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Dissociation between two subgroups of the suprachiasmatic nucleus affected by the number of damped oscillated neurons

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In mammals, the main clock located in the suprachiasmatic nucleus (SCN) of the brain synchronizes the body rhythms to the environmental light-dark cycle. The SCN is composed of about 2×10^4 neurons which can be classified into three oscillatory phenotypes: self-sustained oscillators, damped oscillators, and arrhythmic neurons. Exposed to an artificial external light-dark cycle with a period of $22h$ instead of $24h$, two subgroups of the SCN can become desynchronized (dissociated). The ventrolateral (VL) subgroup receives photic input and is entrained to the external cycle and a dorsomedial (DM) subgroup oscillates with its endogenous (i.e., free running) period and is synchronized to the external light-dark cycle through coupling from the VL. In the present study, we examined the effects of damped oscillatory neurons on the dissociation between VL and DM under an external $22h$ cycle. We found that, with increasing numbers of damped oscillatory neurons located in the VL, the dissociation between the VL and DM emerges, but if these neurons are increasingly present in the DM the dissociation disappears. Hence, the damped oscillatory neurons in different subregions of the SCN play distinct roles in the dissociation between the two subregions of the SCN. This shows that synchrony between SCN subregions is affected by the number of damped oscillatory neurons and the location of these cells. We suggest that more knowledge on the number and the location of these cells may explain why some species do show a dissociation between the subregions and others do not, as the distribution of oscillatory types of neurons offers a plausible and novel candidate mechanism to explain heterogeneity.

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I. INTRODUCTION

In mammals, the main endogenous clock located in the suprachiasmatic nucleus (SCN) of the brain drives body rhythms to be synchronized with the external $24h$ light-dark cycle [1–4]. The SCN is a neuronal network, which consists of about 2×10^4 neuronal oscillators with intrinsic periods centered around $24h$ [5,6]. These neurons are coupled and generate a coherent periodic output [3,4,7], which is dependent on environmental clues. Under constant darkness, the so-called free running period is about $24h$ [8–11]; and under an external light-dark cycle with a period of T , the period of the SCN is precisely equal to T [12,13], provided that the difference between the free running period and T is not too large.

If the difference between the endogenous free running period and the external light-dark cycle period (T) is too large, the SCN cannot be entrained to the external light-dark cycle. In individual rats, exposed to an artificially external $T = 22h$ light-dark cycle ($11h$ light alternating with $11h$ darkness), the behavioral activity expresses two separate circadian rhythms, with one rhythm entrained to the external cycle, showing a period exactly equal to T , while the other is not entrained and expresses a period visibly larger than $22h$ and close to its endogenous free running period [14–16]. Analysis of SCN gene expression data suggested that these two rhythms are controlled by two subgroups of the SCN which are forced desynchronized (or dissociated). These subgroups are a light-information-sensitive subregion located in the ventrolateral SCN (VL) and a light-information-insensitive subregion in

the dorsomedial SCN (DM), respectively, in rats [14,17]. A similar dissociation is also found in the day-active *Octodon Degus* [18] but has not been found in other species [19]. In this paper we want to understand how this dissociation between the two SCN regions can be invoked, and why this is different across species.

The light-information-sensitive VL subgroup contains about 25% of all SCN neurons and relays the photic information from the retina to the remaining 75% of SCN neurons located in DM in rats [20–22]. Neurotransmitters that play key roles in cellular coupling are bound to the specific subregions. For example, in the VL, the neurons mainly express vasoactive intestinal polypeptide (VIP) [23], while neurons in the DM mainly express arginine vasopressin (AVP) [24]. Gamma aminobutyric acid (GABA), which is present throughout the SCN, links the VL and the DM [25]. Next to the neurotransmitter phenotypes, oscillatory phenotypes exist in the neurons. Three oscillatory phenotypes have been observed for SCN neurons: self-sustained oscillatory neurons, damped oscillatory neurons and arrhythmic neurons [26–32]. Recently, it has been found that the oscillatory phenotypes are not bound to specific subregions, in other words, these three oscillatory phenotypes are all observed within both the VL and the DM, while the exact proportion of the different type of neurons has not been found [29].

