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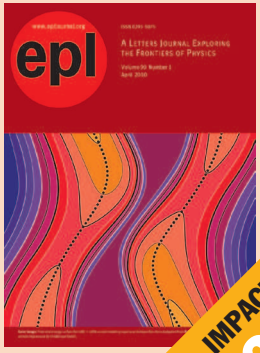

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Asymmetry and basic pathways in sleep-stage transitions

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Abstract – We study dynamical aspects of sleep micro-architecture. We find that sleep dynamics exhibits a high degree of asymmetry, and that the entire class of sleep-stage transition pathways underlying the complexity of sleep dynamics throughout the night can be characterized by two independent asymmetric transition paths. These basic pathways remain stable under sleep disorders, even though the degree of asymmetry is significantly reduced. Our findings demonstrate an intriguing temporal organization in sleep micro-architecture at short time scales that is typical for physical systems exhibiting self-organized criticality (SOC), and indicates nonequilibrium critical dynamics in brain activity during sleep.

Introduction. – Over the last decades sleep research has focused on how different factors affect sleep, and how sleep influences physiologic and cognitive functions [1]. Phenomenological studies at the system level, based on EEG and other polysomnographic recordings, have been used to identify sleep stages and to quantitatively assess sleep. Sleep is governed by interactions between networks of neurons located in many brain regions [2,3], that are described to act as a sleep-wake switch producing stable sleep and wakefulness [4,5]. Oscillatory models have been proposed to quantify the quasi-cyclic patterns in sleep dynamics over time scales of hours and days, accounting for homeostatic, circadian and ultradian influences [6–11]. However, the complex dynamics of sleep-stage transitions and arousals which occur at time scales of seconds to minutes during healthy sleep and constitute the sleep micro-architecture are not yet understood.

Here we ask whether the seemingly irregular sequences of transitions between sleep stages at short time scales (fig. 1) can be represented by several basic and stable sleep-stage transition pathways. We propose a transition probability matrix approach to probe asymmetry properties of sleep-stage transitions. We also analyze the probability of remaining in a given sleep stage. We investigate how these statistical properties change under sleep disorders which affect the sleep structure. Our findings indicate that asymmetry is a fundamental feature of sleep-stage transitions, and that at short time scales sleep dynamics are not homeostatic but exhibit a degree of self organization typical for physical systems out of equilibrium.

Data. – We analyze 48 healthy subjects and 48 age-matched patients with obstructive sleep apnea (healthy: 50.9 ± 9.4 years, sleep apnea: 51.3 ± 8.9 years). Data were collected in eight European sleep laboratories participating in the SIESTA project [12]. For each subject, polysomnographic recordings including the electroencephalogram (EEG), electrooculogram (EOG), and submental (chin) electromyogram (EMG) were taken for two consecutive nights. Based on Rechtschaffen and Kales criteria, signals were scored visually in epochs of 30 seconds into six stages: wakefulness, rapid-eye-movement (REM) sleep, and non-rapid-eye-movement (NREM) sleep stages including light sleep 1 and 2, and deep sleep 3 and 4. The average sleep time, defined as the interval between the start of the first sleep stage and the end of the last sleep stage, is 7.6 h for both healthy and sleep apnea groups.

NREM stage 3 has polysomnographic characteristics similar to those of stage 4, but very different from those of stages 1 and 2. Therefore, to simplify the analysis, we group light sleep stages 1 and 2 into a single light sleep stage, and deep sleep stages 3 and 4 into a single deep sleep

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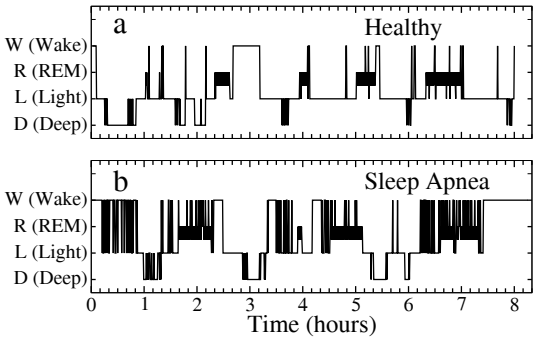

Fig. 1: Typical profiles of sleep-stage transitions during nocturnal sleep: (a) healthy, and (b) sleep apnea subject. In addition to $\approx$ 90–110 min ultradian cycles, there are a large number of rapid sleep-stage transitions without apparent periodicity. The sleep apnea subject experiences fragmented sleep, and shows a much larger number of rapid sleep-stage transitions and brief arousals than healthy subjects.

stage. We denote the stages REM, light sleep, deep sleep, and wake as R, L, D, and W, respectively. In our analyses we use data from the second night only, since subjects are better habituated to the laboratory environment during the second night of sleep.

