Central sleep apnea alters neuronal excitability and increases the randomness in sleep-wake transitions

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Abstract*—*Objective: **While most studies on Central Sleep Apnea (CSA) have focused on breathing and metabolic disorders, the neuronal dysfunction that causes CSA remains largely unknown. Here, we investigate the underlying neuronal mechanism of CSA by studying the sleep-wake dynamics as derived from hypnograms.** ***Methods:*** **We analyze sleep data of seven groups of subjects: healthy adults (n=48), adults with obstructive sleep apnea (OSA) (n=48), adults with CSA (n=25), healthy children (n=40), children with OSA (n=18), children with CSA (n=73) and CSA children treated with CPAP (n=10). We calculate sleep-wake parameters based on the probability distributions of wake-bout durations and sleep-bout durations. We compare these parameters with results obtained from a neuronal model that simulates the interplay between sleep- and wake-promoting neurons.** ***Results:*** **We find that sleep arousals of CSA patients show a characteristic time scale (i.e., exponential distribution) in contrast to the scale-invariant (i.e., power-law) distribution that has been reported for arousals in healthy sleep. Furthermore, we show that this change in arousal statistics is caused by triggering more arousals of similar durations, which through our model can be related to a higher excitability threshold in sleep-promoting neurons in CSA patients.** ***Conclusions:*** **We propose a neuronal mechanism to shed light on CSA pathophysiology and a method to discriminate between CSA and OSA. We show that higher neuronal excitability thresholds can lead to complex reorganization of sleep-wake dynamics.** ***Significance:*** **The derived sleep parameters enable a more specific evaluation of CSA severity and can be used for CSA diagnosis and monitor CSA treatment.**

***Index Terms*—central sleep apnea, excitability threshold, exponential distribution, power-law distribution, sleep arousals, sleep modeling, sleep-wake dynamics, wake-bout durations**

I. Introduction

The first systematic description of sleep apnea as cessation of airflow through nose and mouth was provided by Gastaut et al. in 1966 [1]. However, sleep apnea patients are mentioned much earlier in the literature such as in Dickens' "The Posthumous Papers of the Pickwick Club" (1837) and in Shakespeare's "King Henry IV Part I" (1597), indicating that sleep apnea is a common clinical disorder with long history. Nowadays, about 3-27% of the general population is affected by sleep apnea (depending on age, gender and definition of criteria [2], [3]). Sleep apnea as the most common form of sleep-related breathing disorders, greatly impairs daily function and quality of life, and is a major contributor to cardiac, cerebrovascular, and metabolic disorders as well as to premature death [3]. The main characteristics of sleep apnea, breathing disturbances, pause or shallow breathing during sleep, are caused by obstruction of the upper airways and a subsequent blockage of airflow (obstructive sleep apnea, OSA) or by lack of respiratory drive (central sleep apnea, CSA). While the origins of OSA are well understood, the mechanisms leading to CSA have not been fully described yet [4], although CSA is very common in elderly subjects and present in approximately 25% to 40% of patients with chronic heart failure [5].

The control of respiration requires the coordinated activity among several neuronal centers in the brainstem [6]. During sleep, respiratory drive is dominated by changes in $\mathrm{P_{CO_2}}$ and spontaneous nocturnal breathing is maintained when the arterial $\mathrm{P_{CO_2}}$ is higher than the apneic $\mathrm{P_{CO_2}}$ threshold. In contrast, if the apneic $\mathrm{P_{CO_2}}$ threshold is above the arterial $\mathrm{P_{CO_2}}$, inspiration does not occur resulting in CSA that lasts until either arterial $\mathrm{P_{CO_2}}$ increases above the apneic threshold or an arousal occurs [7]. While in many cases the exact cause of CSA is not known, it can often result from medical conditions such as stroke and congestive heart failure that damage neuronal centers in the lower brainstem or from high altitude and various drugs [4], [8]. Interestingly, $\mathrm{CO_2}$ inhalation efficiently reduces CSA events probably due to a widening of the difference between $\mathrm{P_{CO_2}}$ and the apneic

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threshold [9], [10]. However, treatment with inspired CO_2 does not improve sleep quality nor does it reduce the arousal index [9]–[11].

