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"Struggle" between three switching mechanisms as the underpinning of sleep stages and the pattern of transition between them

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Abstract Complex systems are occasionally switching between several qualitatively different modes of behavior, even in the absence of external influences. An example of such mode-switching behavior of a complex system is a sequence of changes in sleep stages observed on approximately 90-min interval of sleep cycle. We examined whether relatively stable stages and relatively rapid transitions between them can be linked to the observed markers of underlying processes of sleep–wake regulation. Using data on two napping attempts of each of 28 university students, we described how scores on principal components of the EEG spectrum and rates of transitions between stages can serve as objective markers of interaction between three underlying on–off switching mechanisms that, in turn, can reflect strengths of the mutually inhibiting drives for sleep, wake, and REM sleep. A sequence of transitions between five stages over sleep cycle can be viewed as representing a sequence of episodes of the "struggle" between these three permanently competing mechanisms. Each of typical stage transitions in sleep cycle can be interpreted as a relatively rapid change in state of one or two of these three on–off switchers. It seems that only one of them is capable to maintain the switch on state during a stage with the exception of transient stage 1 sleep during which all switches remain in switch off state. An aim of future research of stages and their transitions during normal and disturbed sleep can be aimed on identification of a switching mechanism involved into a certain disturbance of sleep.

1 Introduction

When any external influences are absent, internal state variables of complex systems often continue their more or less regular fluctuations. Usually, such systems have multiple dynamical attractors, i.e., a set of qualitatively different modes of behavior, between which the system occasionally switches. These transitions are typically characterized by a relatively sudden change of the statistical properties of a fluctuating state variable contrasting with its fairly slow change over the preceding time interval [1]. A typical example of such mode-switching behavior is a sequence of states called "sleep cycle". This cycle has a duration of roughly 90 min during which the brain is passing through a sequence of seemingly distinct sleep stages [2, 3]. Multi-channel electroencephalographic (EEG) recordings offer a convenient way of quantification of the ongoing changes in the brain on the intervals of either afternoon nap or night sleep episode. They usually include, partly or fully, one or more than just one such cycle, respectively [4–8].

Notably, the scientific study of human sleep has been initiated more than 90 years ago by the discovery of Loomis et al. [9] that sleep proceeds through a series of states with distinct brain wave patterns instead of being a homogeneous state of the brain. Starting from the 60 s

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of XXth century, the method of classification of sleep into sleep stages has become the essence of the generally accepted representation of sub-states of sleep. Beginning with the introduction of conventional methodology of standard rules of sleep scoring [4], these originally proposed criteria for distinction between sleep stages had remained almost unchanged. For instance, the vast majority of these criteria [4] have been included in the most recent and generally accepted classification of stages [6, 7].

Sleep cycle is usually described (e.g., [10]) as the following sequence of alternations between 5 stages: wake, the 1st, 2nd, and 3rd stages of Non-Rapid-Eye-Movement (NREM) sleep, 2nd stage again, Rapid-Eye-Movement (REM) sleep, and N1 or wake again (in short, W → N1 → N2 → N3 → N2 → R → N1/W). A short period of wakefulness (W) is observed with eyes closed before the subject falls asleep. This stage may last for 5–20 min in healthy subjects. Then follows a short period of stage N1 as a transient state. The next stage, N2, is usually much longer in duration than N1. In young healthy subjects, stage N2 is typically followed by stage N3 (slow wave sleep) with the following return to stage N2. After that, a relatively short period of REM sleep is observed. Finally, the cycle is often completed by a very short awakening, W [10].

Such chain of transitions between stages is usually complicated by the returns to a previous stage as well as by appearance of some other, albeit much rare, transitions between stages [3, 10]. Notably, there are several possible transitions that were either practically unobserved or observed in patients with sleep disorders (e.g., from W → N3 or W → R, respectively). This non-randomness and huge difference in the rates of transitions between stages require explanation. Definitely, the transitions between stages reflect certain specific rules of functioning of the underlying mechanisms designed to govern changes in several modes of human behavior.

Under the theoretic framework developed by Saper et al. [11–13], the job of such mechanisms is to respond to slowly accumulating external and internal influences by their integration over time and conversion into sharp transitions in behavioral state. The reciprocal promoters/inhibitors of sleep, wake, and REM sleep tended to remain in the same state throughout the entire stage. Such stage-stabilizing mechanisms can be viewed as sleep–wake state switchers that resist switching until sufficiently strong influences are accumulated to a critical level. Therefore, the changes of a current EEG pattern are fairly slow over time, while, during the transitions between stages, the EEG rapidly switches into a new pattern. Overall, it seems that such states as wakefulness, NREM sleep, and REM sleep have mutually inhibitory relationships and the switching in and out of five stages is governed by these underlying switching mechanisms [13].

Previously, we used data on the EEG signals and amounts of stages calculated on the interval of 50-min napping attempt of university students for demonstrating that the states of two competing driving forces, for sleep and wake, can be uncovered by scoring the 1st and 2nd principal components of the EEG spectrum, respectively [14]. These two drives can work as two on–off switching mechanisms in such a way that, during a stage, their states ("on" or "off") cannot be changed and they cannot be simultaneously in "on" state during the stage. Each transition from W to NREM sleep and each of the following transitions (between N1, N2, and N3) can be described as a change in the state of a switching mechanism. The events of turning from "on" to "off" and from "off" to "on" states in the sequence of such transitions can be indicated by changes in the signs (from positive to negative and from negative to) of two principal component scores [14].

The current study was aimed on the extension of these previous results using data on transitions between stages observed during longer (90-min) napping attempts of university students. Such data provided a possibility to include stage R in the analysis of the underlying switching mechanisms. Presumably, this stage reflects the work of the 3rd (REM sleep) on–off switching mechanism. We tried to explain the functioning of three underlying switching mechanisms using not only data on principal component scores but also data on differential percentages of transition between stages W, N1, N2, N3, and R in sleep cycle of approximately 90-min duration.

