



# A relay model of human sleep stages

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**Abstract** Sleep is quantitatively described by subdividing polysomnographic records into intervals each of which is allocated to one of the just 5 all-or-nothing variables called “sleep–wake stages”. What are the mechanisms governing the establishment of such 5 relatively stable stages and rapid transitions between them? We modeled these stages as resulting from the competing interactions between the mutually inhibiting drives for wake, NREM sleep, and REM sleep that are proposed to work in a similar way as two-, two-, and one-way switch, respectively. The electromechanical counterparts of the stages were visualized as 5 variants of an electrical circuit connecting these switches with three lamps. During *W* and transient state N1, two sleep switches are switched off, and three lamps are turned off. During other transitions, one of these lamps is turning on after changing in on–off state of one or two of three switches. During transitions to N2, one (N2) lamp is turning on. During the following transitions to N3, one more (N3) lamp is turning on. During transitions from N2 to R, the N2 lamp is turning off, while the *R* lamp is turning on. Estimates of stage-specific scores on the 1st and 2nd principal components of the electroencephalographic spectra provided empirical evidence for such on–off states of these switches.

## 1 Introduction

In a simple system, state variables usually fluctuate around fixed mean values with fixed pattern of variation. In a complex system, the occasional switching usually occurs between several qualitatively different modes of behavior, even in the absence of external influences. Such transitions are typically associated with a sudden change of the properties of the fluctuating state variables [1]. A sequence of changes of sleep stages during a sleep episode can serve a typical example of this mode-switching behavior of a complex system [2]. A convenient way of quantification of such changes is offered by recordings of the multi-channel electroencephalographic (EEG) signal as a part of polysomnographic methodology [3, 4]. The development of this methodology has been initiated almost 9 decades ago by the discovery [5] that sleep in humans is not a homogeneous state of the brain. Rather, it proceeds through a series of states with distinct brain wave patterns. During such a state, the EEG signal changes fairly slowly over time, while it rapidly switches into a new pattern during transitions between these states [4, 5]. Identification of such relatively stable patterns allows an economical quantitative description of sleep by subdividing any EEG record into intervals each of which is allocated to one of the just 5 all-or-nothing variables called “sleep–wake stages”. They include wake stage (*W*), three stages of NREM (Non-Rapid-Eye-Movement) sleep (N1, N2, N3), and stage of REM (Rap-id-Eye-Movement) sleep (*R*) [3].

In the theoretic framework developed by Saper et al. [6–8] on the basis of experiments on laboratory rodents, the transitions between sleep–wake states are viewed as reflecting the mutually inhibitory interactions between the wake- and sleep-promoting neurons, and the REM-on and REM-off neurons. The job of such underlying neuronal mechanisms is to respond to slowly accumulating external and internal influences by their integration over time and conversion into sharp transitions in sleep–wake states. Such stage-stabilizing mechanisms can be viewed as a sleep–wake state switch, because, throughout the entire stage, the reciprocal promoters/inhibitors of wake, NREM sleep, and REM sleep tend to remain in the same state. A switch resists switching until sufficiently strong influences are accumulated to a critical level. Consequently, the analysis of the EEG signal reveals that a

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current EEG pattern are changing fairly slow over time, while the EEG rapidly switches into a new pattern during the transitions between stages [6–8].

The switching mechanism proposed by Saper et al. [6–8] can be modeled as a single three-position switch with its positions assigned to just three states, wake, NREM sleep or SW (Slow Wave) Sleep, and REM sleep. Unfortunately, such simple single switch model cannot be applied for the explanation of switching between human sleep stages. Unlike the rodent EEG signals, the human EEG signals usually include as many as three distinct EEG patterns of NREM sleep that are conventionally classified as sleep stages N1, N2, and N3. Therefore, it is necessary to hypothesize a more complex switching mechanism for explaining the switching between 5 different human stages, W, N1, N2, N3, and R.

Another simple model postulating the interactions between mutually inhibiting mechanisms as the basic regulators of the sleep–wake states was developed in the field of circadian biology on the basis of primate experiments [9]. Later, it was applied for explanation of the human sleep–wake cycle as the circadian rhythm controlled by the opposing drives for sleep and wake [10]. We additionally pointed at scores on the 1st and 2nd principal components of the human EEG spectrum as potential markers of states of these competing drives [11, 12]. The relationships between three drives (for wake, sleep, and REM sleep) were conceptualized as the mutually inhibiting interactions between three on–off switching mechanisms that have state-stabilizing effect on a current stage and govern its relatively rapid transition to the following stage [13, 14]. Therefore, the assumption of as many as three switching mechanisms can better account for the relative complexity of human stage classification. Since any of sleep–wake states (e.g., wake, NREM sleep, and REM sleep) and any of most probable transitions between these states can originate from the competing interactions between just three on–off switching mechanisms [14], empirical support to such three-switch conceptualization of 5 stages can be provided by the comparison of principal component scores calculated for these stages. Such approach to empirical support of the model includes the assignment of 5 stages and transitions between them to the unique combinations of two principal component scores and the unique alternations between these combinations, respectively.

In the present concept paper, we proposed a model explaining how can three underlying on–off switching mechanisms govern the maintenance of sleep–wake stages and switching in and out of them. Several variants of the formal model of 3–5 sleep–wake stages were deductively developed. These variants were visualized using their electro-mechanical counterparts. Additionally, we used the previously published results on principal component scores and rates of transitions between human sleep stages to provide empirical support for this formal model.

## 2 Methods

The proposed model belongs to the class of deductive models. Such a model is characterized by the employing “top–down” approach to research methodology, when a study begins with a hypothesis based on existing knowledge about most general properties of a system under investigation and then seeks to examine an established model empirically.

The methods, results, and illustrations of the empirical study on the principal component structure of the EEG spectra of human stages were previously reported in [15]. Therefore, the most important details of this study are included in Supplementary Materials. Data on napping attempts of 55 university students (Table 1) were used to calculate scores on the 1st and 2nd principal components (PC1 and PC2, respectively) for these 5 stages (wake or W, three stages of NREM sleep, N1, N2, N3, and REM sleep or R). The SPSS<sub>23.0</sub> statistical software package (IBM, Armonk, NY, USA) was applied for principal component analysis of the sets of 16 ln-transformed single-Hz power densities (1–16 Hz) from 5 derivations. PC1 and PC2 were averaged across 5 derivations for each stage of each of 55 study participants. These individual scores were subjected to repeated measure ANOVAs with the following post hoc pairwise comparison of pairs of scores (Table 1). The within-subjects’ measure was “PC score” (Table 1A and B) and the between-subjects’ factor was “Stage” (W, N1, N2, N3, and R).

The rates of transition from each stage to 4 other stages (Table 2) were obtained by averaging over the rates reported in 16 publications. These references are listed in Supplementary Materials. Moreover, Supplementary Materials contain the references of 15 publications reporting the locations of the competing brain networks associated with wakefulness, NREM sleep, and REM sleep (Figs. 4 and S4B).

**Table 1** Post hoc pairwise Bonferroni comparisons of 5 stages on principal component scores

A Comparison of 5 stages on the 1st PC (Principal Component) score									
Stage	Compared to 0	Mean	SEM	W	N1	N2	N3	R	n
<b>W</b>	<u>&lt; 0</u>	− 0.518	0.076						54
<b>N1</b>	<u>&lt; 0</u>	− 0.526	0.076	<i>0.01</i>					54
<b>N2</b>	<u>&gt; 0</u>	0.422	0.076	− 0.94 <sup>***</sup>	− 0.95 <sup>***</sup>				54
<b>N3</b>	<u>&gt; &gt; 0</u>	0.904	0.086	− 1.42 <sup>***</sup>	− 1.43 <sup>***</sup>	− 0.48 <sup>***</sup>			43
<b>R</b>	<u>&lt; 0</u>	− 0.526	0.169	<i>0.01</i>	<i>0.00</i>	0.95 <sup>*</sup>	1.43 <sup>***</sup>		11
B Comparison of 5 stages on the 2nd PC (Principal Component) score									
Stage	Compared to 0	Mean	SEM	W	N1	N2	N3	R	n
<b>W</b>	<u>&gt; 0</u>	0.909	0.069		1.15 <sup>***</sup>	1.24 <sup>***</sup>	1.69 <sup>***</sup>	1.37 <sup>***</sup>	54
<b>N1</b>	<u>&lt; 0</u>	− 0.242	0.069			0.09	0.54 <sup>***</sup>	0.23	54
<b>N2</b>	<u>&lt; 0</u>	− 0.336	0.069				0.45 <sup>***</sup>	0.13	54
<b>N3</b>	<u>&lt; &lt; 0</u>	− 0.783	0.078					− 0.32 <sup>*</sup>	43
<b>R</b>	<u>&lt; 0</u>	− 0.467	0.154						11

