiting enhanced negative masking behavior.

In our study, we used *Per1*$^{-/-}$, *Per2*^{Brdm1} and double mutant *Per1*$^{-/-}$ *Per2*^{Brdm1} mice, all of which retain the ability to entrain to a 12:12 LD cycle (Zheng, Larkin et al., 1999; Zheng, Albrecht et al., 2001). Among them, *Per1*$^{-/-}$ and mice show rhythmic behavior in constant darkness (DD) with shorter periods, whereas *Per2*^{Brdm1} mice lose their rhythmicity in such conditions (Zheng, Larkin et al., 1999; Zheng, Albrecht et al., 2001). By contrast, *Per1*$^{-/-}$ *Per2*^{Brdm1} mice are arrhythmic under DD (Zheng, Albrecht et al., 2001). To the best of our knowledge, no masking studies were performed using the same mixed background mice as used in the present study. However, it is known that *mPer1*$^{ldc-/-}$, *mPer2*$^{ldc-/-}$ *and mPer1*$^{ldc-/-}$*mPer2*$^{ldc-/-}$ mice on a C57BL/6J background show robust masking responses (Pendergast & Yamazaki, 2011).

The interrelationship between masking and the circadian system is complex (Shuboni, Cramm et al., 2012). In nocturnal animals (e.g. mice), light is most effective in suppressing activity in the early dark phase of the light-dark cycle (ZT14) (Shuboni, Cramm et al., 2012). This suppressing effect is also observed in the early subjective night (CT14, i.e. 14h after the onset of constant darkness) in mice (Shuboni, Cramm et al., 2012). Moreover, light pulses administered in the early dark phase can reduce wakefulness in mice ("photosomnolence") (Lupi, Oster et al., 2008; Morin & Studholme, 2009; Tsai, Hannibal et al., 2009). In the present study, the light pulses were also administered in the early dark phase (ZT14-17). As expected, we observed that light suppressed the activity in all mice. This suppressive effect is similar to the one elicited by a 75-85 lux (Pendergast & Yamazaki, 2011). Our results suggest that a light suppressed the activity of *Per1*$^{-/-}$ compared to *WT*, *Per2*^{Brdm1} and *Per1*$^{-/-}$ *Per2*^{Brdm1} mice.

It is not clear why the *Per1* gene represses behavioral masking. However, enhanced negative masking responses were observed in mice carrying a mutation in the circadian clock gene *Rev-Erbα*, which suggest that a common

converging pathway underlies the masking phenomenon. A hypothetical model was proposed in which masking responses are driven by ipRGC output (Ait-Hmyed Hakkari, Acar et al., 2016; Felder-Schmittbuhl, Buhr et al., 2018). This output results from a summation of intrinsic light stimulation (*Opn4*-dependent) and synaptic input from rod and cone-specific bipolar cells. At lower light intensities, this input is insufficient to depolarize ipRGCs of WT mice. By contrast, *Rev-Erbα*$^{-/-}$ mice have increased *Opn4*-dependent intrinsic sensitivity and input from the rod pathway, thus eliciting enhanced masking at lower light intensities (Ait-Hmyed Hakkari, Acar et al., 2016; Felder-Schmittbuhl, Buhr et al., 2018). It is plausible that *Per1*$^{-/-}$ mice may have higher expression of *Opn4* and/or enhanced rod sensitivity.

An alternative explanation is that *Per1* inhibits masking responses by a pathway in the brain. This possibility is supported by studies on effects of *Per* genes in entrainment. For example, *Per1*$^{-/-}$ mice show a greater phase response curve (PRC) amplitude compared to *WT* mice, whereas *Per2*$^{-/-}$ mice were not significantly different compared to *WT* mice (Pendergast, Friday et al., 2010). Others have found that *Per1* mutant mice cannot advance the phase of the clock in response to a nocturnal light pulse at ZT22, whereas *Per2* mutant mice cannot delay the phase of the clock in response to a light pulse at ZT14 (Albrecht, Zheng et al., 2001). Yan and Silver reported differential localization of *Per1* and *Per2* mRNA expression in the SCN upon light pulses that entrain the clock (Yan & Silver, 2002). In the SCN shell, they found that a phase advancing light pulse increased *Per1*, but not *Per2* mRNA expression. By contrast, they found that *Per2*, but not *Per1* mRNA was increased in the SCN shell after a phase delaying light pulse (Yan & Silver, 2002). Because there is an intertwined relationship between masking and entrainment (Shuboni, Cramm et al., 2012), it is tempting to speculate that there is a link in the neuronal circuitry underlying these processes. In our study, pulses were given at ZT14 (i.e. phase delaying). Thus, it is plausible that enhanced masking responses of *Per1*$^{-/-}$ mice is mediated by neural processing of light by the SCN.

There are limitations in our study. Although the suppression of locomotor activity in *Per1*$^{-/-}$ is observed at dim light, the light pulse is higher than the one required for *Rev-Erbα*$^{-/-}$ mice (0.1 lux) (Ait-Hmyed Hakkari, Acar et al., 2016). Therefore, the contribution of *Per1* for masking is of less significance compared to other clock genes such as *Rev-Erbα*$^{-/-}$(Ait-Hmyed Hakkari, Acar et al., 2016) or *Clock* (Redlin, Hattar et al., 2005). Another limitation is that we used only one day between the light pulses. Previous masking studies used study designs in which the periods between pulses were at least 3 days (Shuboni, Cramm et al., 2012), and even 5-6 days (Morin & Studholme, 2014). Thus, there may be a confounding effect of the previous pulse(s) on masking responses in the present study. However, our short protocol is less than a week and minimizes the need for animal handling (e.g. we do not need to replenish feed, water, no cage cleaning). Thus, our protocol might have removed the

potential confounding effects of handling on masking responses (Mrosovsky, Reebs et al., 1989). Also, prior work showed that this protocol was sufficient to detect masking responses in the *Rev-Erbα*$^{-/-}$ mice (Ait-Hmyed Hakkari, Acar et al., 2016).

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Declaration of interest statement

The authors have no conflicts of interest to disclose.

Data availability statement

Raw data that support the findings of this study are available from the corresponding authors, upon reasonable request.

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