The study hypotheses were:

1) Three drives (for wake, sleep, and REM sleep) have mutually inhibitory relationships that can be conceptualized as the competing 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.
2) Since a stage and its transition to the following stage are associated with unique combinations of two principal component scores and with unique change in combinations of two principal component scores, respectively, these scores can be used for the conceptualization of any stage and any of its transitions as a result of competing interactions between three on–off switching mechanisms designed to control the maintenance of states of wakefulness, NREM sleep, and REM sleep and to initiate the switching in and out of them, respectively.
3) Data indicating huge difference between stage transitions in their rates can be used to support the conceptualization of stages and their transitions as reflecting the competing interactions between three underlying on–off switching mechanisms.

2 Methods

All procedures performed in this nap study of human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later

amendments, and in accordance with the ethical standards of the institutional research committee. The Ethics Committee of the Institute approved the experimental protocol in June 2019 (Approval#12402-02-7112). This protocol resembles the protocol of the previously published study [14] with the only important difference in the duration of napping attempt (90 min instead of 60 min). The study participants were informed in detail about all procedures, and informed written consent was obtained from each participant.

2.1 Participants of nap study

Unpaid volunteers were 28 university students (20 females) with mean age and standard deviation of 20.0 years and 1.1 years, respectively. After the structured interview with a sleep researcher, the students were invited to participate in this nap study. The interview was focused on exclusion criteria, such as age either younger than 18 or older than 23 years, pregnancy or breastfeeding (for female participants), history of mental or sleep disorder, any complaints about poor physical condition and functioning, current mild cold and missing classes due to any sickness in 2 previous weeks, involvement in shift or night work, crossing several time zones in the previous month, irregularity of sleep–wake schedule exemplified by more than 1-h difference in weekday bedtimes, frequent sleep reduction exemplified by, at least, one night of partial sleep deprivation in the previous week.

2.2 Study protocol

The visits to a sleep laboratory were preceded and followed by the attending classes in the same building. Within a less than a month interval, each study participant had three 90-min napping attempts with intervals between visits varying from 3 days to 2 weeks. Each visit to the sleep laboratory was scheduled at the same afternoon hour (between 12:30 and 15:30) and lasted for more than one hour and a half. The first 90-min napping attempt was regarded an adaptation nap, while the analysis of the 2nd and 3rd 90-min polysomnographic records was performed for the current study.

2.3 Polysomnographic recordings

During the preparation to polysomnographic recordings, a participant was instructed to try to relax and to nap for 90 min after light off. The recordings were performed using a Neurovisor BMM-36 (Medical Computer Systems LLC, Moscow), the MCScap Sleep electrode helmet, and the NeoRec 1.4 software. The electrodes were applied in accord with the standard monitoring montage known as the International 10–20 system of electrode placement. The EEG signals were obtained from 19 channels connected by a monopolar 10–20 scheme with two reference electrodes on the mastoid bones. Other recorded polysomnographic signals included two electrooculogram channels, one electromyogram channel, and one electrocardiogram channel. The recorded signals were conditioned by the high-pass, low-pass and notch filters (0.5 Hz, 35 Hz, and 50 Hz frequencies, respectively). The sampling frequency of the signal was 1000 Hz.

2.4 Sleep scoring

In accord with the conventional scoring procedure [6], visual scoring on 30-s epochs of each 90-min record was performed. Such record was independently scored by two experienced scorers. The initial disagreement varied, depending upon a stage, from 10% (N1) to 2% (N3). In order to finally produce consensus scores, they reexamined together all intervals with discrepant scores. The scorers were uninformed about names of participants and orders of their napping attempts. The 30-s epochs were classified into five stages: wake stage (W), three stages of NREM sleep (N1, N2, N3), and REM sleep (R). The amounts of sleep stages and percentages of transitions between stages were calculated for all study participants (Table 1, middle and lower part). For providing a possibility of comparisons of the obtained percentages with those reported for the whole night episode, the published results on stage transitions reported in six studies of night sleep in healthy subjects [2, 10, 15–18] were averaged and presented in the upper part of Table 1.

2.5 Analysis of the EEG signals

The EEG spectral power densities were calculated from data on the EEG signals recorded from electrodes placed at five derivations (Fz, F4, Cz, Pz and O2 referenced to the ear mastoid sites, M1/M2). The records of the signals from these derivations were visually inspected on 1-s epochs to remove all epochs containing artifacts from further analysis. Spectral power densities for the artifact-free epochs were computed using the FFTW (Fastest Fourier Transform in the West) package [19] (see www.fftw.org for more detail). Hamming window taper was used on 1-s epochs in calculations of absolute spectral power densities (μV^2). Further analysis was performed on 16 single-Hz frequency bandwidths, between 1 and 16 Hz (i.e., 0.50–1.49 Hz for 1 Hz, 1.50–2.49 Hz for 2 Hz, 2.50–3.49 Hz for 3 Hz, ..., 15.50–16.49 Hz for 16 Hz). These sets of 16 single-Hz power densities were averaged within each 30-s interval of EEG records and ln-transformed. For the purposes of statistical analyses, the individual powers (180 per each derivation of each napping attempt) were further averaged, e.g., over derivations, within stages (Fig. 1a), etc.

Table 1 Amount and percentage of transitions to and from each of 5 stages

Stage		W		N1		N2		N3		R	
Direction	# 1–4	Transition	%	Transition	%	Transition	%	Transition	%	Transition	%
Night sleep: To		W →		N1 →		N2 →		N3 →		R →	
	1	***W → N1***	***75***	N1 → W	21	N2 → W	24	N3 → W	14	*R → W*	34
	SEM		6		5		4		5		7
	2	W → N2	20	***N1 → N2***	***67***	*N2 → N1*	*27*	N3 → N1	8	*R → N1*	43
	SEM		5		4		7		5		10
	3	**W → N3**	**0**	**N1 → N3**	**0**	*N2 → N3*	*31*	***N3 → N2***	***75***	R → N2	23
	SEM		0		0		2		8		4
	4	W → R	4	N1 → R	12	N2 → R	17	N3 → R	3	**R → N3**	**0**
	SEM		2		3		4		1		0
Nap: To		W →		N1 →		N2 →		N3 →		R →	
	1	***W → N1***	***98***	*N1 → W*	*28*	N2 → W	24	*N3 → W*	*27*	***R → W***	***38***
	2	W → N2	2	***N1 → N2***	***72***	***N2 → N1***	***50***	N3 → N1	16	*R → N1*	*31*
	3	**W → N3**	**0**	**N1 → N3**	**0**	N2 → N3	20	***N3 → N2***	***57***	*R → N2*	*31*
	4	**W → R**	**0**	N1 → R	< 1	N2 → R	6	**N3 → R**	**0**	**R → N3**	**0**
	Total	$n = 238$	100	$n = 369$	100	$n = 285$	100	$n = 49$	100	$n = 13$	100
Nap: From		→ W		→ N1		→ N2		→ N3		→ R	
	1	***N1 → W***	***54***	***W → N1***	***60***	W → N2	2	**W → N3**	**0**	**W → R**	**0**
	2	*N2 → W*	*36*	*N2 → N1*	*37*	***N1 → N2***	***88***	**N1 → N3**	**0**	N1 → R	5
	3	N3 → W	7	N3 → N1	2	N3 → N2	9	***N2 → N3***	***100***	***N2 → R***	***95***
	4	R → W	3	R → N1	1	R → N2	1	**R → N3**	**0**	**N3 → R**	**0**
	Total	$n = 189$	100	$n = 387$	100	$n = 302$	100	$n = 57$	100	$n = 19$	100