Asymmetry and pathways in sleep-stage transitions. – Let N be the total number of all sleep-stage transitions recorded from a subject during the entire nocturnal sleep period, and $N_{k\ell}$ be the number of transitions from sleep stage k to sleep stage ℓ. We define a transition probability matrix $\overleftrightarrow{\boldsymbol{T}}$ with elements $T_{k\ell} = N_{k\ell}/N$, which quantify the probability of having a $k \to l$ transition during the entire sleep period. If the probability of transition from stage k to stage ℓ, $k \to \ell$ equals the probability of the transition $\ell \to k$, *i.e.*, $T_{k\ell} = T_{\ell k}$, the transition between stages k and ℓ is "symmetric" (fig. 2(a)). Note that this definition does not require that a transition $k \to \ell$ is immediately followed by a transition $\ell \to k$; intermediate transitions are allowed. If $T_{k\ell} \neq T_{\ell k}$ the transition between stages k and ℓ is "asymmetric" (fig. 2(b), (c)).

We next present the probability matrix $\overleftrightarrow{\boldsymbol{T}}$ of sleep-stage transitions in the following form: Each pair of matrix elements $T_{k\ell}$ and $T_{\ell k}$ is expressed in terms of their mean $M_{k\ell} = (T_{k\ell}+T_{\ell k})/2$ and difference $\delta_{k\ell} = (T_{k\ell}-T_{\ell k})$. Since the differences $\delta_{k\ell}$ quantify the degree of asymmetry in the transitions between sleep stages k and ℓ, $\delta_{k\ell}$ represent the *asymmetry terms* in the transition matrix $\overleftrightarrow{\boldsymbol{T}}$ (eq. (1)). When the asymmetry terms $\delta_{k\ell} = 0$ for all pairs of sleep stages k and ℓ, then the transition matrix $\overleftrightarrow{\boldsymbol{T}}$ is symmetric.

See eq. (1) *on top of the next page*

The elements of the transition matrix $\overleftrightarrow{\boldsymbol{T}}$ have to satisfy several conditions:

i) Since $\overleftrightarrow{\boldsymbol{T}}$ is a probability matrix, the sum of all elements $T_{k\ell}$ has to be equal to one: $\sum_{k,\ell} T_{k\ell} = 1$.