Mean and SEM: PC score and Standard Error of this Mean from the repeated measure ANOVAs of the EEG records of 60- or 90-min napping attempts of 55 university students; PC1 and PC2 of each of 55 study participants were obtained by averaging across 5 derivations and within each of the 5 sleep–wake stages; n: number of participants varies from 11 to 54 depending upon the presence of a stage in participant’s records [15]. The within-subjects’ measure was “PC score” and the between-subjects’ factor was “Stage” (wake stage **W**, three stages of NREM sleep, **N1**, **N2**, **N3**, and REM sleep, **R**). Results of post hoc pairwise Bonferroni comparisons of PC1 and PC2 scores (A and B, respectively); \* $p < 0.05$  and \*\*\* $p < 0.001$  for  $t$  are shown behind the estimates of difference between two scores. The non-significant differences (below 0.25) are printed in *italic*. Mean PC scores were classified into 4 categories: higher than 0 (PC1  $> 0$  and PC2  $> 0$ ), lower than 0 (PC1  $< 0$  and PC2  $< 0$ ), much higher than 0 (PC1  $> > 0$ ), and much lower than 0 (PC2  $< < 0$ ). Thus, there might be only three significantly different values for each PC. They can determine three positions of two-way switches representing the hypothetical drives for sleep and wake. Negative PC indicates that a switch is switched off (a drive is silenced), while positive PC indicates that a switch is switched on (a drive is activated). The 3rd value for PC1 ( $> > 0$ ) and PC2 ( $< < 0$ ) during **N3** indicates that this state is strengthened in the 3rd position of a two-way switch (i.e., the switched-on and switched-off states of the drives for sleep and wake, respectively) differ from their switched-on and switched-off states during **N2** only in strength. Note that both PC1 and PC2 for R and N1 are practically identical and they both are negative thus suggesting the switched-off state of the wake and sleep (NREM) switches. Despite the absence of direct link of the states of the REM drive to the spectral EEG markers, such two PC scores (PC1  $< 0$  and PC2  $< 0$ ) also provide important cues for the states of this drive. Given that two stages, N1 and R, are characterized by practically identical scores, the REM sleep drive can become strong (i.e., activated) only when both other drives (for sleep and wake) are weak (i.e., silenced) as indicated by PC1  $< 0$  and PC2  $< 0$ , respectively. However, when these other drives are silenced, this can be also the transitional stage between wakefulness and sleep known as N1. In terms of the switches, the REM sleep switch can be switched on only when two other switches are switched off (i.e., either R or N1). In other words, the REM sleep drive is always silenced (i.e., its switch is turned off) when, at least, one of the two other drives is activated (either PC1  $> 0$  or PC2  $> 0$ , respectively), and, in contrast, this drive can be activated (i.e., its switch is turned on) when both other drives are silenced. Overall, REM sleep (R) cannot occur when either stage N1 occurs or one of the two other switches is in switched-on state (i.e., in stages W, N2, and N3). See also Figures S3 and S4A

### 3 Results

#### 3.1 Two three-stage variants of the relay model and their electromechanical counterparts

The word “relay” is usually used to name a simple electromechanical switch that is designed to switch to close or open an electrical circuit. The relays are usually classified depending on the number of contacts and number of circuits they switch. A single pole single throw relay (one-way switch) can control one circuit and can be connected to one output (i.e., there might be two states of such a switch, only on or only off state). A single pole double throw relay (two-way switch) connects one input circuit to one of the two outputs (i.e., in such a switch, there might be either only on and two off states or only off and two on states).

Here, the term “relay” was coined to a simple deductive model of the mechanism underpinning sleep–wake stages because an electromechanical switch can serve as a technical counterpart of the model. In particular, we found that

**Table 2** Rates of 20 transitions between 5 stages

Transitions from each of 5 stages (W, N1, N2, N3, and R) to 4 other stages															
Total	From	→ to	Mean	SEM	→ to	Mean	SEM	→ to	Mean	SEM					
S	1.000	W	→ N1	0.672	0.050	→ N2	0.209	0.039	→ N3	0.010	0.004	→ R	0.108	0.034	
t	1.000	N1	→ W	0.206	0.024	→ N2	0.636	0.035	→ N3	0.013	0.007	→ R	0.145	0.024	
a	1.000	N2	→ W	0.228	0.030	→ N1	0.282	0.038	→ N3	0.334	0.022	→ R	0.155	0.018	
g	1.000	N3	→ W	0.121	0.030	→ N1	0.072	0.036	→ N2	0.797	0.043	→ R	0.011	0.006	
e	1.000	R	→ W	0.272	0.048	→ N1	0.426	0.059	→ N2	0.296	0.044	→ N3	0.007	0.006	
Sleep (NREM-REM) cycle as a sequence of 6 step-by-step transitions and jumps over the steps															
From	Next	Jump	Forward	Backward				Forward jump				Opposite jump			
Stage	Step	To	To	From	SEM	From	Mean	SEM	To	Mean	SEM	From	Mean	SEM	
W	N1	N1	N1	N1	0.050	N1	0.206	0.024	N2	0.209	0.039	N2	0.228	0.030	
W	N3	N3	N3	N2	0.035	N2	0.282	0.038	N3	0.121	0.030	N3	0.010	0.004	
N1	N2	N2	N2	N2	0.022	N2 before N3			N3	0.013	0.007	N3	0.072	0.036	
N2	N3	N3	N3	N3	0.043	N3 before N2 again			R	0.011	0.006	R	0.007	0.006	
N3	N2	R	R	R	0.018	R	0.296	0.044							
N2	R	R	R	R	0.059	N1	0.145	0.024	W	0.272	0.048	W	0.108	0.034	
R	N1	W	N1	N1	0.059	N1	0.145	0.024	W	0.272	0.048	W	0.108	0.034	

For each of 5 stages, rate = 1.000 is a sum of rates of transition from this stage to 4 other stages. Mean: Rate obtained by averaging over rates reported in 16 publications (the references to Table 2 are listed in Supplementary Materials); SEM: Standard Error of this Mean. Transitions from each of 5 stages to 4 other stages (20 in total) can be grouped into 4 categories: forward and backward step-by-step transitions in sleep (NREM-REM) cycle, and the jumps over, at least, one of such steps in forward and opposite direction. Forward and backward step-by-step transitions differ in number (6 and 4, respectively) because one of the 5 stages, N2, has two forward step-by-step transitions: first, to N3 and, second, to R after the returning to N2 from N3 (i.e., being, formally, a backward step-by-step transition, the transition from N3 back to N2 usually occurs as one of the forward step-by-step transitions in sleep cycle). See also Figs. 3B and S4A

such a switch can be easily visualized (Figs. 1 and 2). Since the sleep–wake continuum observed in the experiments on laboratory rodents is usually classified into only three stages, the rodents’ stage switching mechanism can be modeled as a single pole double throw relay (Fig. 1A). Such a relay connects one input circuit to one of the two outputs (i.e., two-way switch). Consequently, this variant of the relay model parsimoniously explains the origin of wake, NREM or SW Sleep, and REM sleep. In such a switch, the state of wake can be assigned to only off state, while the state of sleep can be assigned to two on states. Figure 1A illustrates this simplest switching mechanism modeled as a single two-way switch (either SW Sleep or REM sleep). A state of the switch is changing during a transition from one stage to one of the two other states. The result is either opening or closing of the circuit during either wakefulness or sleep, respectively. To illustrate these opening and closing, the images of two light bulbs are added in figures. They are either not illuminated or illuminated, respectively. During wake state, all connections are in dark color, sleep is switched off (i.e., the circuit is open, electricity does not flow, and none of light bulbs is illuminated). When one of the bulbs is illuminated, green color of connections around the switch indicates that sleep is switched on during a stage, i.e., the circuit is closed and electricity flows. Two switched-on states of this switch explain the division into two sleep states, SW Sleep and REM sleep. In any of these two sleep states, the circuit is closed (connections are in green color), electricity flows, and one of the bulbs is illuminated (either the bulb of SW Sleep or the bulb of REM sleep).