Night sleep and Nap: Literature data [3, 10, 15–18] on the whole Night sleep episode and data of our Nap study. Direction: Direction of possible (but might be unobserved) transition from one stage to (→) one of four other stages; Total: Total number (n =) or total percentage (100%) of transitions from one stage to another in our nap study; %: Each of 4 either observed or unobserved transitions (#1–4) was expressed as percentage from the total number of transitions (n =) for the stage (> 0% and 0%, respectively). SEM: Standard Error of mean calculated for percentages of transitions calculated from data of 6 studies of healthy people [3, 10, 15–18]. When percentage of a transition is equal to 0%, > 50%, and > 25% but < 50, this transition is printed in **bold**, ***bold italic***, and *italic*, respectively. Figure 2 illustrates and Tables 2 and 3 suggest interpretation of differential percentages of transitions, respectively

2.6 Statistical analysis

The $SPSS_{23.0}$ 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 Hz-16 Hz) obtained from each of 5 derivations (Fig. 1b). Scores on the 1st and 2nd principal components of variation in the EEG power spectra were also obtained in this analysis, averaged withing study participants, and within each of 5 stages (Fig. 1c). In a similar way, 16 ln-transformed single-Hz power densities were averaged within each of 5 stages (Fig. 1a).

3 Results

3.1 Loadings and scores on the 1st and 2nd principal components of the EEG spectrum

As shown in Fig. 1b, the pattern of loadings of 16 single-Hz spectral powers on each of two (the 1st and 2nd) principal components (PC) was almost identical for 5 derivations. This pattern revealed positive loadings of alpha frequencies on both components, positive and negative loadings of delta frequencies on the 1st and 2nd principal component, respectively, and positive loadings of sigma and theta frequencies on the 1st principal component (Fig. 1b). For some of further analyses, scores on the 1st and 2nd principal components were averaged over derivations and naps (Fig. 1c).

3.2 The EEG spectra and principal component scores for 5 stages

As shown in Fig. 1a, the spectra calculated for three NREM sleep stages (N1, N2, and N3) and wake (W) differed one from another. In contrast, the spectrum calculated for REM sleep (R) closely resembled the spectrum calculated for transient state, N1. As shown in Fig. 1c, the same patterns of similarity between R and N1 and dissimilarity between any other stages was found for the scores on the 1st and 2nd principal components of the EEG spectrum (Fig. 1c). For N1 and