In this paper, we hypothesize that CSA is not only caused by malfunctioning of the respiratory centers (and improper response to changing P_{CO_2} levels) but might also lead to higher excitability threshold of sleep-promoting neurons (SPN), similar to what has been found for hippocampal neurons treated with cyclic hypoxia [12] and for GABAergic SNr neurons in hypoxic conditions [13]. We propose a mechanistic model to simulate brief arousals during sleep, and we show how a higher excitability threshold of SPN changes the arousal characteristics of CSA patients from a scale-invariant power-law distribution to an exponential distribution with characteristic time scale. As was shown previously, healthy sleep is characterized by many arousals throughout the night and their durations follow a power-law distribution [14], [15] (Fig. 1), which is consistently observed for several mammalian species [16] and related to different stages of maturation [17]–[19]. This power-law behavior can be explained by a sleep-restoring current [14], [20] that emerges during arousals in order to keep them short and maintain sleep. In CSA patients, however, the onset of the sleep-restoring current may be delayed (due to a higher excitability threshold of SPN), and therefore wake bout durations in CSA follow an exponential distribution rather than a power-law.

The model that we propose here to simulate arousal statistics in CSA, builds upon the intrinsic noise of wake-promoting neurons (WPN) located in several neuronal groups in the brain stem as an important factor for arousal generation [20]. While for healthy sleep regulation, cortical excitation (which triggers an arousal) and SPN excitation (which in turn triggers the inhibitory current) occur simultaneously, for CSA there is a delay between them due to a difference ('GAP') in their excitability thresholds:

$$GAP = \Delta_{\mathrm{SPN}} - \Delta_{\mathrm{cortex}}, \tag{1}$$

where Δ_{SPN} and Δ_{cortex} are the excitability thresholds of SPN and typical cortical neurons, respectively. According to our model (schematically shown in Fig. 2), for healthy subjects as well as for CSA patients, arousals occur when the integrated neuronal voltage of WPN exceeds $V = 0$ mV (Fig. 2, red pathway). We set the threshold potential equal to zero such that for $V > 0$ arousal/nocturnal wakefulness occurs and for $V \leq 0$ sleep is preserved (see also Methods and Materials). While for healthy subjects the sleep restoring current becomes effective if V> 0, for CSA patients the sleep restoring current appears only for V$> GAP$ (Fig. 2, blue pathway). Therefore, if WPN voltage for CSA patients is between $0 < V < GAP$, arousals are generated without attenuating current, and we expect such arousals to be similar in their statistics as sleep bout durations (i.e., if $-\Delta < V \leq 0$) and follow an exponential distribution instead of a power-law.

We compare the results of our model simulations with empirical analysis of data from adults as well as children (Fig. 4). It is well known that premature babies are especially affected by CSA because of immaturity of respiratory centers in the brain stem ("Apnea of Prematurity") [24], and therefore CSA in healthy young children can be considered as a physiological process, which is resolved during maturation (usually after the age of two years) [4], [25]. However, the group of children we study in this paper has an age range between 3 to 12 years, and CSA in these children is more likely to be of pathological origin. We also study CSA in a group of adults (mean age: $\sim$50 years), and we compare CSA children and CSA adults to age-matched groups of healthy controls and subjects with OSA. Moreover, we introduce a novel diagnostic measure of CSA severity that is based on the distribution of wake bout durations.