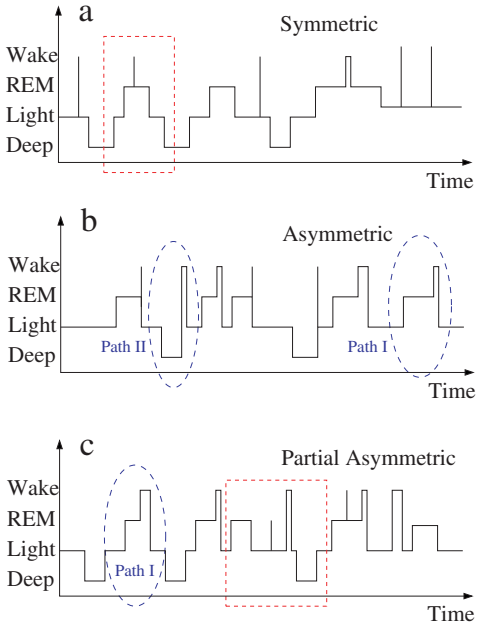

Fig. 2: (Colour on-line) Schematic examples of sleep dynamics with different types of sleep-stage transition pathways. (a) Completely symmetric transitions: a transition from stage k to stage ℓ is always accompanied by a transition from stage ℓ back to stage k, *e.g.*, the pathway shown in the rectangular box. (b) Completely asymmetric transitions: a transition from stage k to ℓ is not followed by a transition from ℓ to k. Such transition path involves asymmetric transitions between at least three sleep stages. Two basic asymmetric pathways, **Path I** ($L \to R \to W \to L$), and **Path II** ($L \to D \to W \to L$), are shown in the ovals. (c) Partially asymmetric transitions: for some pathways, transitions from stage k to ℓ are accompanied by transitions from ℓ to k (example shown in the rectangular box), while for other pathways, transitions from stage k to ℓ are not followed by a transitions from ℓ to k (ovals). All transitions between L and D, some of the transitions between L and R, and some of the transitions between L and W are symmetric in this example. According to our observations, sleep-stage transitions in human sleep are partially asymmetric.

ii) The sum of probabilities of entering a given sleep stage ℓ from all other sleep stages k has to equal the sum of probabilities of transferring from that sleep stage ℓ to all other stages k (otherwise one could not enter or leave the sleep stage ℓ). Thus, the sum of the matrix elements $T_{k\ell}$ in each row k has to be equal to the sum of the matrix elements in each column $\ell = k$. This leads to the following three relations for the asymmetry terms $\delta_{k\ell}$:

$$\delta_{RW} + \delta_{LW} + \delta_{DW} = 0, \tag{2}$$

$$-\delta_{RW} + \delta_{LR} + \delta_{DR} = 0, \tag{3}$$

$$-\delta_{LW} - \delta_{LR} + \delta_{DL} = 0. \tag{4}$$

When these three relations are met, the sum over the fourth row in $\overleftrightarrow{\boldsymbol{T}}$ automatically equals the sum over the fourth column, *i.e.*, $\delta_{DW} + \delta_{DR} + \delta_{DL} = 0$.

The above relations completely quantify the asymmetry properties of the transition matrix $\overleftrightarrow{\boldsymbol{T}}$. Since there

$$\overleftrightarrow{\boldsymbol{T}} \equiv \begin{array}{c} \\ W \\ R \\ L \\ D \end{array} \begin{array}{c} \begin{array}{cccc} W & R & L & D \end{array} \\ \begin{bmatrix} 0 & T_{WR} & T_{WL} & T_{WD} \\ T_{RW} & 0 & T_{RL} & T_{RD} \\ T_{LW} & T_{LR} & 0 & T_{LD} \\ T_{DW} & T_{DR} & T_{DL} & 0 \end{bmatrix} \end{array} = \begin{array}{c} \begin{array}{cccc} W & R & L & D \end{array} \\ \begin{bmatrix} 0 & M_{RW} - \delta_{RW}/2 & M_{LW} - \delta_{LW}/2 & M_{DW} - \delta_{DW}/2 \\ M_{RW} + \delta_{RW}/2 & 0 & M_{LR} - \delta_{LR}/2 & M_{DR} - \delta_{DR}/2 \\ M_{LW} + \delta_{LW}/2 & M_{LR} + \delta_{LR}/2 & 0 & M_{DL} - \delta_{DL}/2 \\ M_{DW} + \delta_{DW}/2 & M_{DR} + \delta_{DR}/2 & M_{DL} + \delta_{DL}/2 & 0 \end{bmatrix} \end{array}. \tag{1}$$

are three relations for six asymmetry terms $\delta_{k\ell}$, only three of these terms can be independent. Hence, one can completely quantify the degree of asymmetry in the complex dynamics of sleep-stage transitions throughout the night using only three asymmetry terms.

As an example, let us consider three potential scenarios for the dynamics of sleep-stage transitions (fig. 2).

1) *Completely symmetric dynamics:* Throughout the sleep period, each transition from stage k to stage ℓ is always accompanied by a transition from stage ℓ to k, even when the transition $\ell \to k$ does not immediately follow the transition $k \to \ell$ (fig. 2(a)). This holds for each pair of sleep stages k and ℓ, provided there are transitions between them. Such dynamics result in $T_{k\ell} = T_{\ell k}$ for all matrix elements. Therefore, all six asymmetry terms $\delta_{k\ell} = 0$, indicating a completely symmetric matrix $\overleftrightarrow{\boldsymbol{T}}$ and a completely symmetric dynamics of sleep-stage transitions.