However, another, more complex variant of the switching mechanism can be proposed (Fig. 1B). As many as three simplest (one-way) switches can be connected in a single electrical circuit. In the only switched-off state of each of three switches, the circuit is either open (black color) or closed (green color). When all three switches are shown in switched-off state, this is the wake state (electricity does not flow and none of two bulbs is illuminated). Note that, since wake state is the opponent of two sleep states, such position of the wake switch (on the left) in this and other variants of the model is interpreted as the switch on state of the underlying drive for wake (i.e., the regulatory mechanism represented by this switch). In the only switched-off state of this wake switch, the circuit is closed (green color), electricity flows, and one of the two bulbs is illuminated (i.e., either the bulb of SW Sleep or the bulb of REM sleep).

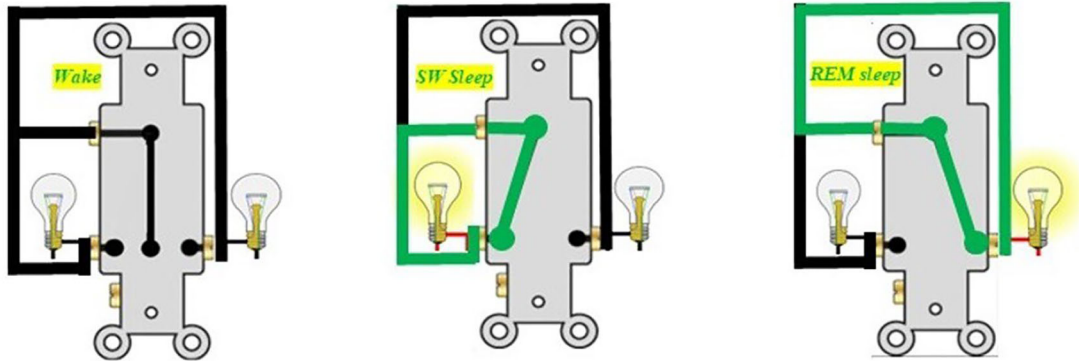
Thus, two rather simple variants of the relay model can parsimoniously explain the mechanism of stage switching in rodents. The 1st variant is visualized as a single electromechanical switch. This is a single-pole double-throw relay (in accordance with the classification of relays on the number of contacts and number of circuits they switch), i.e., a two-way switch connecting one input circuit to one of the two outputs. There is the only one off state (wake) and two off states (SW Sleep and REM sleep). Moreover, the 2nd variant of the rodents’ stage switching mechanism is visualized as three simplest (single pole single throw) switches. In this variant, three such one-way switches are included in a common electrical circuit. Each of them controls one variant of this circuit. It is connected to just one output (i.e., only on and only off states of each of these three one-way switches).

### 3.2 The 4- and 5-stage variants of the relay model and their electromechanical counterparts

Unlike NREM sleep in the rodent EEG records, NREM sleep in the human EEG records can be further divided in accord with two or, most often, three different EEG patterns known as stages N1, N2, and N3 sleep (Figs. 2 and 3). The simplest variant of the model of human stages can include only 4 stages (Figs. 2A and 3A), while the most common variant must explain all 5 stages (Figs. 2B and 3B). The one-switch variant of the rodents’ model cannot explain the switching in and out of  $\geq 4$  human sleep stages. However, another (the three-switch) variant of the rodents’ model can parsimoniously explain the switching in and out of 4 human sleep stages (when stage N3 is not included in the model). In such a 4-stage variant, NREM sleep and REM sleep are assigned to switched-on states of their own switches (Figs. 2A and 3A). In this switched-on state, the circuit is closed (green color), electricity flows, and one of the light bulbs is illuminated. Three switches are also included in the most complex variant of human sleep stages. It visualizes all 5 stages as 5 variants of an electrical circuit connecting three switches with three lamps. The lamps are turned off during *W* and they are also turned off during the transient state between wakefulness and sleep known as N1 (i.e., because the sleep switches remain in off state during both *W* and N1). During the transitions to other three stages (N2, N3, and R), one of the three lamps is turning on in response to changing in on–off state of one or two of three switches. The 1st lamp (for N2) is turning on during the transition to N2, one more lamp (for N3) is turning on during the following transition to N3 (i.e., in addition to the 1st lamp of N2 that remains turned on). This 1st (N2) lamp is turning off, while the 3rd (R) lamp is turning on during the transition from N2 to *R* (Figs. 2B and 3B).

To sum up, Figs. 1, 2, 3 illustrate 4 different variants of the deductive relay model of stages and transitions between them. Stages are visualized as the variants of an electrical circuit connecting switches with lamps. In switched-off states of sleep switches, the circuit is open (black color), electricity does not flow, and bulbs are not illuminated, while, in switched-on states of sleep switches, the circuit is closed (green color), electricity flows, and, at least, one bulb is illuminated. In three three-switch variants of the model (Figs. 1B and 2), wake state is assigned to switched-on state of the wake switch, and off states of two sleep switches. During *W* and the transient state N1, all connections are in dark color, sleep is switched off (i.e., the circuit is open, electricity does not flow, and none

**(A) One two-way switch regulating the transitions between three stages, wake, Slow Wave (SW) sleep, and REM sleep.**

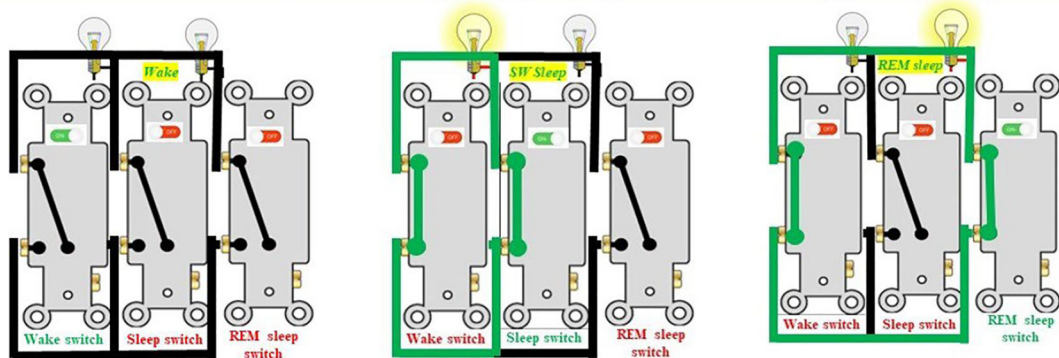


**A single switching mechanism in rodents:**

Two-way switch for wake, (NREM) sleep, and REM sleep.

Stages: *Wake*, Slow Wave (SW) Sleep and REM sleep  
(three states, wake, sleep, and REM sleep, of the single switch)

**(B) Three one-way switches regulating the transitions between three stages, wake, Slow Wave (SW) sleep, and REM sleep.**



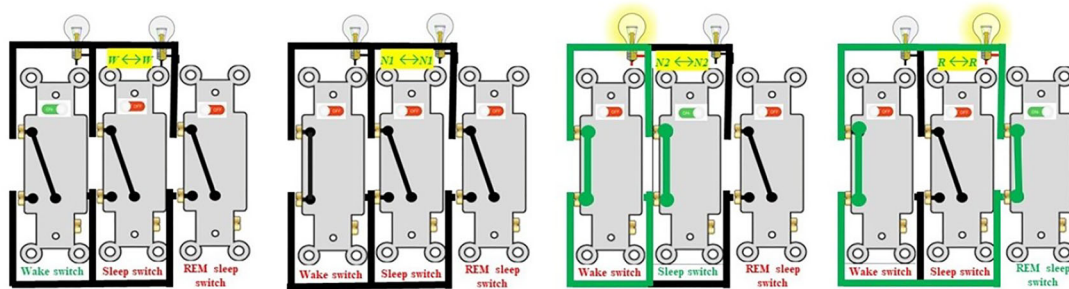
**Three switching mechanisms in rodents:**

Three one-way switches for wake, (NREM) sleep, and REM sleep.