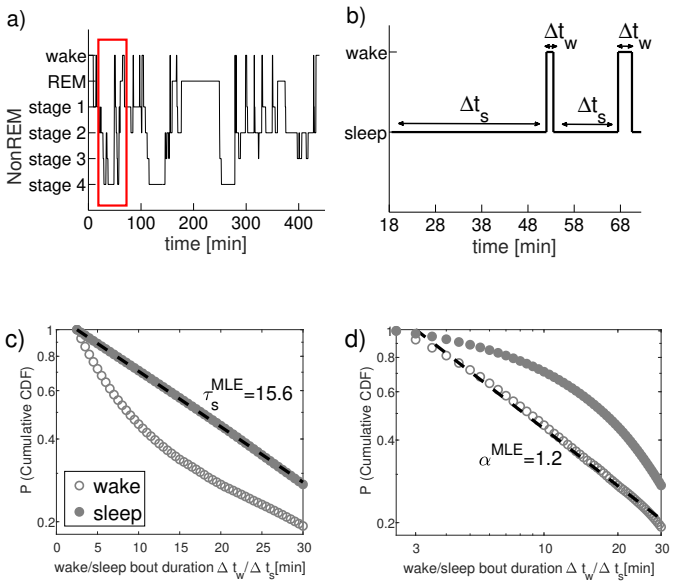

Fig. 1. **Frequent short arousals during sleep and probability distributions of wake and sleep bout durations of healthy adults.** a) Healthy sleep is characterized by frequent arousals and sleep-stage transitions throughout the night (shown is the full-night hypnogram of a healthy subject). b) Magnification of the area marked by the red box shown in a), and definition of sleep bout durations Δt_s and wake bout durations Δt_w. Panel b) is obtained from panel a) by grouping the five sleep stages into a single sleep state. Cumulative CDF of sleep bout durations (filled circles) and wake bout durations (open circles) for the pooled data of 48 healthy adults on c) a log-linear plot and d) a log-log plot. Sleep bout durations typically show an exponential distribution with characteristic time τ as demonstrated by the straight line in panel c), whereas a straight line in panel d) suggests that wake bout durations follow a power law with exponent α. We calculate α and τ by maximum likelihood estimation (MLE) [20], [21] that does not dependent on the choice of binning. The Akaike weights [22] for each distribution also indicate that sleep bout durations are best represented by an exponential distribution (exponential Akaike weights of $\approx$1 vs. power-law Akaike weights of $< 10^{-30}$), and wake bout durations by a power-law (power-law Akaike weights of 0.971 vs. exponential Akaike weights of 0.029).

II. Methods and Materials

A. Modeling arousability in Central Sleep Apnea (CSA)

Recently, we have shown that the integrated neuronal voltage fluctuations of wake promoting neurons (WPN) during consolidated sleep can be modeled by [20]

$$V = -\Delta \qquad \text{for} \qquad -\Delta > V \tag{2a}$$
$$dV = \sigma \cdot dw \qquad \text{for} \qquad -\Delta \leq V \leq 0, \tag{2b}$$

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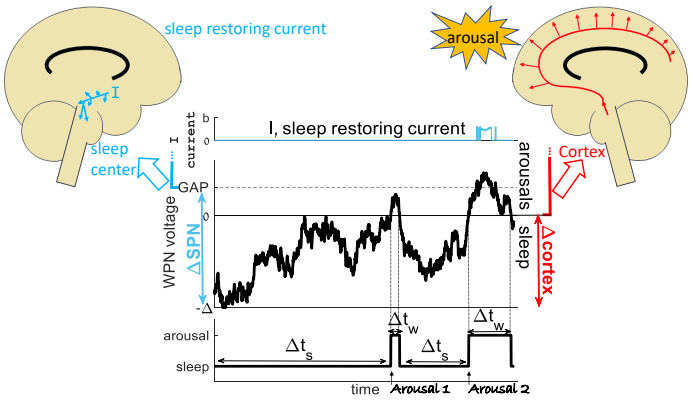