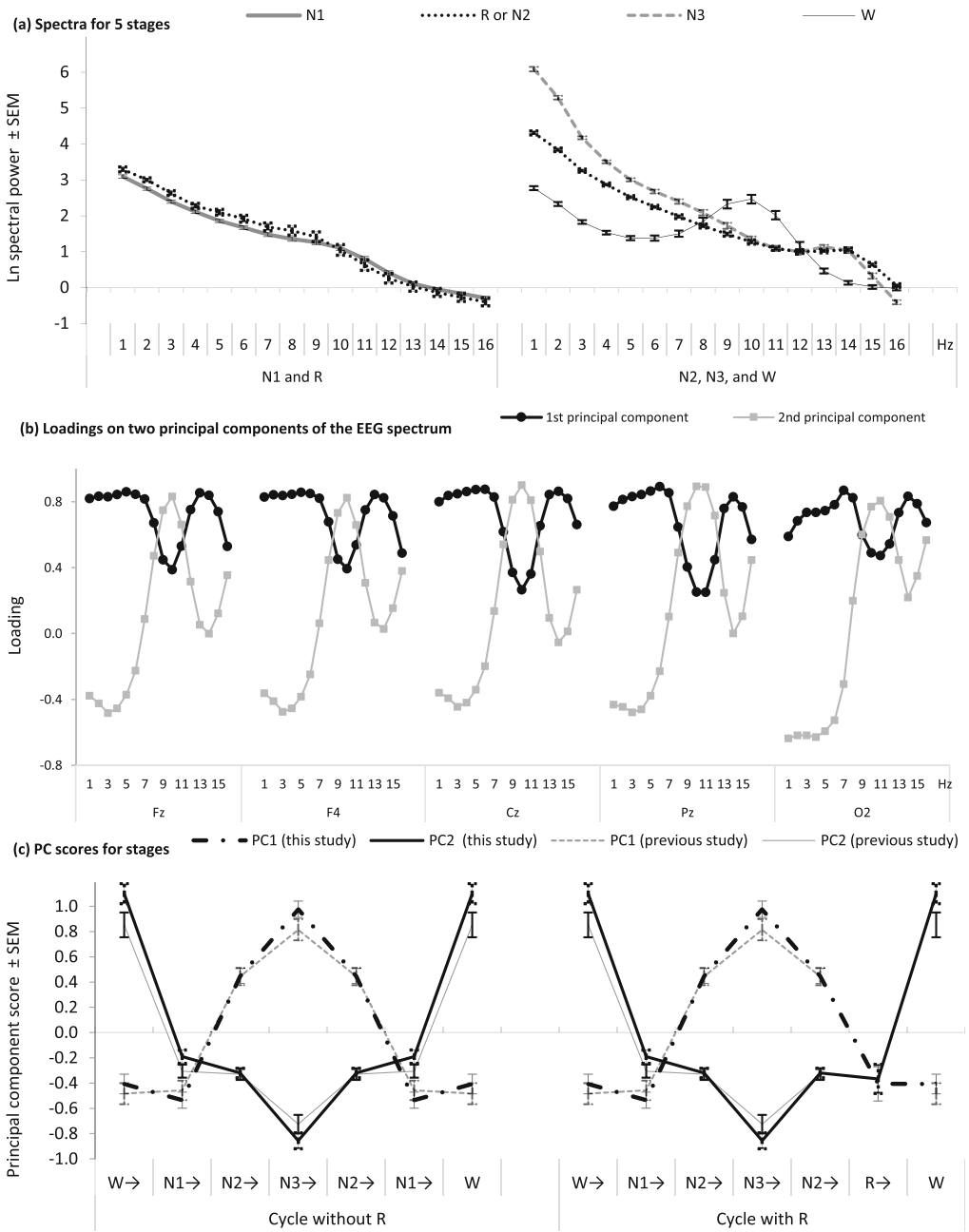

Fig. 1 Power spectra, loadings and scores on two largest principal components. (**a**) Spectral analysis was separately performed on the EEG recordings obtained from five derivations, Fz, F4, Cz, Pz, and O2. The initial 1080 spectral power densities in the range from 1 to 16 Hz were calculated by averaging spectra computed on 1-s artifact-free epochs of each of 30-s epochs of each of two naps (n = 28 participants * 2 naps * 180 epochs per nap for each of 5 derivations). Each epoch was assigned to one of 5 stages (W, N1, N2, N3, and R). Individual spectral powers were obtained for each of 5 stages after ln-transformation of initial spectral power densities and their averaging over derivations, epochs, and naps. Finally, mean spectral powers and their SEM (Standard Error of Mean) illustrated in the graphs were obtained by averaging over participants. (**b**) The 1st and 2nd principal components: Two largest principal components yielded by principal component analysis of 16 ln-transformed single-Hz power densities of each of 5 initial sets of 1080 spectra obtained for derivations Fz, F4, Cz, Pz, and O2. The variation explained by these two principal components varied, depending on derivation, from 50 to 55% and from 19 to 32% for the 1st and 2nd principal component, respectively, and their eigenvalues varied from 7.9 to 8.8 and from 3.1 to 5.1, respectively. (**c**) Scores on the 1st and 2nd principal components of the EEG spectrum for 5 stages. Individual scores were obtained for each stage and mean scores and SEM were calculated by averaging over 28 participants. For comparison, scores from the previous study of 50-min napping attempts (Dorokhov et al., 2021) [14] were added to the graphs (due to such a shorter duration of these napping attempts, R stages were rare and, therefore, PC scores for R were not calculated in [14]). Scores are interpreted as the spectral EEG indicators of the sleep and wake drives (in other terms, three-way switching mechanisms). Positive PC score was interpreted as a state of switch on, while negative PC score was interpreted as a switch off state. See also Fig. 2 and Table 4

R, both scores were negative and they were very similar one to another. Other combinations of scores were unique for W and remaining stages of NREM sleep. Namely, the 1st score was negative and the 2nd score is positive for W, the 1st score was positive and 2nd score was negative for N2 and N3 with either a smaller or a bigger contrast between scores obtained for N2 and N3, respectively (Fig. 1c).

3.3 Principal component scores as the EEG indicators of two switching mechanisms

As we previously shown [14], principal component scores can serve as the spectral EEG markers of the opposing driving forces for sleep and wake and their changes reflect the competition between two on–off switching mechanisms. Positive and negative scores can be interpreted as indicating, respectively, a switch on and a switch off state of a drive (or, in another term, a switching mechanism). Therefore, the combinations of two scores (Fig. 1c) can indicate the differential relationship of four stages (W, N1, N2, and N3) with the states of these two underlying drives or switches. Namely, negative score on the 1st principal component (a representative of the 1st—sleep—switching, mechanism associated with the sleep drive) in both W and N1 can be interpreted as indicating that the drive for sleep (the sleep switching mechanism) remains to be inhibited (switched off) until the end of N1. This implies that not only during W but also during and after transition from W to the 1st stage of NREM sleep (W → N1 and during N1, respectively) the 1st mechanism is switched out. When the 1st score remains negative during N1 (i.e., the switch off state of the 1st—sleep—switching mechanism), a significant decline of the 2nd score occurs during the transition to sleep (W → N1). This decline can indicate that the drive for wake was silenced during this transition (i.e., the switch off state of the 2nd—wake—switching mechanism associated with the wake drive). In contrast to W → N1, the 2nd score remains unchanged not only during the following transition (N1 → N2) but also on the whole interval of N2. When the 2nd—wake—switching mechanism remains in switch off state, the 1st—sleep—switching mechanism can change its state from off to on, i.e., it can be turned on during N1 → N2 and it can remain in switch on state during N2) this is indicated by positive scores on the 1st principal component during this stage. As for transition from N2 to the slow wave sleep (N3), it is characterized by further increase of the 1st score and further decrease of the 2nd score (Fig. 1c). This can be interpreted as the strengthening of switch on and switch off states of the sleep and wake drives, respectively.

3.4 General switching rules of the two (sleep and wake) switching mechanisms

The EEG signal during the differentiated vigilance states (i.e., wakefulness and sleep stages) changes fairly slowly over time, while during transitions between these states, the EEG signal rapidly switches into a new pattern. Such behavior of this complex system can reflect the mutual inhibition of the drives for sleep and wake. It reveals itself in the observation that only one of the drives can be disinhibited during a stage (i.e., in the terms of switching mechanism, to be in switch on state). Another drive must be, therefore, silenced (i.e., in the terms of switching mechanism, to be in switch off state). Moreover, these mechanisms can be described as more complex three-way switches. If a change in state of one switching mechanism from on to off occurs during transition to one stage, only thereafter, during the following transition, a change of state of another switching mechanism from off to on occurs (e.g., W → N1 is characterized by change in state of the wake switcher that is turning off, while N1 → N2 is characterized by change in state of sleep switcher that is turning on). Further changes occur during transition from lighter sleep to slow wave sleep and back to lighter sleep that were interpreted as additional changes of states of these two switching mechanisms that is a strengthening and a weakening of on or off states of these switches.