Stages: *Wake*, Slow Wave (SW) Sleep, and REM sleep  
(combination of two - on and off - states of the separate switches for wake, sleep, and REM sleep)

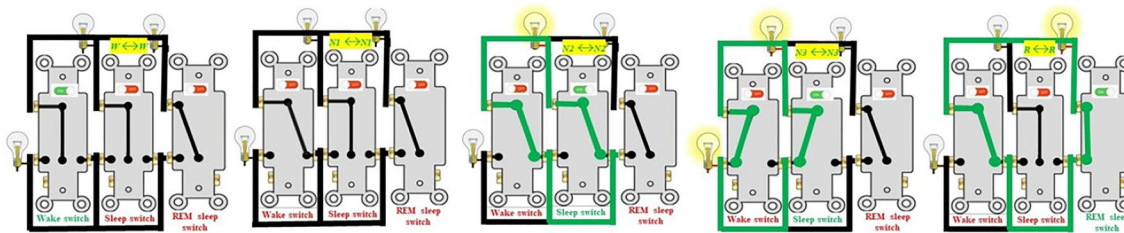
**Fig. 1** Two three-stage variants of the relay model. The proposed relay model explains three stages that are conventionally differentiated in recordings of rodent's sleep. The switching mechanism is modeled either as either the single two-way switch (A) or three one-way switches (B). In the single two-way switch, switch's state is changing during a transition from one stage to one of the two other stages. In each of three one-way switches, switch's state (either on or off) can or cannot be changing during a transition from one stage to another. Switches from left to right: wake, SW (Slow Wave) Sleep or, in another term, NREM sleep, and REM sleep. The results of changes in three states are visualized as the closing and opening the circuit during sleep and wakefulness, respectively. Such closing/opening is additionally illustrated by the images of two light bulbs that are either illuminated (yellow color) or not illuminated (gray color), respectively. Green color of connections around the switch indicates that, during a stage, sleep is switched on (i.e., the circuit is closed, electricity flows, and one of the two light bulbs is illuminated). Black color indicates wakefulness (i.e., the circuit is open, electricity does not flow, and none of two light bulbs is illuminated)

**(A) Three one-way switches regulating the transitions between 4 stages, W, N1, N2, and R.**



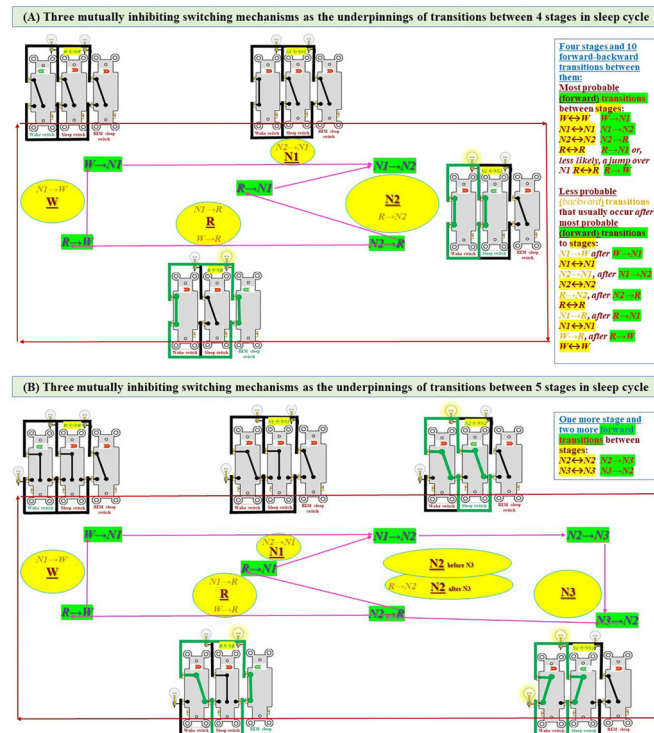
**Three (simplest) switching mechanisms in humans:**  
 Three one-way switches for wake, (NREM) sleep, and REM sleep.  
**Stages:** wake  $W \leftrightarrow W$ , two stages of NREM sleep - stage 1  $N1 \leftrightarrow N1$  and stage 2  $N2 \leftrightarrow N2$ , -  
 and REM sleep  $R \leftrightarrow R$   
 (combination of two - on and off - states of the separate switches for wake, sleep, and REM sleep)

**(B) Two two-way switches and one-way switch regulating the transitions between 5 stages, W, N1, N2, N3, and R.**



**Three (more complex) switching mechanisms in humans:**  
 Two-way switches for wake and (NREM) sleep, and one-way switch for REM sleep.  
**Stages:** wake  $W \leftrightarrow W$ , three stages of NREM sleep - stage 1  $N1 \leftrightarrow N1$ , stage 2  $N2 \leftrightarrow N2$ , and stage 3  $N3 \leftrightarrow N3$ , - and REM sleep  $R \leftrightarrow R$   
 (combination of states of the separate switches for wake (one on and two off states), sleep (two on and one off state), and REM sleep (one on and one off state))

**Fig. 2** The 4- and 5-stage variants of the relay model. A relay model explains either only 4 (A) or all 5 sleep–wake stages that are conventionally differentiated in recordings of human’s sleep (B). Three switching mechanisms are visualized as three switch images. Switches from left to right: wake, (NREM) sleep, and REM sleep. A One of the rodent’s models (Fig. 1B) resembles the 4-stage variant of the human’s model (without N3). It differs in the pattern of transition from wakefulness to NREM sleep. In the rodent’s variant, such a transition is viewed as the simultaneous switching off and on of the states of the wake and (NREM) sleep switches, respectively, during the transition from wakefulness to the only NREM sleep stage (SW Sleep). In the human’s variant, the switching off event occurs during the transition from W to the transient state N1, while the switching on event occurs later, i.e., during the following transition from N1 to N2. B Two one-way switches (for wake and NREM sleep) of the 4-stage variant of the model were replaced by two two-way switches to account for as many as 5 human stages (i.e., including N3). The transition from N2 to N3 is viewed as the simultaneous alternations between two off/on states of the wake/sleep switch. This transition strengthens sleep as illustrated by the turning on one more lamp (N3) in addition to the N2 lamp that was previously turned on during the transition from N1 to N2. In both switched-on states of the sleep switch, the circuit is closed (green color), electricity flows, and either one (N2) or two light bulbs (N2 and N3) are illuminated. See also the legend to Fig. 1



**Fig. 3** Changes in switches' states during the transitions between stages in human sleep cycle. **(A and B)**. The 4-stage variant (without N3) and the 5-stage variant (with N3). Arrows depict a sequence of most probable (forward) step-by-step transitions between either 4 **(A)** or 5 stages **(B)** of human sleep (NREM-REM) cycle. A sequence of such forward transitions is shown in green ( $W \rightarrow N1 \rightarrow N2 \rightarrow N3 \rightarrow N2$  again  $\rightarrow R \rightarrow N1$  or  $W$  again). Backward (less probable) transitions are shown within yellow ellipses of 5 stages, i.e.,  $N1 \rightarrow W$ ,  $N2 \rightarrow N1$ ,  $R \rightarrow N1$ . Three switching mechanisms are illustrated as three switch images. Switches from left to right: wake, (NREM) sleep, and REM sleep. They are connected in an electrical circuit. Step-by-step changes in state of one or, less likely, two switches during a forward transition from one stage to another are illustrated as the closing and opening of the circuit during sleep and wakefulness, respectively. The images of three light bulbs that are either illuminated or not illuminated are added. Green color of connections around switches indicates that sleep is switched on during a stage (i.e., the circuit is closed, electricity flows, and one or two bulbs are illuminated). When all connections are in dark color, sleep is switched off during stages N2, N3, and R (i.e., the circuit is open, electricity does not flow, and none of light bulbs is illuminated). Note that, to illustrate the mutual inhibition of wake and sleep switches, the positions of switched-on and switched-off states of the two-way wake switch (the left switch) oppose the same positions of switched-on and switched-off states of the (NREM) sleep switch (the central switch). In the only switched-on state of the wake switch, the circuit is open (black color), electricity does not flow, and the bulbs are not illuminated, while, two switched-off states of this switch can suggest that the circuit is closed (green color), electricity flows, and either one or two light bulbs are illuminated (in either N2 or N3, respectively). The opposite is true for the positions of switched-off and switched-on states of the two-way (NREM) sleep switch. Its only switched-off state has the same location as the only switched-on state of the wake switch (i.e., the open circuit is shown in black color, electricity does not flow, and all light bulbs are not illuminated), while, in two switched-on states, the circuit is closed (green color), electricity flows, and either one or two light bulbs are illuminated (either the N2 bulb or both N2 and N3 bulbs, respectively). Simultaneous illumination of two light bulbs in N3 indicates that the states of two two-way switches (switched on and switched off, respectively) were strengthened during the transition from N2 to N3. The 3rd (REM sleep) switching mechanism (the right one-way switch) has the only switched-on and the only switched-off state, i.e., either the circuit is closed (green color), electricity flows, and the R bulb is illuminated or the open circuit is shown in black color, electricity does not flow, and the R bulb is not illuminated (i.e., during 4 other than R stages. See also Figs. S3 and S4A for more details

of light bulbs is illuminated). During any other (definitely sleep) stage, some of connections are in green color, and sleep is switched on (i.e., the circuit is closed, electricity flows, and, at least, one light bulb is illuminated).