Fig. 2. **Mechanistic model of central sleep apnea (CSA).** The superposition of uncorrelated neuronal noise currents from a group of wake-promoting neurons (WPN) located in the upper brain stem can be modeled as a Wiener process [23]. WPN voltage occasionally exceeds the excitability threshold and via the ascending arousal pathway (drawn schematically in red) can trigger an arousal in the cortex [20]. In order that arousals are kept short, there exists an inhibitory current $I = b/(V+1)$ (schematically shown by blue lines on the left hand side) due to the excitation of sleep promoting neurons (SPN) located predominantly in the ventrolateral preoptic nucleus (VLPO). In healthy sleep, cortical excitation and triggering of the inhibitory current happen simultaneously. However, we hypothesize that for patients with central sleep apnea (CSA) there is a delay between the excitation of the cortical neurons and VLPO neurons because of a difference in their excitability thresholds denoted by GAP. For healthy subjects and even patients with obstructive sleep apnea (OSA), $GAP = 0$. In contrast, for CSA patients we assume $GAP > 0$, which yields more arousals of intermediate duration (Appendix Fig. A1). This is because for WPN voltage between 0 and GAP there is no sleep-restoring current I that will attenuate arousals (e.g., Arousal 1). Nevertheless, if WPN voltage exceeds the GAP, there is a sleep-restoring current with $I > 0$ that counteracts arousal formation (see upper panel during Arousal 2).

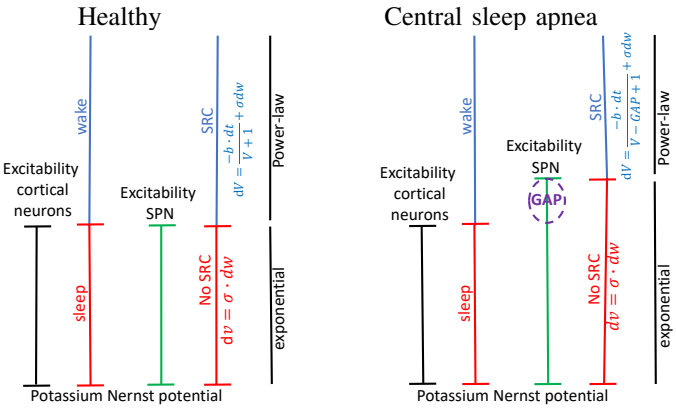

Fig. 3. **Differences in the excitability thresholds of healthy sleep versus CSA.** For healthy subjects the excitability thresholds of SPN and cortical neurons are equal, whereas for CSA patients, SPN excitability threshold is increased leading to a 'GAP' (marked in purple) and a delay in generating a sleep restoring current (SRC) that attenuates the arousal. Therefore, for CSA patients, wake bouts show exponential distribution due to the GAP and because the voltage during an arousal/wake fluctuates mostly in the interval $[0, GAP]$ (see also Fig. 2). Note that there are also attenuated arousals (for $V > GAP$), which show power-law distribution, however, their contribution to the overall arousal statistics is only in the order of 10%.

whereas during nocturnal arousals/wake

$$dV = -\frac{b}{V+1} \cdot dt + \sigma \cdot dw, \text{ for } V > 0. \tag{3}$$

We set the threshold potential equal to zero so that arousal/nocturnal wakefulness are characterized by $V > 0$ and for sleep $V \leq 0$ (see also Fig. 3). The lowest possible voltage of neurons is given by the Nernst potential of potassium ions so that the parameter $-\Delta$ is the relative difference between threshold potential and potassium Nernst potential (Δ can also be related to sleep depth [14], [26]). The sleep inertia parameter b (first introduced in a stochastic model to simulate the dynamics of sleep-wake transitions [14], [26]) is proportional to the maximal inhibitory current from sleep promoting neurons, w is a standard Wiener process, and σ is the standard deviation of the integrated neuronal voltage fluctuations of WPN.