Thus, the sleep and wake switches resist switching until a sufficiently strong stimulus accumulates to a critical level. This ensures relative stability of a stage. During more rapid event of stage transition, a state of a switching mechanism can be changed from off to on or from on to off. In other terms, the transitions are associated with a change of a drive strength, from its inhibition/silencing to its disinhibition/exciting. Since these two switches are opposing one another, they simultaneously reach a state of switch on, and if one was turned off, another cannot be turned on. As a result, more than two stages, not just NREM sleep and wake, were identified by the rules of scoring system developed for the human EEG. NREM sleep consists of three stages, each with has its own unique EEG pattern and is characterized by a rather stable EEG spectrum until the transition to another stage (Fig. 1a). Each stage was interpreted as reflecting a stage-specific combination of strengths of the drives for sleep and wake or, in other terms, by the state-specific result of interaction between two three-way switching mechanisms (Figs. 1c and 2).

3.5 REM sleep and the 3rd switching mechanism

Although two drives underlying sleep stages can be described using data on the signs of principal component scores (Fig. 1c), changes of these scores can reflect only changes in the states of two drives, for sleep and wake (SD and WD, respectively). Analysis of associations between scores and stages did not reveal a marker for REM sleep drive (RD). Despite this, principal component scores can help to reveal the state of the 3rd (REM sleep) on–off switching mechanisms. Given that R and N1 do not differ in scores or spectra and that both the 1st and 2nd scores are negative during R and N1 (Fig. 1c), the sleep and wake on–off switching mechanisms can be proposed to be turned off not only during transient stage N1, but also during rather stable R.

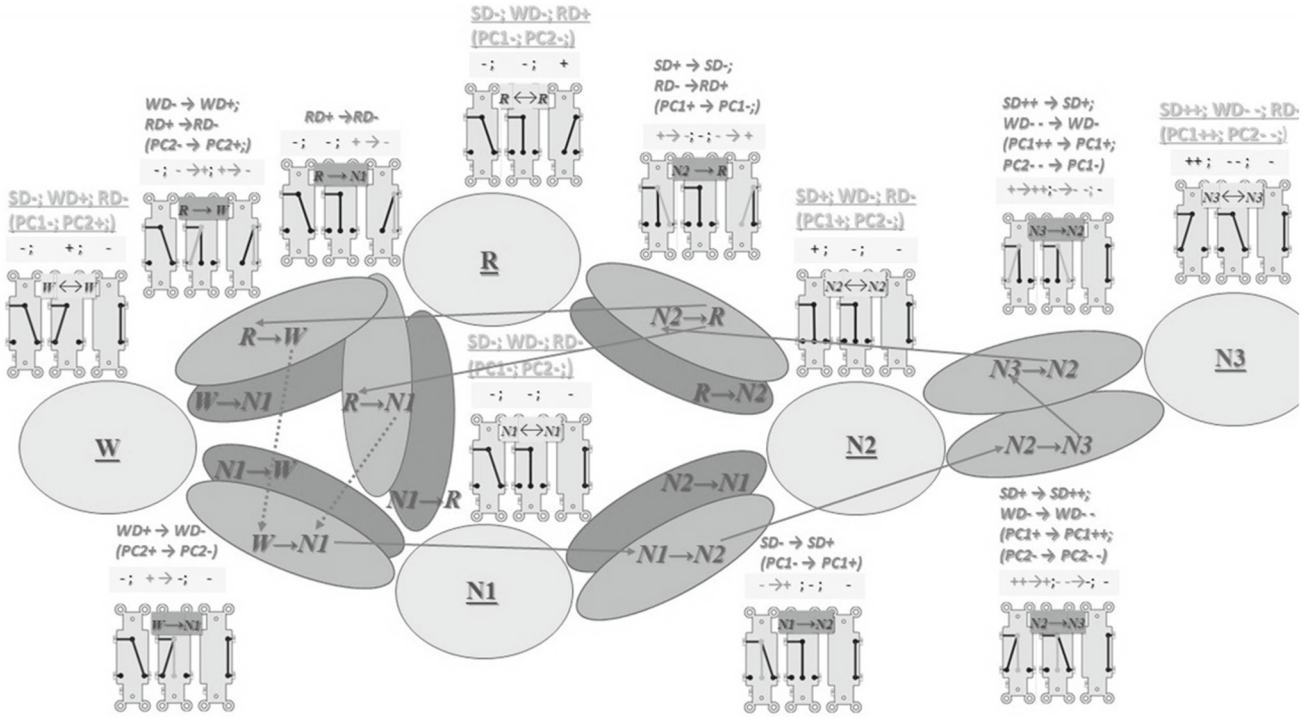

Fig. 2 Three drives (switchers) as underpinnings of transitions between stages in sleep cycle. As in Tables 1 and 2, transition is printed in bold italic or italic when percentage is $> 50\%$ or $> 25\%$ but $< 50\%$, respectively; as in Table 2, stages are printed in bold underlined. A sequence of transitions over sleep cycle is shown by arrows (W → N1 → N2 → N3 → N2 again → R → W again). A less likely backward transition is also shown (N1 → W; N2 → N1; and R → N2/N1). Arrows depict the most probable sequence of transitions in sleep cycle; SD, WD, and RD: Drives for sleep, wake, and REM sleep, respectively, that can be conceptualized as three switching mechanisms shown, SD and WD as three-way switches, and RD as two-way switch. Since these three mechanisms have mutually inhibitory relationships, two of them cannot be simultaneously in switch on state during a stage. Therefore, a score on either the 1st or the 2nd Principal Components of the EEG spectrum (either PC1 or PC2, respectively; Fig. 1c) that is one of two EEG markers of two drives (either SD or WD), is positive during this stage ("+"), another must be negative ("−"). During most of transitions between stages (in green and blue), one of these three-way switches can be changing its state, i.e., it can be turning either on or off (either "→+" or "→−", respectively). Therefore, PC score can be reflecting this changing by changing either from positive to negative or from negative to positive (either "→+" or "→−", respectively). The exception is one of the transitions, to N3, when the switch on and off states of SD and WD, respectively, are strengthened (PC1 +→++ and PC2−→−−; respectively). Under high sleep pressure, such states of these two three-way switchers prevents the REM sleep switching mechanism (two-way switcher) from the switching on. However, when sleep pressure is dropping, these two states can be weakened again (during the transition back to N2, PC1 + + → + and PC2−− → −, respectively). Further dropping (during N2) can allow the following transition, the change of state of the REM sleep switching mechanism from off to on. Only changes in the states of two drives, for sleep and wake (SD and WD), can be linked to a PC score (PC1 and PC2, respectively), while there is no marker for REM sleep drive (RD) in features of the EEG signal. However, given that R and N1 do not differ in PC1 and PC2 and that they both are having two PC < 0, the sleep and wake switching mechanisms can be in the switched off states during R. Therefore, R differs from N1 in the state of RD: the 3rd switching mechanism is in either on or off state of during R and N1, respectively. Due to relatively short bouts of N1, this stage is regarded a transient state. Indeed, since this is the only stage at which all three drives can be silenced, N1 cannot be maintained for a longer time interval compared to other stages that are supported by one of the switches. Therefore, this transient state cannot be very stable because N1 represents "no man's land" between the opponent driving forces for wake, NREM sleep and REM sleep. See also Table 4