The dissociation between the VL and the DM under the $22h$ cycle is explained by the distinct functions of the two subgroups. The VL is directly sensitive to the photic information, thus it is feasibly entrained to the external cycle, while the DM indirectly receives the photic information through the VL so that the DM desynchronizes with the VL and also the external $22h$ cycle [14]. Thus far, no studies

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have investigated the effects of the properties of individual neurons on the dissociation. Our aim here is to investigate whether the damped oscillatory neurons play a role in the dissociation under the external $T = 22h$ cycle based on a networked Goodwin model [30,31]. A ratio of the number of damped oscillatory neurons to the total number of neurons within one subgroup is defined. The role of the ratio of damped neurons in the dissociation between the VL and the DM is studied, by comparing the periods of the VL and DM with the period $T = 22h$ of the external cycle.

II. METHODS

The Goodwin model is the simplest physiological model to describe the circadian clock. Each neuronal oscillator is driven by a negative feedback loop consisting of a gene mRNA, its protein, and an inhibitor [33–39]. Thus far, the topology of the SCN network is largely unknown. Accordingly, for simplicity, the SCN network is taken into account as an all to all network where the neuronal oscillators are coupled or linked through a neurotransmitter mean field in most of the circadian models [10,12,15,33–38]. Here, the Goodwin model is composed of N neuronal oscillators, and reads as

$$\begin{aligned}\dot{X}_i &= \alpha_1 \frac{k_1^n}{k_1^n + Z_i^n} - \alpha_2 \frac{X_i}{k_2 + X_i} + \alpha_c \frac{gF}{k_c + gF} + L_i, \\ \dot{Y}_i &= k_3 X_i - \alpha_4 \frac{Y_i}{k_4 + Y_i}, \\ \dot{Z}_i &= k_5 Y_i - \alpha_6 \frac{Z_i}{k_6 + Z_i}, \\ \dot{V}_i &= k_7 X_i - \alpha_8 \frac{V_i}{k_8 + V_i}, \\ F &= \frac{1}{N} \sum_{j=1}^N V_j, \quad i = 1, 2, \dots, N,\end{aligned}\quad (1)$$

where each neuronal oscillator is described by four variables, including gene mRNA X_i , a protein Y_i , an inhibitor Z_i , and the transmitter V_i . The neuronal oscillators are coupled through the mean field F , which is the mean value of the transmitter V_i from all the neuronal oscillators, with the cellular coupling strength (absorbing ability) g . The key difference between the VL and the DM lies in the light term L_i . Because only about 25% of SCN neurons situated in VL are sensitive to light information, the light term L_i is represented by

$$L_i = K_f, \quad \text{mod}(t, T) < T/2 \quad i = 1, 2, \dots, N_V, \quad (2)$$

$$L_i = 0, \quad \text{mod}(t, T) \geq T/2 \quad i = 1, 2, \dots, N_V, \quad (3)$$

$$L_i = 0, \quad i = N_V + 1, N_V + 2, \dots, N,$$

where N_V is the number of SCN neurons sensitive to light information, K_f is the light intensity, and T is the period of the external T cycle. For the self-sustained oscillatory neurons, the values of the parameters are set as in Ref. [33]: $\alpha_1 = 0.7$ nM/h, $k_1 = 1.0$ nM, $n = 4.0$, $\alpha_2 = 0.35$ nM/h, $k_2 = 1.0$ nM, $k_3 = 0.7$ /h, $\alpha_4 = 0.35$ nM/h, $k_4 = 1.0$ nM, $k_5 = 0.7$ /h, $\alpha_6 = 0.35$ nM/h, $k_6 = 1.0$ /h, $k_7 = 0.35$ /h, $\alpha_8 = 1.0$ nM/h, $k_8 = 1.0$ nM, $\alpha_c = 0.4$ nM/h,

$k_c = 1.0$ nM, $g = 0.5$. In order to mimic the damped oscillatory neurons, the values of the parameters are the same as for self-sustained oscillatory neurons except $n = 3$ and $\alpha_2 = 0.5$ nM/h [31]. The key parameters in the present study are P_{VL} and P_{DM} . P_{VL} represents the ratio of the number of damped VL neurons to the total number of VL neurons. The range of P_{VL} is from 0 to 1, where 0 means that there are no damped VL neurons and 1 represents the case where all VL neurons are damped oscillators. Similarly, P_{DM} represents the ratio of the number of damped DM neurons to the total number of DM neurons. Note that in this study the damped neuronal oscillators are all located in only one subgroup, in other words, if these damped neurons are in one subgroup, there are no damped neurons in the other subgroup.