### 3.3 Empirical support from results of principal component scoring of the EEG spectrum

The deductive model introduced in the previous subsections is based on existing knowledge about most general properties of sleep stages and it definitely seeks for its empirical examination. Therefore, the question arises: what kind of empirical evidence can be provided in support of this deductive model? In this and the following



subsection we show that such empirical evidence can be obtained from the results on principal component (PC) scores of the EEG spectrum (this subsection) and, additionally, from the rates of transitions between stages (the next subsection). Since each of three stages of human NREM sleep has unique EEG pattern, the differences in PC scores for such stages can explain the differences between human sleep–wake states in terms of the competing interactions between three on–off switching mechanisms. Table 1 contains the results of statistical comparison of 5 stages on scores on the 1st and 2nd Principal Components of the EEG spectrum (PC1 and PC2, respectively), and Fig. S3 in Supplementary Materials illustrates their links to the visualization of 5 stages.

PC1 score for three stages, *W*, *N1*, and *R*, is significantly lower than zero ( $< 0$ ), and it is significantly ( $p < 0.001$ ) lower than PC1 score for *N2* ( $> 0$ ), that, in turn, is significantly ( $p < 0.001$ ) lower than PC1 score for *N3* ( $> > 0$ ). In contrast, PC2 score for *W* is significantly higher than zero ( $> 0$ ), and it is significantly ( $p < 0.001$ ) higher than PC2 score for *N1*, *N2*, and *R* ( $< 0$ ), that, in turn, is significantly ( $p < 0.001$ ) higher than PC2 score for *N3* ( $< < 0$ ). Such relationships between scores calculated for these stages were interpreted as three possible states of each of two hypothetical drives, for sleep and wake. The sleep drive is weak (i.e., silenced) in *W*, *N1*, and *R*, but it is strong (i.e., activated) in *N2* to be further strengthened in *N3*. In contrast, the wake drive is strong (i.e., activated) in *W*, but it is weak (i.e., silenced) in *N1*, *N2*, and *R* to be further weakened in *N3* (Table 1 and Figs. S3 and S4A).

In the terminology of the three switching mechanisms, PC scores can be interpreted as the indicators of on–off states of the switching mechanisms. Namely, the (NREM) sleep switch can be turned off (position 1), turned on (position 2), and turned on further (position 3), while, in contrast, the wake switch can be turned on (position 1), turned off (position 2), and turned off further (position 3), respectively. Therefore, the two drives—for wake and (NREM) sleep—can be viewed as two-way switches. Significant differences between stages in PC scores suggested the way of their classification into three groups. PC1 score, a representative of the drive for sleep, can be either low ( $< 0$ ) or high ( $> 0$ ) or very high ( $> > 0$ ). PC2 score, a representative of the drive for wake, can be either high ( $> 0$ ) or low ( $< 0$ ) or very low ( $< < 0$ ). Therefore, these significant differences in scores can be interpreted as the following switching events. Sleep drive can be turned off (PC1  $< 0$ ), turned on (PC1  $> 0$ ), and further on (PC1  $> > 0$ ). The competing wake drive can be turned on (PC2  $> 0$ ), turned off (PC2  $< 0$ ), and further off (PC2  $< < 0$ ). Since stages *R* and *N1* are characterized by the same combination of scores (PC1  $< 0$  and PC2  $< 0$ ), the 3rd (REM sleep) drive can be viewed as one-way switch with only switched-on and only switched-off state during *R* and *N1*, respectively. This switch also remains in the same switched-off state during *W*, *N2*, and *N3* (Fig. S3).

Figure S4A in Supplementary Materials summarizes such associations of PC scores with 5 stages and most probable transitions between these stages governed by just three switching mechanisms. In this figure and Figs. 2B, 3B, and S3, such three switches are included in a common electrical circuit, and, depending upon PC score, one of the variants of this circuit (i.e., a stage) is maintained. One or two of three lamps can be, depending upon PC score for a stage, turned either on or off by changing in on–off state of either one or two of these three switches. Namely, during *W* in the very beginning of sleep (NREM-REM) cycle, the wake switch is turned on. This is indicated by PC2  $> 0$ . In contrast, the sleep switch is turned off during this stage. This is indicated by PC1  $< 0$ . The REM switch is also turned off, because one of the PC scores is not lower than zero. Since PC2  $> 0$ , this is wake state. Such positions of three switches prevent any of the lamps from turning on. During the transition from *W* to *N1*, a state of only one switch, the wake switch, is changing from on to off. This is indicated by the change of PC2 from  $> 0$  to  $< 0$ . In contrast, a state of the (NREM) sleep switch is not changing during this transition (PC1 remains  $< 0$ ). Therefore, this stage is viewed as a transitional state between wakefulness and sleep. True sleep state is not achieved during this stage, and, therefore, this state is similar to wake state in that none of the lamps is illuminated.

During three other stages (*N2*, *N3*, and *R*), at least, one of the three lamps is turned on (i.e., this implies that true sleep is maintained). These stages differ one from another in combination of turned on and off lamps (Figs. 3, S3, and S4A). Namely, the only change occurring during the transition from *N1* to *N2* is the change in state of the (NREM) sleep switch from switched off to switched on. This transition is indicated by the change of PC1 score from  $< 0$  to  $> 0$ . Given that a state of the wake switch remains the same as it was in the previous stage, *N1* (PC2  $< 0$ ), such combinations of states of the sleep and wake switches (switched on and switched off, respectively) provides a possibility turning on of one of the three lamps (i.e., this is the *N2* lamp, one of the two lamps of NREM sleep stages *N2* and *N3*).

During the following transition from *N2* to *N3*, another lamp is additionally turned on. This can be explained by the following changes in scores and switching states. One of switched-off states of the wake switch (i.e., a two-way switch) changes to another switched-off state (from PC2  $< 0$  to PC2  $< < 0$ ). The sleep switch (i.e., another two-way switch) changes one of its switched-on states to another switched-on state (from PC1  $> 0$  to PC1  $> > 0$ ). Such configuration of electrical circuit is stronger than the previous configuration (in *N2*), because it does not allow further transition from *N3* directly to *R* without the returning back from *N3* to *N2*. Therefore, further strengthening on and weakening off (of the sleep drive and drive, respectively) is visualized by two turned on lamps (both the *N2* and *N3* lamps). Due to such strengthening of the states of the drives, the return from *N3* to *N2* is almost always precedes the following transition to *R*. In terms of PC scores, such strengthening is associated with,

first, the change from  $PC2 < 0$  to  $PC2 < 0$  simultaneously with the change from  $PC1 > 0$  to  $PC1 > 0$  and, second, the change from  $PC2 > 0$  to  $PC2 < 0$  and simultaneously with the change from  $PC1 > 0$  to  $PC1 < 0$ .

Since the final combination of scores achieved after these transitions is  $PC1 < 0$  and  $PC2 < 0$ , it suggests the maintenance of the switched-off states of both drives for sleep and wake, respectively. Switching off (i.e., further weakening) the drives for sleep and wake allows the transition to the last stage, R. This is the change from switched-off state of the REM sleep drive (i.e., one-way switch) to its switched-on state (i.e., its activation). Consequently, the last of two lamps of NREM sleep is tuning off, while the only lamp of REM sleep is turning on during the transition from N2 to R.

The loop of sleep (NREM–REM) cycle is usually closed by the transitions from the last cycle's stage R to either N1 or, less likely, directly to W. The only the lamp representing REM sleep is turning off during the most likely transition from R (i.e., from R to N1). This transition suggests that the wake and (NREM) sleep switches remain in their switched-off states (i.e., the drives for sleep and wake are silenced as indicated by  $PC1 < 0$  and  $PC2 < 0$ , respectively). A less probable transition from R directly to W requires an additional change of off-state of the wake drive, from  $PC2 < 0$  to  $PC2 > 0$ . Therefore, the R and N2 lamps are simultaneously turning off and on, respectively, during this transition (Figs. 3B, S3, and S4A).