It seems that the sleep drive has priority when sleep pressure is high (i.e., when the homeostatic sleep drive remains strong). This ensures the transition N1 → N2, but not the transition N1 → R, and further transition N2 → N3, but not N1 → R. However, the transition N2 → R also observed, but later, after dropping sleep pressure (i.e., when the homeostatic sleep drive became weaker and weaker during the 2nd and 3rd stages of NREM sleep). The weakening of the drive for sleep and its silencing during N2 → R allows the 3rd—REM sleep—on–off switching mechanisms to immediately change its state from switch off to switch on.

Therefore, REM sleep drive can be interpreted as one-way switching mechanism that can be switching on simultaneously with the changing in state of the sleep

switching mechanism from off to on N2 → R. Similarly, this one-way switching mechanism can be switching off simultaneously with the changing in state of the wake switching mechanism from off to on (R → W). The 3rd option (R → N1) can be also allowed indicating that this one-way switching mechanism can be also switching off in the absence of changing in states of two other—wake and sleep—switching mechanisms.

3.6 Difference between R and N1 in the states of underlying switching mechanisms

It seems that R can be differentiated from N1 only on the state of the 3rd switching mechanism that either in switch on state during R or in switch off state during N1. Due to relatively short bouts of N1, this stage is regarded a transient state. Such difference from any of four other stages can be explained in terms of three switching mechanisms. The unique feature of N1 is that all three drives can be silenced during this stage. Therefore, it can be seen as "no man's land" between the opponent driving forces for wake, NREM sleep and REM sleep. Consequently, this stage cannot be maintained for a longer time compared to any other stage during which one of the switches is in the state of switch on. When sleep pressure is high (i.e., when the homeostatic sleep drive is strong in the beginning of sleep cycle), N1 is typically followed by the next stage of NREM sleep (N2). However, when, during N2, sleep pressure already dropped down (i.e., the homeostatic sleep drive became weaker after bouts of N2 and N3), the 1st—sleep—switching mechanism can be forced to switch off. As a result, the transition N2 → R can be permitted. Consequently, the change in state of the 3rd—REM—sleep switching mechanisms, from off to on, can be expected. Thereafter, the change of state of this switching mechanism from on to off can be expected (i.e., the transitions R → N2, R → N1, and R → W).

3.7 Percentages of transitions between stages point at three switching mechanisms

Table 1 presents the results suggesting that the percentages of transitions in our nap studies were similar to those calculated from six studies of the whole night episode. Percentages of transitions between stages in our nap study (Table 1) were used for further confirmation of the interpretation of stages in terms of three competing drives represented by three on–off switching mechanisms. The differences between possible transitions in percentage were found to be extremely large. When some of transitions were not observed during the nap study (W → N3, W → R, N1 → N3, and N3 → R), some other transitions constituted the majority of transitions of a stage, $> 50\%$ of total transition from a stage (W → N1 and N1 → W, N1 → N2 and N2 → N1, N2 → N3 and N3 → N2, and N2 → R and R → W).

Figure 2 and Tables 2 and 3 provide an explanation of such drastic differences between stage transition in their percentage (from none to 98%). The general rule of transition was found to be the following. When only one of two—sleep and wake—switching mechanisms is required for a transition, it constitutes the majority of transitions from a stage or to a stage in sleep cycle (e.g., W → N1, then N1 → N2, then N2 → N3, then N3 → N2, then N2 → R, then R → W or R → N1). In contrast, if a transition requires "jumping" over one or more such switching events, a stage was either rare observed or not observed at all (e.g., W → N2 requires a jump over N2, N3 → R requires a jump over N2 → R, W → R or N1 → R requires a jump over N2, N3, and N2 again, etc.). As a result, the change in state of the wake switching mechanism from on to off occurs during W → N1. Thereafter, the change in state of the sleep switching mechanism from off to on occurs during N1 → N2. Finally, to further prevent the switching to R under high sleep pressure, N2 → N3 occurs and can be interpreted as the strengthening of the off state of the wake switching mechanism and of the on state of the sleep switching mechanism.

Such interpretation of the results of analysis of stage transitions is summarized in Fig. 2. It shows the typical sequence of stage transitions in sleep cycle (W → N1 → N2 → N3 → N2 → R → N1/W) and its association with the sates of three on–off switching mechanisms and strengths of three driving forces. Moreover, Table 4 clarifies the relationships of stages with these underlying mechanisms, drives, switchers, and, additionally, hypothetical promotors and inhibitors of the states of sleep, wakefulness, and REM sleep in the human brain.