2) *Completely asymmetric dynamics:* Throughout the sleep period, each transition from stage k to stage ℓ is not accompanied by a reverse transition from stage ℓ to k (fig. 2(b)). From eq. (1) this yields $\delta_{k\ell}/2 = M_{k\ell}$ for all matrix elements. Thus, all asymmetry terms $\delta_{k\ell}$ take maximum possible values indicating a completely asymmetric transition matrix $\overleftrightarrow{\boldsymbol{T}}$ and a completely asymmetric dynamics of sleep-stage transitions.

3) *Partial asymmetric dynamics:* In fig. 2(c) we show one possible type of a asymmetric transition path: $L \to R \to W \to L$. In this local path, the transition $L \to R$ is not accompanied by a transition $R \to L$, suggesting that $T_{LR} > T_{RL}$, and thus $\delta_{LR} > 0$. This asymmetric transition path also leads to asymmetry in the transitions $R \leftrightarrow W$ and $L \leftrightarrow W$, yielding $T_{RW} > T_{WR}$ and $T_{WL} > T_{LW}$, respectively. Therefore, in addition to $\delta_{LR} > 0$, the asymmetric transition path $L \to R \to W \to L$ also leads to $\delta_{RW} > 0$ and $\delta_{LW} < 0$. Because in fig. 2(c) we allow for stages D to transfer only to stage L and not to other sleep stages, $\delta_{DW} = \delta_{DR} = 0$. Further, because the transitions $D \leftrightarrow L$ are symmetric throughout this example, we have $\delta_{DL} = 0$. From eqs. (2), (3) and (4), we obtain $\delta_{RW} = -\delta_{LW} = \delta_{LR}$. Thus, all three asymmetry terms δ_{RW}, δ_{LW} and δ_{LR} are equal measures, and each one of them is sufficient to quantify the asymmetric transition path $L \to R \to W \to L$ shown in fig. 2(c). Since in this example the transition dynamics are characterized by both asymmetric and symmetric transitions, this is a case of partially asymmetric dynamics of sleep-stage transitions.

Results. – We calculate the matrix $\overleftrightarrow{\boldsymbol{T}}$ for each healthy subject. Group-averaged values for the matrix elements $T_{k\ell}$ are presented in table 1(a). For the asymmetry terms $\{\delta_{k\ell}\}$ in the transition matrix $\overleftrightarrow{\boldsymbol{T}}$ we obtain the following group-averaged values: $\{\delta_{k\ell}\} \equiv \{\delta_{RW}, \delta_{LW}, \delta_{LR}, \delta_{DW}, \delta_{DR}, \delta_{DL}\} = \{0.04, -0.06, 0.04, 0.02, 0, -0.02\}$ (fig. 3(a)).

We find that for all varieties of sleep-stage transitions, the empirically observed asymmetry transition terms $\{\delta_{k\ell}\}$ can be obtained by a linear combination of *two basic asymmetric transition paths*:

$$\textbf{Path I}: L \to R \to W \to L$$

with $\{\delta_{k\ell}\} = \{p_1, -p_1, p_1, 0, 0, 0\}$ and $p_1 \approx 0.04$;

$$\textbf{Path II}: L \to D \to W \to L$$

with $\{\delta_{k\ell}\} = \{0, -p_2, 0, p_2, 0, -p_2\}$ and $p_2 \approx 0.02$.

We note that the combination of **Path I** and **Path II** is not a unique solution to the empirically observed $\{\delta_{k\ell}\}$ values. For example, a path $D \to L \to R \to W \to D$ with $\{\delta_{k\ell}\} = \{p_1, 0, p_1, -p_1, 0, p_1\}$, where $p_1 \approx 0.04$, combined with another path $D \to W \to L \to D$ with $\{\delta_{k\ell}\} = \{0, -p_2, 0, p_2, 0, -p_2\}$ and $p_2 \approx 0.06$, also lead to the empirically observed $\delta_{k\ell}$. However, the transition $W \to D$ that is involved in the path $D \to L \to R \to W \to D$, rarely occurs (probability matrix element $T_{WD} < 1\%$) in the sleep-stage transition data (table 1(a)), thus reducing this solution to **Path I** above, and rendering such a solution redundant. Similarly, all other solutions to the observed $\{\delta_{k\ell}\}$ are redundant because they involve transitions which do not (or very rarely) occur in the data. Thus, all combinations of sleep-stage transition pathways during the entire sleep period can be reduced to the two basic paths **Path I** and **Path II**.