In the present study, we will examine the role of the ratios in the synchronization between the VL and the DM subregions, and in the entrainment ability of these two subgroups to the external $T = 22h$ cycle. If the period difference between these two subgroups is smaller than or equal to $0.001h$, we define that the VL and DM are synchronized. If the difference is larger than $0.001h$, these two subgroups lose synchronization and dissociate. Similarly, the entrainment of the subgroup to the external $T = 22h$ cycle is determined by the difference ($0.001h$) between the subgroup period and T . In order to measure the periods of the SCN, the VL, and the DM, F , F_{VL} , and F_{DM} are taken as markers for the evolutions of the SCN network, the VL subgroup, and the DM subgroup, respectively. Based on the evolutions, the periods are calculated as in Ref. [40].

For numerical simulation, the fourth-order Runge-Kutta method was used with time increments of 0.01 h. The initial 5×10^6 time steps (5×10^4 h) were neglected in order to avoid the influence of transients. In the simulations, the damped oscillators would not show any rhythms when in isolation, as the rhythms already died out during the initial phase. The number of neuronal oscillators was set as $N = 40$ for the numerical simulations. The initial conditions for each variable (x, y, z, v) were randomly chosen from a uniform distribution in the range (0–1) in the Goodwin model.

To confirm our findings, we also performed the same simulations with $N = 1000$. In addition, to examine generality of our results, we used another SCN oscillator model based on the Poincaré model. The numerical simulations and the mathematical analysis support our results from the Goodwin model (see Supplemental Material [41] for methods and results).

III. RESULTS

A. The dissociation between the VL and the DM rely on the ratios

Examples are presented to illustrate the effects of the ratios of damped oscillators in one SCN subregion subjected to an external cycle with a period $T = 22h$, where the light intensity is $K_f = 0.02$ in Fig. 1. In (a), when the ratio is $P_{VL} = P_{DM} = 0$, i.e., all the SCN neuronal oscillators are self-sustained oscillators with intrinsic amplitude larger than zero, the VL neurons and the DM neurons are synchronized, and both are entrained to the external cycle. In (b), when

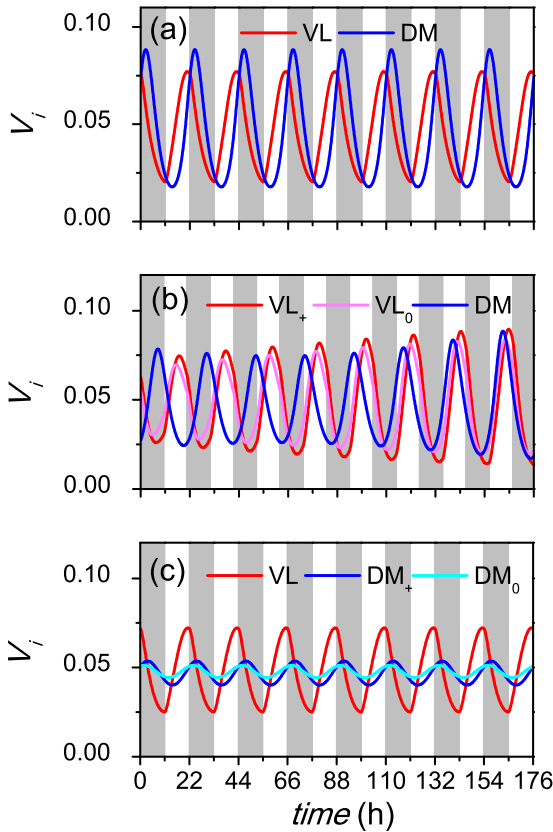


FIG. 1. The evolutions of different subgroups to an external $T = 22h$ cycle. The ratios are $P_{VL} = P_{DM} = 0$ in (a), $P_{VL} = 0.8$ in (b) and $P_{DM} = 0.8$ in (c). VL_0 or DM_0 represents the neurons with zero amplitude, and VL_+ or DM_+ represents the neurons with > 0 amplitude. The grey region corresponds to darkness.