4 Discussion

In a simple system, state variables usually fluctuate around fixed mean values with fixed pattern of variation. In contrast, the complex systems are occasionally switching between several qualitatively different modes of behavior, even in the absence of external influences. When described as time series, such transitions are typically observed as sudden changes of the properties of the fluctuating state variables [1]. A chain of changes of stages observed on the time interval of sleep cycle can serve as an example of such mode-switching behavior of complex systems [2, 3]. When sleep research applies the methodology of identification of the patterns of brain waves, this allows an economical quantitative description of sleep by subdivision of the EEG recording into intervals each of which is allocated to one of five all-or-nothing variables called "sleep stages" [4, 6]. However, it remains to be explored whether these relatively stable stages and rapid transitions between them can be explained as reflecting the stable states of the underlying sleep–wake regulating mechanisms and the changes in these states, respectively. In the current study, we demonstrated a possibility to describe the sequence of changes in stages on the interval of one sleep cycle in terms of the underlying sleep–wake regulating processes. The theoretic framework considers sleep–wake

Table 2 Explanation of transitions between 5 stages in terms of three switches and PC scores

From → to	→ %	% →	Drive is viewed as a switch in on or off state & score is either > 0 or < 0
Transition from wakefulness to deeper sleep: W → N1 → N2 → N3 (→ R)			
W → N1	***98***	***60***	***Switching off wake switch (PC2 > 0 → < 0), sleep switch is still switched off***
W → N2	2	2	Unlikely to jump over N1 (before switching off wake switch)
W → N3	**0**	**0**	**Lack of jump over N1 & N2 (before switching off/on wake/sleep switch)**
W → R	**0**	**0**	**Lack of jump over N1, N2, N3 & again N2 (sleep pressure is too high)**
N1 → N2	***72***	***88***	***Switching on sleep switch (PC1 < 0 → > 0), wake switch is still switched off***
N1 → N3	**0**	**0**	**Lack of jump over N2 (before switching on sleep switch)**
N1 → R	< 1	5	Unlikely to jump over N2, N3 & again N2 (sleep pressure remains high)
N2 → N3	20	***100***	***Strengthening wake/sleep switch off/on (PC2 < 0 → < < 0/PC1 > 0 → > > 0)***
N2 → R	6	***95***	***Switching off/on sleep/REM switch (PC1 > 0 → < 0) (sleep pressure dropped)***
N3 → R	**0**	**0**	**Lack of jump over N2 (before weakening sleep switch)**
Transition from sleep to awakening: N3 → N2 → R (N1) → W			
N1 → W	*28*	***54***	***Switching on wake switch (PC2 < 0 → > 0), sleep switch is still switched off***
N2 → W	24	*36*	*Less likely to jump over N1 (before switching off sleep switch)*
N2 → N1	***50***	*37*	***Switching off sleep switch (PC1 > 0 → < 0), wake switch is still switched off***
N3 → W	*27*	7	*Less likely to jump over N1 & N2 (before switching off sleep switch)*
N3 → N1	16	2	Less likely to jump over N2 (before switching off sleep switch)
N3 → N2	***57***	9	***Weakening wake/sleep switch off/on state (PC2 < < 0 → < 0/PC1 > > 0 → > 0)***
R → W	***38***	3	***Switching off/on REM/wake switch (PC2 < 0 → > 0)***
R → N1	*31*	1	*Switching off REM switch, sleep & wake switches are still switched off*
R → N2	*31*	1	*Switching off/on REM/sleep switch (PC1 < 0 → > 0)*
R → N3	**0**	**0**	**Lack of jump over N2 (before switching on sleep switch)**

From → to: Transition from one stage to other stages (might be observed or unobserved); → % or % → : Percentages of a transition for stages on either left or right side from the sign " → " (see Table 1), and, as in Table 1, a transition is printed in **bold**, ***bold italic***, and *italic* when its percentage is equal to 0%, > 50%, and > 25%, but < 50%, respectively. PC1 and PC2: The 1st and 2nd Principal Component scores, respectively; they can serve as the spectral EEG indicators of the states of the sleep and wake drives, respectively. Due to having a mutually inhibitory relationship, they can be represented by two three-way switching mechanisms. If a score > 0, a switch is on, if a score < 0, a switch is off (Fig. 1c). The states of on and off switching can be also strengthened during the transition to N3 (PC > 0 → > > 0 or PC < 0 → < < 0) thus preventing R under high sleep pressure. The states are weakened back during the transition back to N2 thus allowing the following transition to R under dropped sleep pressure. Since R does not differ from N1 in PC scores, both switching mechanisms for sleep and wake are in switch off state during these two stages. They differ in a state of the third—two-way switching mechanism representing the 3rd—REM sleep—drive that is in either on or off state during either R or N1, respectively

state transitions as reflecting one of the most remarkable features of the state control systems: the mutually inhibitory interactions between the wake- and sleep-promoting neurons, and the REM-on and REM-off neurons [11–13]. In the framework, the whole set of events constituting sleep cycle can be viewed as the result of underlying interactions between three on–off switching mechanisms representing the drives for sleep, wake, and REM sleep (Fig. 2).

It seems that the Rechtschaffen and Kales rules [4] captured the fundamental laws of interaction between the mechanisms of sleep–wake regulation associated with three sets of mutually inhibitory neuronal circuits [11–13]. This link of simple rules to fundamental underlying mechanisms can, at least partly, explain their surprising success in providing the continuity of the scientific and clinical description of the sleep process for more than a half of century. Our current results offered

Table 3 Explanation of stages and typical transitions in terms of three switches and PC scores

	Transition	PC score		Switch is turned on or off (stage) and turning on or off (transition)		
Stage	from → to	PC1	PC2	Sleep	Wake	REM sleep
W		**< 0**	**> 0**	**off**	**on**	**off**
	W → N1	***< 0***	***→ < 0***	***remains off***	***on → off***	***remains off***
	N1 → W	***< 0***	***→ > 0***	***remains off***	***off → on***	***remains off***
N1		**< 0**	**< 0**	**remains off**	**off**	**remains off**
	N1 → N2	***→ > 0***	***< 0***	***off → on***	***remains off***	***remains off***
	N2 → N1	***→ < 0***	***< 0***	***on → off***	***remains off***	***remains off***
N2		**> 0**	**< 0**	**on**	**remains off**	**remains off**
	N2 → N3	***→ > > 0***	***→ < < 0***	***on → on strengthening***	***off → off strengthening***	***remains off***
	N3 → N2	***→ > 0***	***→ < 0***	***on strengthening → on***	***off strengthening → off***	***remains off***
N3		**> > 0**	**< < 0**	**on strengthened**	**off strengthened**	**remains off**
	N2 → R	***→ < 0***	***< 0***	***on → off***	***remains off***	***off → on***
	R → N2	*→ > 0*	*< 0*	*off → on*	*remains off*	*on → off*
R		**< 0**	**< 0**	**remains off**	**remains off**	**on**
	R → N1	*< 0*	*< 0*	*remains off*	*remains off*	*on → off*
	R → W	***< 0***	***→ > 0***	***remains off***	***off → on***	***on → off***