However, Eqs. 2-3 assume that the excitability thresholds of sleep promoting neurons (SPN; predominantly located in the ventrolateral preoptic nucleus (VLPO)) and of cortical neurons are equal. While this assumption is true for healthy sleep, here we hypothesize that for CSA patients there is a difference between excitability threshold of SPN and cortical neurons as quantified by GAP. Therefore, for CSA nocturnal arousals/wake dynamics can be modeled by

$$dV = \sigma \cdot dw, \qquad \text{for } 0 < V \leq GAP \tag{4a}$$

$$dV = -\frac{b}{V - GAP + 1} \cdot dt + \sigma \cdot dw, \text{ for } \qquad V > GAP. \tag{4b}$$

According to this model, an arousal occurs if the neuronal voltage of WPN is higher than the cortical threshold (i.e., $V > 0$), however, only when $V > GAP$, SPN are activated causing a 'sleep restoring current' (represented by $-\frac{b}{V-GAP+1}$ in Eq. 4b) to attenuate the arousal. Note that Eq. 4a for unattenuated CSA arousals and Eq.2b for sleep bout durations, are very similar and have the same statistics (i.e., both show exponential distribution). Figure 3 summarizes the difference between healthy sleep and CSA. Note that the sleep restoring current is equal to $-\frac{b}{V-GAP+1}$ with maximum $|I| = b$ at $V = GAP$.

B. Calculating the GAP from arousals/wake bout distributions

Wake bout durations in healthy subjects are characterized by a power-law distribution whose origin can be explained by the sleep restoring current (SRC) that is triggered at the time of arousal generation. For CSA, SRC occurs only after a delay when $V > GAP$. Therefore, in the interval $0 < V \leq GAP$, WPN voltage can be described by a pure Wiener process, Eq. 4a, without bias (i.e., SRC). We integrate Eq. 4a from 0 to maximum voltage GAP and obtain

$$\int dV = \int \sigma \cdot dw \tag{5}$$

$$GAP = \sigma \cdot \int dw \tag{6}$$

$$GAP^2 = \sigma^2 \cdot \left(\int dw \right)^2 \tag{7}$$

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Since the differentials of a Wiener process, dw_i, are independent and identically distributed (i.i.d.) with zero mean, averaging over all arousals in the interval $0 < V \leq GAP$ yields

$$GAP^2 = \sigma^2 \cdot \int \left\langle (dw)^2 \right\rangle \quad (8)$$

$$GAP^2 = \sigma^2 \cdot \int dt \quad (9)$$

$$GAP^2 = \sigma^2 \cdot \tau_w \quad (10)$$

$$GAP = \sigma \cdot \sqrt{\tau_w} \quad (11)$$

The variance of the standard Wiener process differential dw is its time interval dt (Eq. 9), and τ_w is the characteristic exponential time decay of the wake bout durations in the interval $0 < V \leq GAP$ (see Fig.4). Equation 11 describes the GAP as a function of σ and τ_w and is valid only when $GAP > 0$. We obtained GAP for each individual in our database using arousals within the intervals [1min, 10min] and [4min, 10min] for adults and children, respectively.

C. Calculating excitability thresholds from sleep and wake bout distributions

During sleep, WPN voltage values are in the range $-\Delta_{\rm cortex} \leq V \leq 0$ and can be described by a Wiener process (Eq. 2b). Similar to Eqs. 5-11 integrating and averaging over all sleep bouts yields

$${\Delta_{\rm cortex}}^2 = \sigma^2 \cdot \int \langle (dw)^2 \rangle \quad (12)$$

$$\Delta_{\rm cortex} = \sigma \cdot \sqrt{\tau_s} \quad (13)$$

Equations 11 and 13 describe GAP and $\Delta_{\rm cortex}$, respectively, as a function of neuronal noise (σ) and exponential time decay. The main difference between the equations is that Eq. 11 uses the statistics of wake bout durations, whereas Eq. 13 uses sleep bout durations. Therefore, the WPN voltage ranges are different: for Eq. 11, $0 < V \leq GAP$, and for Eq. 13, $-\Delta_{\rm cortex} \leq V \leq 0$. Moreover, the exponential time decay in Eq.13 is of the sleep bout durations (Fig. 5), whereas in Eq. 11 the exponential time decay is of the wake bout durations in CSA (Fig. 4). The excitability threshold of sleep promoting neurons, $\Delta_{\rm SPN}$ can be estimated by (Fig. 3)