$P_{VL} = 0.8$, i.e., the ratio of the number of damped VL neurons to the total number of VL neurons is 0.8, the VL and DM show quasiperiodic behavior. All the VL neurons are synchronized to the external $T = 22h$ cycle, since the phase difference between the peaks or troughs of the VL neurons and the external cycle is fixed. However, the DM neurons are not synchronized to the external cycle, because the phase difference fluctuates over time. As a result, the VL and DM subgroups are dissociated. In (c), when the ratio is $P_{DM} = 0.8$, i.e., the ratio of the number of damped DM neurons to the total number of DM neurons is 0.8, both the VL neurons and the DM neurons maintain synchronized, and all the SCN neurons are entrained to the external cycle, similar as shown in (a). Note that average amplitude of the oscillations decreases due to less neurons contributing to it in (b) or (c). For example for the DM in (c) only 20% of the neuronal oscillators contribute to the overall pattern, because 80% of the neurons is damped to zero amplitude. Thus, the ratio P_{VL} plays a role in the DM period and contributes to the dissociation between the VL and the DM under the external $T = 22h$ cycle.

We continued to systematically examine the effect of ratio values on the periodic behavior of the SCN to the external T cycle. Figure 2 shows the quantitative relationships of the periods of VL and DM to the different ratios under an external cycle with period $T = 22h$ and light intensity $K_f = 0.02$. In

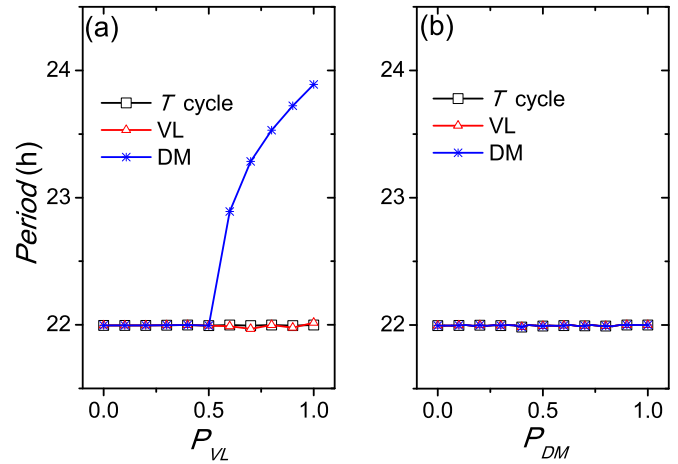


FIG. 2. Dependence of the periods of VL and DM on the ratios P_{VL} (a) and P_{DM} (b) to an external cycle of $T = 22h$ for high light intensity ($K_f = 0.02$). Number of neurons for this simulation is $N = 40$. Entrainment to external T -cycle is lost for DM if $P_{VL} > 0.5$.

(a), a transition emerges at a threshold ratio of 0.5. If $P_{VL} \leq 0.5$, the periods of both subgroups are equal to the period of the external T cycle ($22h$), and the VL and DM are synchronized. If $P_{VL} > 0.5$, the VL period is equal to $22h$, but the DM period is larger than $22h$, and approaches the free running period ($24h$) with the increase of P_{VL} . As a consequent, the VL and the DM lose synchrony and dissociate. In (b), the increase of P_{DM} does not influence the periods of both subgroups which are entrained to the external cycle with a period $T = 22h$, and remain synchronized over the whole investigated ratio range.