Stage is printed in bold underlined. As in Tables 1 and 2, a transition from → to is printed in bold italic and italic when its percentage > 50% and > 25% but < 50%, respectively. Principal Component (PC) scores (PC1 and PC2, respectively) are the spectral EEG markers of the sleep and wake drives, respectively, having a mutually inhibitory relationship. They can be viewed as two three-way switching mechanisms opposing one another in the "struggle" for determination of a current stage. During a stage, a switching mechanism can be in the states of switching on or off. To maintain the following stage, this state can be changed during the transition to this following stage (i.e., to off or on, respectively). During transition to N3, the switch on and off states can be additionally strengthened to resist the change a state of the 3rd—REM sleep—switching mechanism from off to on under high sleep pressure. The switches can be weakened during the transition back to N2 thus allowing the switching on state of the 3rd two-way switching mechanism after the drop of sleep pressure during the previous bouts of N2, N3, and again N2. Since R does not differ from N1 in PC scores (Fig. 1c), these two stages can occur after silencing both sleep and wake switching mechanisms. The difference between R and N1 can be limited to the difference in the state of REM sleep drive (i.e., the 3rd switching mechanism). It can be switched on and off during R and N1, respectively. See also Fig. 2

plausible answers to such questions as why it is possible to subdivide the sleep–wake cycle into just five stages in accord with their specific patterns of brain wave activity, and how the difference between people in stage transitions can be interpreted in the light of the underlying on–off switching mechanisms.

Data of current study provided a possibility to confirm the previously proposed explanation of mechanisms underlying stages [14] with data on transitions between stages observed during the whole interval of sleep cycle. We found that stage percentages in our nap study fit very well to percentages known from the analyses of the whole night episode (e.g., [3, 10, 15–18]). We proposed an explanation of the difference in percentages of possible stage transitions in the sequence observed on the interval of one sleep cycle. In terms of three on–off switching mechanisms representing three competing driving forces, for sleep, for wake, and for REM sleep, the subdivision into stages might be viewed as oscillations between the processes promoting arousal and inhibiting each phase of sleep and the processes promoting one or another phase of sleep and inhibiting arousal [11–13]. In agreement with this concept and in

Table 4 Relationships of five stages to two PC scores, three drives working as three switching mechanisms, and promotors/inhibitors of NREM sleep, wake, and REM sleep states of the brain

	EEG indexes two scores		Driving forces three drives for			They work as three switching mechanisms			Promotors, inhibitors, and both			
									Promotor + /Inhibitor–			Sleep + /
	PC1	PC2	Sleep	Wake	REM	Sleep	Wake	REM	Sleep	Wake	REM	Wake-
Stage	$>0/<0$	$>0/<0$	±	±	±	On/Off	On/Off	On/Off	±	±	±	± or 0
W	<0	>0	−	+	−	Off	On	Off	−	+	−	0
N1	<0	<0	−	−	−	Off	Off	Off	−	−	−	0
N2	>0	<0	+	−	−	On	Off	Off	+	−	−	0
N3	$>>0$	$<<0$	+ +	− −	−	On +	Off +	Off	+	−	−	±
R	<0	<0	−	−	+	Off	Off	On	−	−	+	0

Stages are interpreted in terms of two spectral EEG indexes, Principal Component (PC) scores (PC1 and PC2, respectively): a score can be either >0 or <0 or much higher or much smaller than 0 ($>>0$ and $<<0$, respectively); in terms of Three drives: a drive can be strong, very strong, weak, and very weak (+, ++,−, and −, respectively); in terms of three simple representatives of these three drives: a three-way switch can switch between three states (either Off, On, and On + or Off + , Off, and On) and a two-way drive can switch between two states (either Off or On); in terms of hypothetical brain networks: a network can mostly serve as either a promoter or an inhibitor of Sleep, Wake, and REM states (+ or −, respectively) as well as it can serve as both a promotor of Sleep state and an inhibitor of Wake state (± only during N3, while 0 during other stages)

the light of the concept of regulation of the sleep–wake cycle by the opposing sleep and wake drives [20–23], the transitions between stages can be considered as reflecting abrupt changes in the state of the underlying drives (switches). Notably, these drives are designed not only for promoting a relatively rapid transition to the following stage, but also for stabilization of a current stage.

In practical terms, such analysis of sleep transitions and principal component scores opens a way of evaluation of difference between people with normal and disturbed sleep on the rates of transitions and principal component scores. Future research would be aimed on the identification of which of sleep–wake regulating (switching) mechanisms can be responsible for a certain sleep disturbance.

5 Conclusions

The sequence of changes in sleep stages on the interval of one sleep cycle can be interpreted in terms of competing interaction between three underlying processes of sleep–wake regulation. A transition from one stage to another on this interval can be a result of antagonistic interactions between three on–off switching mechanisms, the representatives of three mutually inhibiting drives, for sleep, for wake, and for REM sleep. We showed that scores of principal components of the EEG spectrum and rates of transitions between stages can serve as objective markers of these three drives (switching mechanisms).

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Author contributions

Conceptualization AAP; funding acquisition AAP, DSS, EBY, and VBD; data curation EBY, VBD, DSS, ANP, DES, EOG, AOT, ONT, NVL, GNA, ZVB, OVM, VIT, and AAP, resources AAP, DSS, and VBD; project administration AAP, DSS, and VBD; supervision AAP and VBD; software DES, DSS, ANP, and AAP; investigation DSS, VBD, ANP, and AAP; methodology AAP, DES, VBD, and ANP; sleep scoring: ANP and EOG; spectra calculation: DES; validation AAP; visualization AAP and DES; writing—review and editing AAP, EBY, VBD, DSS, ANP, DES, EOG, AOT, ONT, NVL, GNA, ZVB,OVM, and VIT.

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Data availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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