### 3.4 Empirical support from results on rates of 20 transitions between 5 stages

Additionally, the relay model can be supported by empirical evidence provided by the results of comparison of the rates of 20 (all possible) transitions between 5 stages. Table 2 shows that 5 stages profoundly differ one from another in these rates. Of 20 transitions, the most probable are the transitions to the following stage in sleep (NREM-REM) cycle ( $W \rightarrow N1 \rightarrow N2 \rightarrow N3 \rightarrow N2$  again  $\rightarrow R \rightarrow N1$ ). Since sleep proceeds in this direction (forward transitions), the transitions in the opposite direction (backward transitions) have somewhat lower rates. In terms of PC scores, such forward and backward transitions are usually associated with just one step change in just one of the two scores (Tables 1 and 3, and Figs. S3 and S4A). For instance, Tables 2 and 3 illustrate the typical example of such pattern of change of one of the two scores during a switch in and out of the transient state between wakefulness and sleep, N1. The wake drive is silencing ( $PC2$  is changing from  $> 0$  to  $< 0$ ) during the transition from W to N1, but the sleep drive is also remaining silenced ( $PC1 < 0$  for both W and N1). During the following transition from N1 to N2, the wake drive remains silenced ( $PC2 < 0$ ), thus allowing the sleep drive to be activated during this rather than previous transition ( $PC1$  changes from  $< 0$  to  $> 0$  after the  $PC2$  change from  $> 0$  to  $< 0$ ).

As for the transitions that are not classified as forward or backward transitions (Table 2), they occur rare, very rare, and almost never (e.g.,  $N3 \rightarrow R$  and  $R \rightarrow N3$ ). Such a jump over one or more consecutive steps in a sequence of stages of sleep cycle requires simultaneous changes of, at least, two scores (e.g., for a jump from N3 to R,  $PC1$  must be changed from  $> 0$  to  $< 0$  and  $PC2$  must be changed from  $< 0$  to  $> 0$ ).

Thus, empirical results on scores on two largest principal components of the EEG spectrum calculated for each of 5 stages (Table 1) and on the rates of 20 transitions between these 5 stages (Table 2) supported the present relay model of three switching mechanisms controlling 5 stages and transitions between them during sleep cycle (Table 3 and Figs. 2B, 3B, S3, and S4A). They provided empirical evidence for a possibility to visualize these switching mechanisms as three switch images representing the competing interactions between the drives for wake, (NREM) sleep, and REM sleep. In particular, they supported the assumption of the 5-stage variant of the model that two of three drives—for wake and (NREM) sleep—can be visualized as two-way rather than one-way switches (Figs. 2B, 3B, S3, and S4A). In two switched-on states of the (NREM) switch, the circuit is closed (green color), electricity flows, and either one or two light bulbs are illuminated (either N2 or N3, respectively). Simultaneous illumination of two light bulbs in N3 indicates that the states of two two-way switches (switched-on state of the sleep switch and switched-off state of the wake switch, respectively) are strengthened during the transition from N2 to N3 (Table 3 and Figs. 2B, 3B, S3, and S4A). Moreover, they supported the assumption of any of two human variants of the model that N1 is a transient state required for the switching off the wake switch prior to the switching on the (NREM) sleep switch (Figs. 2, 3, S3, and S4A).

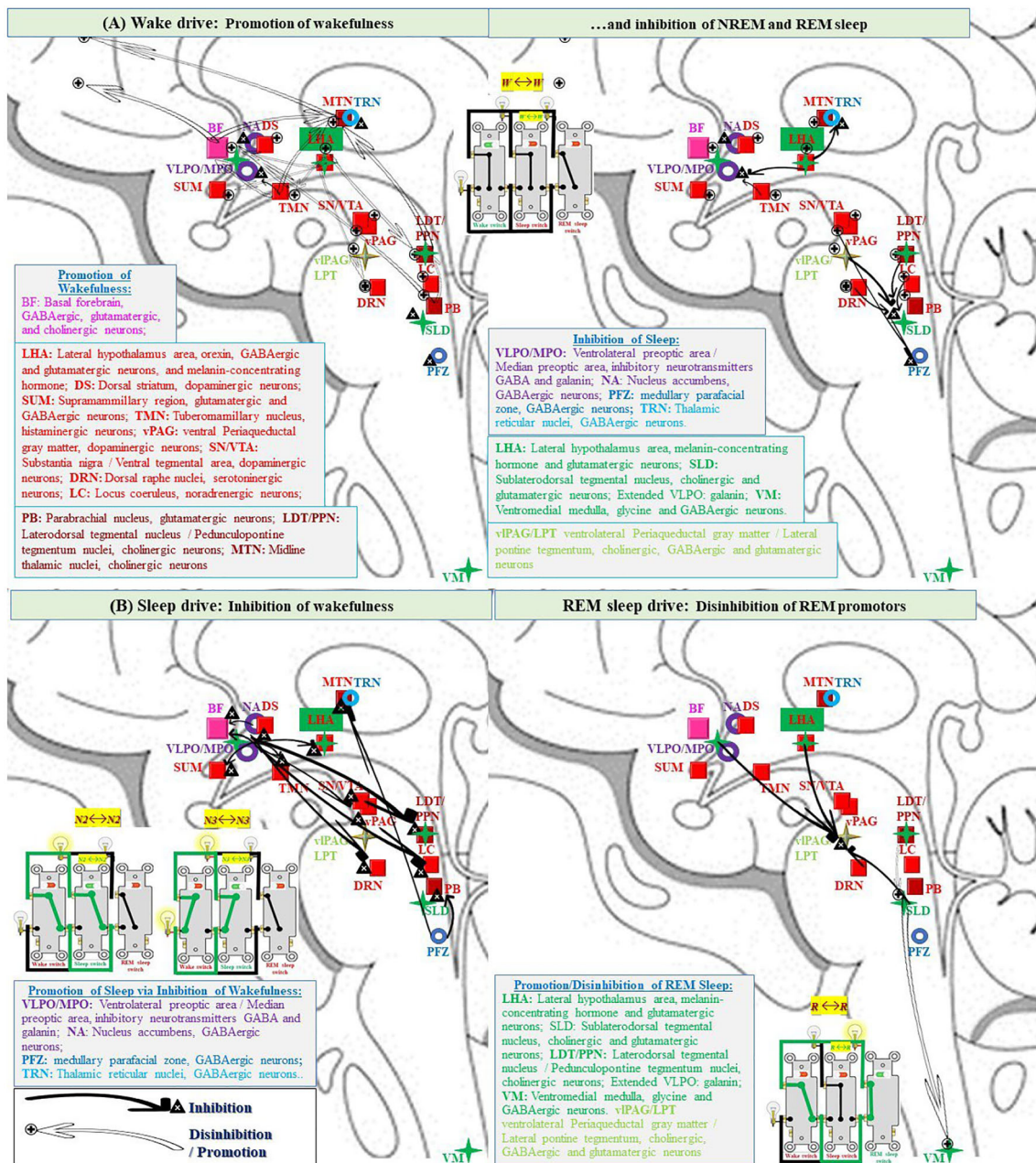
Finally, Figs. 4 and S4B illustrate the relationship of the 5-stage relay model with the brain networks regulating sleep–wake states that were previously identified in the experiments on rodents [6–8]. It seems that these networks seem to reach equilibrium only during the transitional state N1 (Fig. S4B). Figure 4A illustrates how can the drive for wake promote wakefulness (left side) and inhibit NREM and REM sleep (right side). Figure 4B (right side) illustrates how can the drive for REM sleep inhibit NREM sleep in addition to inhibited promoters of wake state (i.e., during the transition to previous stages N1 and N2). Unfortunately, it is impossible to illustrate the relationships of each of 5 stages (Figs. 2B, 3B, S3, and S4A) with such relationships between sleep–wake regulating brain networks due to the lack of division of sleep of rodent species into three NREM sleep stages (N1, N2, and N3). Therefore, the networks of human stages N2 and N3 are not separated one from another in Fig. 4B (left side).