In Fig. 3 the light intensity is reduced to $K_f = 0.008$. In (a), due to the weak light intensity, both subgroups are unable to entrain to the external $T = 22h$ cycle. With the increase of P_{VL} , the periods of VL and DM both increase. In (b), during the increase of P_{DM} , both groups show complicated behavior with two transition points. When $P_{DM} \leq 0.23$, both subgroups

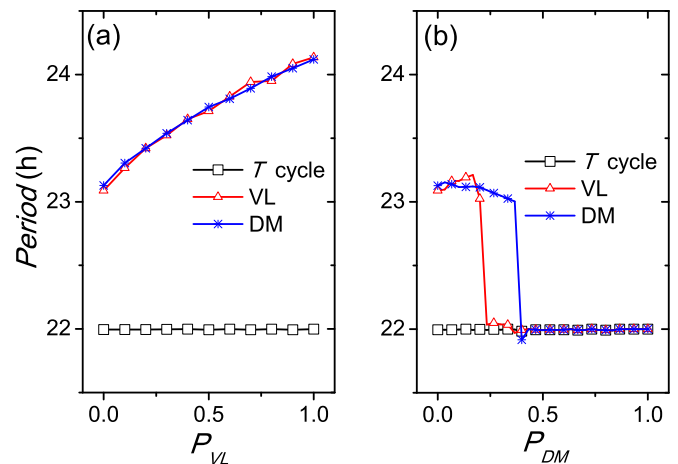


FIG. 3. Dependence of the periods of VL and DM on the ratios P_{VL} (a) and P_{DM} (b) to an external cycle of $T = 22h$ for low light intensity ($K_f = 0.008$). Number of neurons for this simulation is $N = 40$. Entrainment to external T -cycle can only be observed for increased P_{DM} .

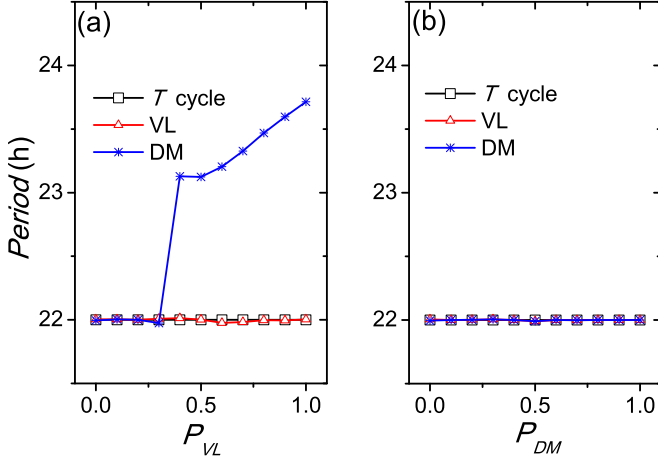


FIG. 4. Dependence of the periods of VL and DM on the ratios P_{VL} (a) and P_{DM} (b) to an external cycle of $T = 22h$ for high light intensity ($K_f = 0.02$). Entrainment to external T -cycle is lost for DM if $P_{VL} > 0.3$. The parameters for this figure are the same as for Fig. 2, except that the intrinsic periods are non-identical and the number of neurons is $N = 1000$.

are not synchronized to neither the external cycle of $T = 22h$ nor to each other, since the DM disturbs the entrainment of the VL so that the VL cannot be entrained to the external cycle. When the ratio is $0.23 < P_{DM} \leq 0.4$, we observed that the dissociation between the VL and the DM grows rapidly. The period of VL is $22h$, and is entrained to the external cycle, while the DM period is much larger than $22h$. When the ratio is $P_{DM} > 0.4$, both subgroups are entrained to the external cycle with a period of $22h$. Here the average amplitude of DM is small, thus the VL becomes dominant over the DM and entrains the DM to the external T cycle.

From Figs. 2 and 3, we observed that the increase of the ratio of damped oscillatory neurons in VL disturbs the synchronization between the subgroups and the external cycle. On the contrary, the increase of the ratio of damped oscillatory neurons in DM enhances the synchronization between the subgroups and the external cycle. These observations are confirmed by the simulation with $N = 1000$ neuronal oscillators of non-identical intrinsic periods (Figs. 4 and 5). In order to model non-identical intrinsic periods, the right hand of each equation in Eq. (1) is multiplied by a factor η_i [33]. The factor η_i satisfies a normal distribution with mean of 1 and standard deviation of 0.02. These observations can be explained by the phase response curve in the next section.