We next obtain the transition probability matrix $\overleftrightarrow{\boldsymbol{T}}$ for the sleep apnea group (table 1(b)). We find that sleep apnea subjects exhibit qualitatively similar asymmetry properties in sleep-stage transitions to those of healthy subjects. However, all asymmetry terms $\{\delta_{k\ell}\} \equiv \{\delta_{RW}, \delta_{LW}, \delta_{LR}, \delta_{DW}, \delta_{DR}, \delta_{DL}\} = \{0.02, -0.03, 0.02, 0.01, 0, -0.01\}$ have approximately 50% lower values for the sleep apnea group compared to the healthy group (fig. 3), indicating significant reduction in the degree of asymmetry in sleep-stage transitions with sleep apnea. The asymmetry terms $\{\delta_{k\ell}\}$ for the sleep apnea group are represented by a linear combination of two arrays

Table 1: Group-averaged transition matrix $\overleftrightarrow{\boldsymbol{T}}$ (eq. (1)) of sleep-stage transitions for (a) healthy and (b) sleep apnea group. The matrix elements $T_{k\ell}$ represent the probability (group mean ± standard error) for a transition from stage k to stage ℓ ($T_{k\ell}$ are rounded to values $> 10^{-2}$, *i.e.*, an accuracy of up to 1%). $\langle N\rangle$ indicates the group average of the number of sleep-stage transitions per subject per night.

(a) Healthy Group: $\langle N\rangle = 97.5 \pm 18.4$				
	W	R	L	D
W	–	$\mathbf{0.01} \pm 0.002$	$\mathbf{0.24} \pm 0.010$	$\mathbf{0.00} \pm 0.001$
R	$\mathbf{0.05} \pm 0.005$	–	$\mathbf{0.07} \pm 0.006$	$\mathbf{0.00} \pm 0.000$
L	$\mathbf{0.18} \pm 0.009$	$\mathbf{0.11} \pm 0.007$	–	$\mathbf{0.16} \pm 0.010$
D	$\mathbf{0.02} \pm 0.002$	$\mathbf{0.00} \pm 0.001$	$\mathbf{0.14} \pm 0.010$	–
(b) Sleep Apnea Group: $\langle N\rangle = 122.8 \pm 39.6$				
	W	R	L	D
W	–	$\mathbf{0.02} \pm 0.004$	$\mathbf{0.25} \pm 0.014$	$\mathbf{0.00} \pm 0.001$
R	$\mathbf{0.04} \pm 0.004$	–	$\mathbf{0.10} \pm 0.011$	$\mathbf{0.00} \pm 0.000$
L	$\mathbf{0.22} \pm 0.014$	$\mathbf{0.12} \pm 0.012$	–	$\mathbf{0.11} \pm 0.010$
D	$\mathbf{0.01} \pm 0.002$	$\mathbf{0.00} \pm 0.001$	$\mathbf{0.10} \pm 0.010$	–