To sum up, empirical data can be provided to support the relay model visualizing the work of three switching mechanisms underpinning 5 sleep–wake stages and transitions between them. These three switches connected in

**Table 3** Combinations of on–off states of three switches in the 5-stage relay model

Stage or transition	Compared to 0		Switch is turned/turning on or off during a stage/transition		
	PC2	PC1	Wake (PC2)	(NREM) sleep (PC1)	REM sleep
<b><u>W</u></b>	<b><u>&gt; 0</u></b>	<b><u>&lt; 0</u></b>	<b><u>on</u></b>	<b><u>off</u></b>	<b><u>off</u></b>
<b><i>W</i> → <i>N1</i></b>	<b><i>→ &lt; 0</i></b>	<b><i>&lt; 0</i></b>	<b><i>→ off</i></b>	<b><i>remains off</i></b>	<b><i>remains off</i></b>
<i>N1</i> → <i>W</i>	<i>→ &gt; 0</i>	<i>&lt; 0</i>	<i>→ on</i>	<i>remains off</i>	<i>remains off</i>
<b><u>N1</u></b>	<b><u>&lt; 0</u></b>	<b><u>&lt; 0</u></b>	<b><u>off</u></b>	<b><u>remains off</u></b>	<b><u>remains off</u></b>
<b><i>N1</i> → <i>N2</i></b>	<b><i>&lt; 0</i></b>	<b><i>→ &gt; 0</i></b>	<b><i>remains off</i></b>	<b><i>→ on</i></b>	<b><i>remains off</i></b>
<i>N2</i> → <i>N1</i>	<i>&lt; 0</i>	<i>→ &lt; 0</i>	<i>remains off</i>	<i>→ off</i>	<i>remains off</i>
<b><u>N2</u></b>	<b><u>&lt; 0</u></b>	<b><u>&gt; 0</u></b>	<b><u>remains off</u></b>	<b><u>on</u></b>	<b><u>remains off</u></b>
<b><i>N2</i> → <i>N3</i></b>	<b><i>→ &lt; &lt; 0</i></b>	<b><i>→ &gt; &gt; 0</i></b>	<b><i>→ off strengthening</i></b>	<b><i>→ on strengthening</i></b>	<b><i>remains off</i></b>
<b><i>N3</i> → <i>N2</i></b>	<b><i>→ &lt; 0</i></b>	<b><i>→ &gt; 0</i></b>	<b><i>→ off</i></b>	<b><i>→ on</i></b>	<b><i>remains off</i></b>
<b><u>N3</u></b>	<b><u>&lt; &lt; 0</u></b>	<b><u>&gt; &gt; 0</u></b>	<b><u>off strengthened</u></b>	<b><u>on strengthened</u></b>	<b><u>remains off</u></b>
<b><i>N2</i> → <i>R</i></b>	<b><i>&lt; 0</i></b>	<b><i>→ &lt; 0</i></b>	<b><i>remains off</i></b>	<b><i>→ off</i></b>	<b><i>→ on</i></b>
<i>R</i> → <i>N2</i>	<i>&lt; 0</i>	<i>→ &gt; 0</i>	<i>remains off</i>	<i>→ on</i>	<i>→ off</i>
<b><u>R</u></b>	<b><u>&lt; 0</u></b>	<b><u>&lt; 0</u></b>	<b><u>remains off</u></b>	<b><u>remains off</u></b>	<b><u>on</u></b>
<b><i>R</i> → <i>N1</i></b>	<b><i>&lt; 0</i></b>	<b><i>&lt; 0</i></b>	<b><i>remains off</i></b>	<b><i>remains off</i></b>	<b><i>→ off</i></b>
<i>N1</i> → <i>R</i>	<i>&lt; 0</i>	<i>&lt; 0</i>	<i>remains off</i>	<i>remains off</i>	<i>→ on</i>
<i>R</i> → <i>W</i>	<i>→ &gt; 0</i>	<i>&lt; 0</i>	<i>→ on</i>	<i>remains off</i>	<i>→ off</i>
<i>W</i> → <i>R</i>	<i>→ &lt; 0</i>	<i>&lt; 0</i>	<i>→ off</i>	<i>remains off</i>	<i>→ on</i>
<i>W</i> → <i>N2</i>	<i>→ &lt; 0</i>	<i>→ &gt; 0</i>	<i>→ off</i>	<i>→ on</i>	<i>remains off</i>
<i>N2</i> → <i>W</i>	<i>→ &gt; 0</i>	<i>→ &lt; 0</i>	<i>→ on</i>	<i>→ off</i>	<i>remains off</i>
<i>N1</i> → <i>N3</i>	<i>→ &lt; &lt; 0</i>	<i>→ &gt; &gt; 0</i>	<i>→ off strengthening</i>	<i>→ twice on strengthening</i>	<i>remains off</i>
<i>N3</i> → <i>N1</i>	<i>→ &lt; 0</i>	<i>→ &lt; 0</i>	<i>→ off</i>	<i>→ on off</i>	<i>remains off</i>
<i>N3</i> → <i>R</i>	<i>→ &lt; 0</i>	<i>→ &lt; 0</i>	<i>→ off</i>	<i>→ on off</i>	<i>→ on</i>
<i>R</i> → <i>N3</i>	<i>→ &lt; &lt; 0</i>	<i>→ &gt; 0</i>	<i>→ off strengthening</i>	<i>→ twice on strengthening</i>	<i>→ off</i>
<i>N3</i> → <i>W</i>	<i>→ &gt; 0</i>	<i>→ &lt; 0</i>	<i>→ off on</i>	<i>→ on off</i>	<i>remains off</i>
<i>W</i> → <i>N3</i>	<i>→ &lt; &lt; 0</i>	<i>→ &gt; &gt; 0</i>	<i>→ twice off strengthening</i>	<i>→ twice on strengthening</i>	<i>remains off</i>

Upper part of the table. **Stage** is printed in **bold underlined**, and 10 **forward** and **backward** transitions are printed in **bold italic** and *italic*, respectively. Most usually, total number of **forward** and **backward** on–off switching events during a transition is not larger than just one or, less often, just two. Two Principal Component (PC) scores, PC1 and PC2, are the spectral EEG markers of the sleep and wake drives, respectively (i.e., the EEG indicators of two two-way switching mechanisms). They have a mutually inhibitory relationship because they are opposing one another in their “struggle” for maintaining a current stage. During a stage, any switching mechanism can be in switched on or switched-off state. To maintain the following stage, one or, less likely, two states can be changed during a relatively rapid transition to either next or previous stage (i.e., either **forward** or **backward** transition, respectively). The rates of forward step-by-step transitions are higher than the rates of transitions of three other categories due to a higher probability of the most typical sequence of transitions in sleep cycle ( $W \rightarrow N1 \rightarrow N2 \rightarrow N3 \rightarrow N2 \text{ again} \rightarrow R \rightarrow N1$ ). The transition from N2 to N3 occurs under high sleep pressure. Compared to N2, switch on and switched-off states are additionally strengthened in N3 to prevent the change from switched off to switched-on state of the 3rd REM sleep (one-way) switching mechanism. Two two-way switches (for wake and sleep) are gradually weakening during each sleep cycle. Therefore, a probability of switching from NREM to REM sleep is increasing due to the dropping of sleep pressure during the previous bouts of N2, N3, and again N2. Since *R* does not differ from *N1* in any of PC scores (both  $PC < 0$ ), these two stages require the silencing of both two-way switching mechanisms. Therefore, they differ only in the state of the 3rd switching mechanism that is switched on and off during *R* and *N1*, respectively. Lower part of the table. A jump over most probable (step-by-step) transitions occurs much rare than the step-by-step (forward–backward) transitions shown in the upper part. Only two stages, *W* and *N3*, are involved in 10 such jumps that are rare, because, to jump over the next or previous stage, the states of two or even all three switching mechanisms must be simultaneously changed. See also Tables 1 and 2, and Figures S3 and S4A



**Fig. 4** Association of stages with promoters/inhibitors of wakefulness, two stages of NREM sleep, and REM sleep. **A** The drive for wake inhibits NREM and REM sleep (right side), thus promoting wake state (left side). **B** To promote NREM sleep (either N2 or N3), the drive for sleep inhibits wakefulness (left side). To promote REM sleep (R), the drive for REM sleep inhibits NREM sleep and wakefulness (right side). Since these sleep–wake regulating structures and areas were identified in experiments on laboratory rodents, NREM sleep cannot be divided into three stages, N1, N2, and N3. In the figure, the circuits for N2 and N3 cannot be separated one from another, and, therefore. These two human stages are assigned to the same brain image (**B**, left). See also Fig. S4B and references to these Figures listed in Supplementary Materials

an electrical circuit are illustrated in Figs. 3B, S3, and S4A. Results of changes in state of one or, less likely, two switches during a forward transition from one stage to another are visualized as the closing and opening of the circuit during sleep and wakefulness, respectively. The images of three light bulbs that are either illuminated or not illuminated, respectively, illustrate the states of true sleep, N2, N3, *R* (illuminated) and wake, *W*, or the transient state between wake and sleep, N1 (not illuminated). Green color of connections around three switches indicates that such true sleep is switched on during three sleep stages. The circuit is closed, electricity flows, and one or two of three light bulbs are illuminated. When all connections are in dark color, sleep is switched off during two other stages. The circuit is open, electricity does not flow, and none of light bulbs is illuminated. In

the only switched-on state of the wake switch (the left switch), the circuit is open (black color), electricity does not flow, and the bulbs are not illuminated, while, in two switched-off states of this switch, the circuit is closed (green color), electricity flows, and one or two light bulbs are illuminated. The opposite is true for the positions of switched off and switched-on states of the two-way (NREM) sleep switch (the central switch). Simultaneous illumination of two light bulbs indicates that the states of two two-way switching mechanisms (switched on and switched off, respectively) are strengthened during the transition from N2 to N3. The 3rd one-way (REM sleep) switching mechanism (the right switch) has the only switched-on state and the only switched-off state. In the on state, the circuit is closed (green color), electricity flows, and the light bulb of *R* stage is illuminated, while, in the off state, the open circuit is shown in black color, electricity does not flow, and the light bulb for this stage is not illuminated during other than *R* stages. The transitional state N1 is characterized by switched-off states of all three switches.