B. The phase response curve

The entrainment ability of the SCN to an external T cycle can be reflected by a phase response curve (PRC) [15]. The PRC quantifies the network's capacity to generate phase advances or delays, which is plotted as following: in constant darkness conditions, discrete light pulses (normally 1 h) are applied at different time points across the circadian cycle. The phase shifts that occurred after each applied light pulse is then plotted against circadian time. If the area covered by the phase response curve is larger, the entrainment ability of the SCN is larger.

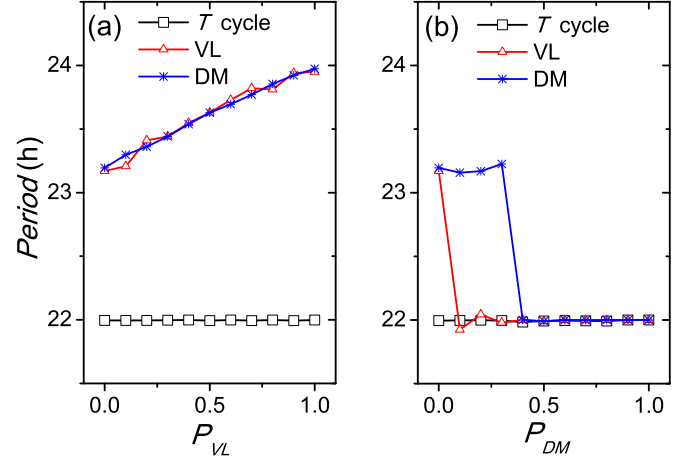


FIG. 5. Dependence of the periods of VL and DM on the ratios P_{VL} (a) and P_{DM} (b) to an external cycle of $T = 22h$ for low light intensity ($K_f = 0.008$). Entrainment to external T -cycle can only be observed for increased P_{DM} . The parameters for this figure are the same as for Fig. 3, except that the intrinsic periods are non-identical and the number of neurons is $N = 1000$.

The phase response curves for different values of the ratios are plotted in Fig. 6. In (a), with light intensity $K_f = 0.01$, the area covered by the curve for $P_{VL} = 0.3$ is smaller than for control situation where $P_{VL} = P_{DM} = 0.0$, and the curve for $P_{VL} = 0.5$ is also smaller than for $P_{VL} = 0.3$. Conversely, the area covered by the curve for $P_{DM} = 0.3$ is larger than for $P_{VL} = P_{DM} = 0.0$, and the curve for $P_{DM} = 0.5$ is also larger than for $P_{DM} = 0.3$. Consequently, with the increase of P_{VL} , the area covered by the phase response curve decreases, but with the increase of P_{DM} , the area increases. We observed similar results when the light intensity increases to $K_f = 0.02$ in (b). Additionally, the area of the phase response curve is larger for $K_f = 0.02$ than for $K_f = 0.01$ for the same value of the ratios.

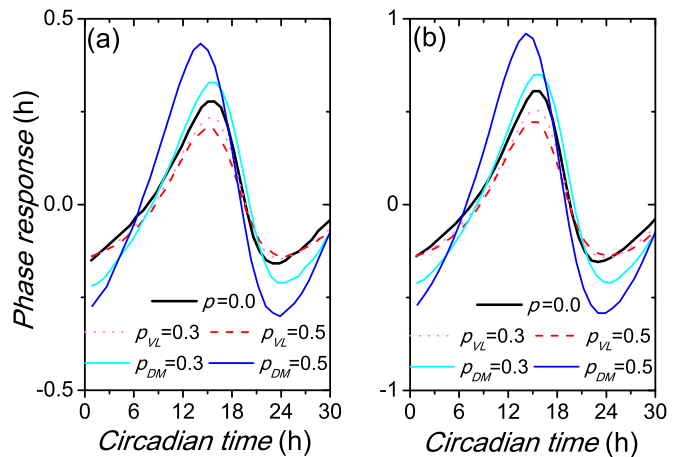


FIG. 6. Phase response curves for different ratios P_{VL} and P_{DM} for different light intensities, with a lower light intensity ($K_f = 0.01$) in (a) and a higher light intensity ($K_f = 0.02$) in (b). A larger area under the phase response curve corresponds to higher entrainment ability.