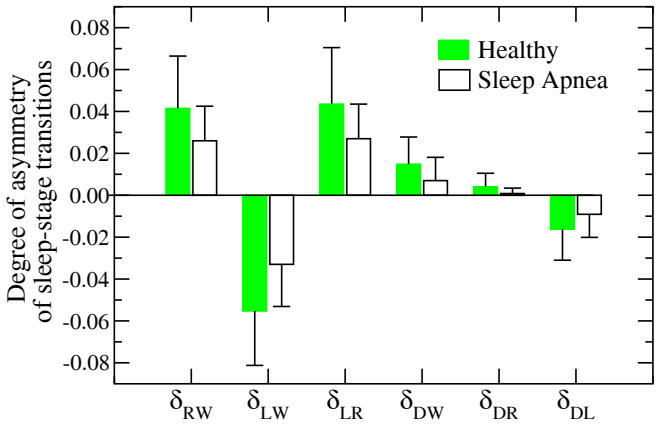

Fig. 3: (Colour on-line) Group-averaged asymmetry terms $\delta_{k\ell}$ of the transition matrix $\overleftrightarrow{\boldsymbol{T}}$ for healthy and sleep apnea subjects quantify the degree of asymmetry for all transitions between sleep stages k, $\ell \in \{W, R, L, D\}$. Error bars show the standard deviation. A significant reduction for all $\delta_{k\ell}$ terms in sleep apnea subjects indicates loss of asymmetry in sleep-stage transitions (pairwise comparison between healthy and sleep apnea subjects for each term $\delta_{k\ell}$ by non-parametric Mann-Whitney Rank test yields $p < 0.03$). The terms $\delta_{k\ell}$ are obtained from the matrix elements $T_{k\ell}$ values in table 1 calculated with accuracy 10^{-5}.

$\{\delta_{k\ell}\} = \{p_1, -p_1, p_1, 0, 0, 0\}$ with $p_1 \approx 0.02$, and $\{\delta_{k\ell}\} = \{0, -p_2, 0, p_2, 0, -p_2\}$ and $p_2 \approx 0.01$. Thus, the complex dynamics of sleep-stage transitions in sleep apnea subjects can be represented by the same two basic asymmetric transition paths as found for the healthy subjects, **Path I**: $L \to R \to W \to L$, and **Path II**: $L \to D \to W \to L$.

Because the asymmetric transition **Path I**, $L \to R \to W \to L$, is fully described by the three equal probability measures $\delta_{RW} = -\delta_{LW} = \delta_{LR} = p_1$ (see the case of *Partial asymmetric dynamics* above), the number n_1 of occurrence of **Path I** per night is given by $n_1 = p_1 \times \langle N\rangle$, where $\langle N\rangle$ is the average total number of sleep-stage transitions per subject per night. For healthy subjects we find an average of $n_1 \approx 4$, while for sleep apnea subjects $n_1 \approx 2.5$, indicating a significant reduction with sleep apnea in the occurrence of **Path I** per subject per night. Similarly, the asymmetric transition **Path II**, $L \to D \to W \to L$, is fully described by the three equal probability measures $-\delta_{LW} = \delta_{DW} = -\delta_{DL} = p_2$, and thus the number n_2 of occurrence of **Path II** per night is given by $n_2 = p_2 \times \langle N\rangle$. Healthy subjects have an average number of $n_2 \approx 2$, which is significantly higher than $n_2 \approx 1.2$ for the sleep apnea subjects. While sleep apnea subjects show the same basic sleep-stage transition pathways, **Path I** and **Path II**, as observed in healthy subjects, the number of occurrence of these basic transition paths in sleep apnea is significantly reduced, leading to a decrease in the asymmetry of the sleep-stage transitions.

Next we empirically test whether the two basic asymmetric transition paths, **Path I** and **Path II**, which we found to underlie sleep dynamics are indeed independent, and thus a linear combination of them can fully describe the variety of sleep-stage transition pathways throughout the night. To that end, we obtain the probability measures $p_1 = \delta_{RW}$ and $p_2 = \delta_{DW}$ for each individual subject, and we calculate the correlation coefficient between these two measures for the entire group of healthy and sleep apnea subjects. We find that the Pearson product-moment correlation coefficient between p_1 and p_2 is $\rho(p_1, p_2) = -0.13$ for the healthy group and $\rho(p_1, p_2) = -0.02$ for the sleep apnea group, indicating that these two types of asymmetric transition paths are mutually independent.

Since the probability measures p_1 and p_2 quantify the number of occurrence n_1 and n_2 of the basic sleep-stage transition pathways **Path I** and **Path II** respectively, we introduce a coefficient of asymmetry A as a function of p_1 and p_2 to define the degree of asymmetry in sleep-stage transitions for each subject in our database. Because the two basic asymmetric transition paths **Path I** and **Path II** are *independent*, we can define

$$A \equiv \sum_{\text{PathI}} |\delta_{k\ell}| + \sum_{\text{PathII}} |\delta_{k\ell}|, \tag{5}$$

which quantifies the overall percentage of independent asymmetric transitions during nocturnal sleep. For a completely asymmetric sleep comprised only of **Path I** and **Path II** transitions, the asymmetry coefficient $A = 1$, while for a completely symmetric sleep dynamics, $A = 0$. From eqs. (2), (3) and (4) we can express the coefficient of asymmetry as

$$A = 3 \times (|\delta_{RW}| + |\delta_{DW}|) = 3 \times (p_1 + p_2). \tag{6}$$

Histograms of the asymmetry coefficient A obtained for each individual subject in the healthy and sleep apnea group are shown in fig. 4. For healthy subjects, the