## 4 Discussion

The present relay model is an attempt to answer to the question about the pattern of competing interaction between mechanisms of sleep–wake regulation underlying the observed features of the human EEG signals that can be parsimoniously described as intervals ( $\geq 30$  s) of 5 relatively stable stages divided by rather rapid ( $< 30$  s) transitions between them. To our knowledge, this is the first attempt to develop a model visualizing the mechanisms governing 5 human sleep–wake stages and switching in and out of them in course of each sleep (NREM-REM) cycle. We started the modeling exercising with the consideration of two variants of relay model of the transitions between 3 rodents' stages. The first variant is a single on–off switching mechanism (two-way switch) that seems to be sufficient only for explaining three sleep–wake states distinguished in the rodent experiments, i.e., when wake, (NREM) SW sleep, and REM sleep can be assigned to only one off-state and two on-states, respectively, of such a two-way switch. In other words, we showed that the switching mechanism proposed from the experiments with laboratory rodents [6–8] can be visualized as a single pole double throw relay connecting one input circuit to one of the two outputs. Moreover, we also showed a plausibility of a three-switch model consisting of three simplest on–off switching mechanisms (one-way switches). To apply a relay model to the human stages, we proposed two variants consisting of no more than three on–off switching mechanisms. They explain the maintenance and switching in and out of either 4 or 5 sleep–wake stages. The most complex of these two variants conceptualizes 5 human sleep–wake stages in terms of two two-way switches (the regulators of wake and NREM sleep) and one-way switch (the regulator of REM sleep).

To provide empirical evidence for this 5-stage variant of relay model, data on scores on the 1st and 2nd principal components of the EEG spectrum and data on the rates of 20 transitions between 5 stages were used to identify a typical sequence of changes in the competing interactions between such three on–off switching mechanisms, the representatives of the mutually inhibiting drives for wake, (NREM) sleep, and REM sleep. We visualized these three drives as two-, two-, and one-way switches, respectively, connected in an electrical circuit. The electromechanical counterparts of 5 stages are 5 variants of this electrical circuit with three switches and three lamps. The lamps are turned off during *W* and they remain in turned-off state during the transitional state N1, because, irrespective of the state of the wake switch, the sleep switches are in switched-off state both during *W* and N1. During the transitions to three other stages, one of the three lamps is turning on in response to changes in on–off state of one or two of the three switches. The 1st (N2) lamp is turning on during the transitions to N2, the 2nd (N3) lamp is additionally turning on during the following transitions from N2 to N3. This lamp is turning off during the return to N2 prior to the following entering to *R* (i.e., during the transitions from N2 to *R*) when the 1st (N2) lamp is turning off, while the 3rd (*R*) lamp is turning on. Since this variant of the model is not as simple as those proposed for the rodent sleep, future studies aimed on testing, validation, and application of this variant might, in particular, address the question of whether such 5-stage model cannot be further reduced (i.e., to even more parsimonious variant).

Since the visualization of as many as 5 human sleep–wake stages requires more complex variants than the variants proposed for the model of rodents' stages, there exists a problem of validation of such 5-stage model against data on sleep–wake regulating brain networks identified in the rodent experiments. Therefore, our results on development of the 5-stage model require validation against empirical human data rather than against data of rodent brain studies cited here. It seems that only human data can provide deeper understanding of the relationships of 5 stages with the states of sleep–wake regulating brain networks.

There exist a possibility to map the transitions between NREM sleep stages in the human brain using functional magnetic resonance imaging (fMRI) by relating the changes in regional cerebral blood flow (rCBF) to the transitions between stages N1, N2, and N3. It is well established that, during NREM sleep, brain activity is organized by two spontaneous coalescent cerebral rhythms: spindles and slow waves in N2 and N3, respectively. Therefore, fMRI offers the opportunity to study the brain structures, at the cortical and subcortical levels (not easily accessible through standard scalp EEG recordings), that participate in the generation or propagation of these two rhythms.

Recent research using mainly EEG/fMRI had successfully characterized the neural correlates of these stages of sleep [16, 17]. For instance, negative correlations were found between slow wave activity and rCBF in the ventromedial prefrontal cortex (vMPFC), basal forebrain, striatum (putamen), insula, posterior cingulate gyrus, and precuneus, but, in contrast, no significant correlation was found in the thalamus. Importantly, an association between slow waves and vMPFC suggests its key role in the generation of these waves. However, the corresponding underlying mechanisms remain unclear [16, 17]. On the other hand, these studies confirmed animal data suggesting an involvement of the thalamus rather than other brain areas in spindle generation. The problem with this only location showing significant correlation with sleep spindles is in the lack of possibility of precise topographical identification of specific nuclei within the thalamic substructure [16, 17]. Therefore, further EEG/fMRI studies in this direction are required to provide deeper insights into location of brain areas involved in generation of three distinct NREM sleep stages. At least, the proposed relay model of 5 human stages highlighted a need for future research aimed on extension of the division into only three stages based on results of rodent experiments to the division into as many as 5 stages based on human EEG/fMRI results.

The proposed model relies on two previously suggested approaches to the conceptualization of sleep–wake regulation mechanisms. One is based on the rodents' sleep experiments [6–8] and another was developed in studies of the EEG markers of the drives underlying the circadian sleep–wake cycle in humans [11–14]. The proposed model can help to gain deeper knowledge about the origin of 5 human sleep–wake stages from the competing interactions between the promoters and inhibitors of the states of wakefulness, NREM sleep, and REM sleep. The relay model can be also applied for development of models of regulatory processes underpinning sleep (NREM–REM) cyclicality. Since our model is purposed on visualization of three switching mechanisms responsible for the maintaining 5 relatively stable sleep–wake stages and relatively rapid transitions between them, it does not directly address the question of how can the underlying mechanisms organize each all-night human sleep episode into a sequence of approximately 90-min cycles. Several models of the regulatory processes underlying these cycles were previously proposed [18–24]. In particular, some of these models suggested the necessity to account for mutually inhibitory interactions between REM-on and REM-off neural populations and low modulations in the neural excitability reflecting the homeostatic need for REM sleep [18, 20]. The next steps of further development of the relay model can be aimed on testing possibility of its integration into one of such models of the processes responsible for generating approximately 90-min cyclicality of human sleep.

Overall, further theoretical and empirical studies are necessary to address several questions raised by the proposed 5-stage model.

## 5 Conclusion

If the changes of a current EEG pattern are fairly slow over time, the EEG rapidly switches into a new pattern during the transitions between stages. Since the reciprocal promoters/inhibitors of wake, (NREM) sleep, and REM sleep tend to remain in the same state throughout the entire stage, such stage-stabilizing mechanisms can be viewed as one or more sleep–wake state switchers that resist switching until sufficiently strong influences are accumulated to a critical level. Here, we introduced a model visualizing 5 human sleep stages as 5 variants of an electrical circuit connecting three switches, the representatives of wake, sleep and REM sleep drives, with three lamps that are turned on during the three truly sleep states, N2, N3, and R. All lamps are turned off during *W* and they remain in the turned off position during N1 that is the transitional state between wakefulness and sleep when only one of the drives (the wake drive) is silenced. During the transition to other three stages (N2, N3, and R), one of the three lamps is turning on in response to changes in on–off state of one or two of three switches. The 1st (N2) lamp is turning on during the transition to N2, the 2nd (N3) lamp is turning on during the following transition to N3. The N2 lamp is turning off, while the 3rd (R) lamp is turning on during the transition from N2 to R. Data on scores on the 1st and 2nd principal components of the EEG spectrum for each stage and data on the rates of 20 transitions between 5 stages provided empirical support for this relay model visualizing three switching mechanisms underpinning 5 human sleep–wake stages and switching in and out of them.

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## Author contributions

AAP: conceptualization; methodology; formal analysis; investigation; data curation; project administration; supervision; visualization; writing—original draft, review and editing. VBD: funding acquisition; supervision; investigation; data curation; writing—review and editing. VMK: conceptualization; writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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## Declarations

**Conflict of interest** The authors declare no conflict of interest.

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