In order to examine our results for generality, a generic amplitude-phase model was examined, i.e., Poincaré model, a model which is also often used to describe the circadian neuronal oscillators (see Supplemental Material [41]). Both the new numerical results (Figures S1 and S2) and theoretical analysis confirm the findings from the numerical simulations based on the Goodwin model.

IV. CONCLUSION AND DISCUSSION

One of the main functions of the SCN is to adapt the body rhythms to the external environment. When the period of the external cycle is out of the entrainment range of the SCN, for example, if the external cycle has a period of $22h$, a dissociation between two subgroups of the SCN has been observed in rats [14]. The reason for this dissociation lies in the functional differences between the two subgroups, more specific, there is a light-information-sensitive subgroup named VL, which is entrained to the external cycle of $22h$, and there is a light-information-insensitive subgroup called DM, which remains free running [14]. In previous work [15], this dissociation is related to the heterogeneous cellular coupling. Thus far, no studies have investigated whether neuronal properties affect the dissociation, such as the neuronal amplitude and period.

A recent study of Tokuda *et al.* employs a model similar to the model described in the present study, where the SCN is represented by self-sustained oscillators as well as damped oscillators [42]. They found that in wild-type mice 36.4% of the neurons are self-sustained oscillators. In knock-out mice only damped oscillators were present. They found differences in entrainment properties between these two configurations, where they investigated the population as one whole. Here we systematically examined the influence of the ratio damped versus self-sustained oscillators on the dissociation properties of the two distinct subgroups in the SCN, being the light-sensitive VL subgroup and the light-insensitive DM subgroup, to an external cycle with a period of $22h$. In previous work, the entrainment ability has been observed to decrease with the increase of the oscillator amplitude [12]. Here we show that the effects of the ratio of damped oscillatory neurons relies on the region where these neurons are located. If the ratio of damped neurons in the VL (P_{VL}) is increased, the synchronization within the SCN is disturbed and the two subgroups dissociate for a light intensity of $K_f = 0.02$. On the contrary, the increase in the ratio of damped oscillatory neurons located in the DM (P_{DM}) shows three different behaviors with a reduced light intensity of $K_f = 0.008$. For small numbers of damped

neurons both subgroups are not entrained to the external cycle. If the ratio increases, the two subgroups dissociate, and if the ratio increases even larger, both subgroups are entrained to the external cycle.

One way to qualitatively explain these results is by looking at the strength (or weakness) of the oscillatory subgroups VL and DM (for a mathematical account of weak versus strong oscillators see Ref. [43]). What we observe in the results is that the VL becomes a stronger (weaker) oscillator when either the light intensity is higher (lower), or the number of damped neurons in the VL region is lower (higher). If the VL oscillator is strong, the VL serves as a driver for DM and is capable of synchronizing the DM to the T -cycle, provided that it is entrained to the external T -cycle. However, if the VL weakens, it loses the ability to synchronize DM, leading to a dissociation between VL and DM. On the other hand, DM exerts an influence on VL as well. If VL becomes weaker because of very low light intensities, DM becomes the stronger oscillator which is able to entrain VL to its endogenous period. In this case, DM drives VL. However, if the number of damped oscillators in DM increases, it becomes weaker as an oscillator. At some point it becomes so weak that it is not able to drive VL, and the VL will entrain to the external T cycle. At some point, DM will be driven again by VL, in lack of the dissociation between both. Thus, weakening DM as such supports synchrony between VL and DM.

Our results show the importance of damped oscillators, depending on their ratio and location, in the entrainment of different subregions in the SCN under different conditions. That a dissociation between VL and DM can occur in some species but not in others, may be related to the ratio between self-sustained oscillatory neurons and non-self-sustained oscillatory neurons. Thus we believe it is important that more research is directed at finding the ratios of the three oscillatory phenotypes of SCN neurons. From these ratios we can learn a lot about the entrainment ability of the circadian timing system under different environmental conditions. The distribution of different oscillatory types of neurons is a plausible and novel candidate mechanism to explain heterogeneity.

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