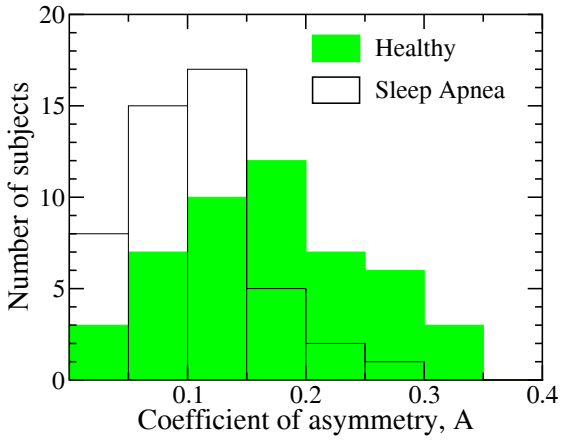

Fig. 4: (Colour on-line) Distribution of the coefficient of asymmetry A for a group of healthy subjects (mean ± stddev: 0.17 ± 0.08), and a group of sleep apnea subjects (0.11 ± 0.06). Healthy subjects exhibit a significantly higher degree of asymmetry in sleep dynamics (Mann-Whitney Rank test: $p < 0.001$ indicating a significant difference between the two distributions).

group average A obtained from the histogram in fig. 4 is $A = 0.17$, which is significantly higher than the group average $A = 0.11$ for the sleep apnea group. This clearly indicates that while healthy sleep dynamics exhibit a significant degree of asymmetry associated with sleep-stage transitions, there is a loss of asymmetry in sleep under pathologic perturbations such as sleep apnea.

In order to obtain a more complete picture of sleep dynamics, we need information not only about the probability of transition between two sleep stages (quantified by the matrix elements $T_{k\ell}$, eq. (1) and table 1) but also the probability of a subject remaining in the same sleep stage. To this end, we study the probability distributions of sleep-stage durations.

The cumulative probability distribution $P_k(d)$ is defined as $P_k(d) \equiv \int_d^\infty p_k(r)\mathrm{d}r$, where $p_k(d)$ is the probability density function for the occurrence of a given sleep stage k with a duration d. We calculate the cumulative probability distribution for each subject, and then we obtain the average cumulative probability distribution $P_k(d)$ for the healthy and sleep apnea group.

We find that for healthy subjects, the duration of wake and arousal periods follows a power-law distribution, $P_W(d) \propto d^{-\alpha}$, indicating a unique scale-invariant organization (no characteristic time scale) of arousal and wake states during sleep. This temporal organization spans over time scales from 30 s to 30 min, and relates to the underlying neuronal mechanisms of sleep regulation [13–16]. One possible hypothesis is that under pathologic perturbation, such as sleep apnea, alterations in the sleep regulatory mechanisms would lead to a breakdown of the scale-invariant organization in the duration of arousal and wake states. However, we find that this scaling behavior is preserved in sleep apnea subjects, where arousal and wake durations also follow a power-law distribution over a

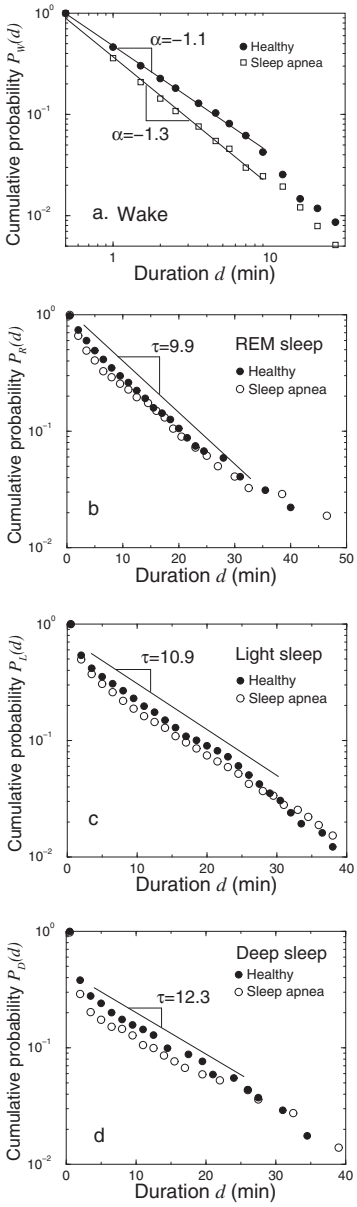

Fig. 5: Cumulative probability distributions of wake (arousal) and sleep-stage durations for the healthy and sleep apnea groups. (a) The distributions $P_W(d)$ of arousals and wake durations follow a power law with scaling exponent α. In contrast, the distributions of durations of (b) REM sleep $P_R(d)$, (c) light sleep $P_L(d)$, and (d) deep sleep $P_D(d)$ decay exponentially with time constant τ.

broad range of time scales, although sleep apnea subjects have high degree of sleep fragmentation. This power-law behavior is characterized by a scaling exponent $\alpha = 1.28 \pm 0.03$ for the sleep apnea group that is significantly larger than $\alpha = 1.11 \pm 0.05$ for the healthy group (fig. 5(a)).

In contrast to arousal and wake durations, we find that the probability distributions of all sleep-stage durations exhibit an exponential behavior (figs. 5(b), (c) and (d)). Further, we find that the exponential distributions of sleep-stage durations have a characteristic time scale, quantified by a time constant τ, that increases from REM

to light and deep sleep but remains practically identical for both healthy and sleep apnea subjects.

Sleep-stage transitions are typically described as following a cyclic pattern of 90–120 min, from light to deep sleep and REM with several brief arousals scattered within REM or light sleep. This traditional view does not address asymmetry in the transitions —for example, sleep cycles can theoretically be constructed using completely symmetric transition paths as shown in fig. 2(a). However, our empirical analysis shows that asymmetry is a basic feature of sleep dynamics.

Our findings of a power-law distribution of wake and arousal durations and exponential distribution of the durations of light sleep, deep sleep and REM, indicate a unique coexistence of both scale-invariant (no characteristic time scale) and exponential (with a characteristic time scale) processes as an output of a single sleep regulatory mechanism at the system level that has not been observed in other integrated physiological systems under neural regulation. Such coexistence of scale-invariant and scale-specific processes is well described by a physiologically motivated biased diffusion model [13]. The dynamics we observe resemble the features of certain physical systems out of equilibrium exhibiting *self-organized criticality (SOC)* [17], where quiet periods following an exponential law are interrupted by recurring active periods having scale-invariant power-law characteristics for their size and duration; and where triggering of frequent active periods over a broad range of time scales [18] is an essential component in the self-organization of the system, needed to maintain its critical state [13,19,20]. Notably, physical systems exhibiting SOC are also characterized by asymmetry in the transitions between quiet states and avalanches as the energy slowly builds up during quiet states toward the critical point and dissipates rapidly when avalanches occur. Our analysis shows an intriguing parallel to SOC systems as both basic asymmetric paths in sleep involve transitions to and from arousal (active "avalanche") states.

Our findings raise the hypothesis that brief arousals and wake states are an integral part of sleep regulation, and are generated by the same SOC-type mechanism that also governs sleep-stage transitions.

Conclusion. – We have investigated dynamical aspects of sleep micro-architecture utilizing a novel probability transfer matrix approach and the conceptional framework of self-organized criticality. Our analyses of brain dynamics during sleep show that the entire class of sleep-stage transition pathways that occur throughout the nocturnal sleep period can be reduced to two basic and independent transition paths. We demonstrate that sleep dynamics are characterized by an endogenous asymmetry in sleep-stage transitions that is universal for all healthy subjects and breaks down with sleep disorders. Further, we find that different sleep-stage transitions exhibit a different degree of asymmetry that is consistent across subjects. Finally, our findings demonstrate that in contrast to the homeostatic equilibrium that describes sleep at ultradian and circadian time scales of several hours, sleep micro-architecture at scales from seconds to minutes exhibits a non-equilibrium behavior of SOC type that is reminiscent of physical systems at criticality.

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