$$\Delta_{\rm SPN} = \Delta_{\rm cortex} + GAP \quad (14)$$

$$\Delta_{\rm SPN} = \sigma \cdot \left(\sqrt{\tau_s} + \sqrt{\tau_w} \right) \quad (15)$$

where Eq. 15 is obtained using Eqs. 11 and 13.

The neuronal noise level σ can be calculated from the sleep bout durations using Eq. 13

$$\sigma = \Delta_{\rm cortex} / \sqrt{\tau_s}. \quad (16)$$

Since $\Delta_{\rm cortex} = 25$mV (see e.g., ref. [23]) we obtain:

$$\sigma = 25 / \sqrt{\tau_s}, \quad (17)$$

where τ_s is calculated using maximum likelihood estimation [20] with $M = 6$min as the minimum sleep bout duration to be included in the calculation.

D. Calculating the CSA$_{\rm GAP}$ index as a measure of CSA severity

According to our model, severity of CSA is mainly determined by the value of GAP and the neuronal noise σ. The WPN voltage (current) fluctuations within the interval $V = [0, GAP]$ can be calculated as follows (cp. Eq. 4a):

$$dV = \sigma \cdot dw \quad (18)$$

$$\frac{dV}{dt} = \sigma \cdot n(t) \quad (19)$$

$$I/C = \sigma \cdot n(t) \quad (20)$$

$$\langle I^2 \rangle = C^2 \cdot \sigma^2, \quad (21)$$

where w is a standard Wiener process, $n(t)$ is Gaussian white noise (from a standard normal distribution) and $\frac{dV}{dt} = I/C$ (i.e., Hodgkin-Huxley model) with neuronal capacitance C that is usually constant [27] (even for different ages [28], [29]). For the CSA$_{\rm GAP}$ index we integrate Eq. 21 over the interval $[0, GAP]$ and obtain

$$\mathrm{CSA_{GAP}\ index} = \int_0^{\mathrm{GAP}} \mathrm{C^2 \cdot \sigma^2 \cdot dV} = \mathrm{C^2 \cdot \sigma^2 \cdot GAP}. \quad (22)$$

Since C is merely a constant factor, we can also write

$$\mathrm{CSA_{GAP}\ index} \propto \sigma^2 \cdot \mathrm{GAP}. \quad (23)$$

In terms of electrical engineering, the CSA$_{\rm GAP}$ index represents a measure of power loss in the GAP due to the variations of the WPN voltage.

E. Akaike weights calculation for exponential and power-law distributions

For an exponential probability distribution $f(x) = \frac{1}{\tau} \cdot exp[-(x - M)/\tau]$ we calculate the Akaike's information criterion [22] (AIC) using the exponent τ and likelihood L as obtained from maximum likelihood estimation [20]

$$AIC_{\rm exp} = -2 \cdot \ln L + 2 = 2 \cdot \left(N \cdot \ln \tau + \frac{\sum_i (x_i - M)}{\tau} \right) + 2 \quad (24)$$

where $\tau = \langle x_i - M \rangle$.

For the power-law probability distribution $f(x) = (\alpha/M) \cdot (x/M)^{-\alpha-1}$ we calculate AIC [22] using the power-law exponent α and likelihood L as evaluated from maximum likelihood estimation [20]

$$AIC_{\rm power-law} = -2 \ln L + 2 = \quad (25)$$
$$= 2 \Big(- N \ln \alpha + N \ln M + (\alpha + 1) \sum_i \ln \left(\frac{x_i}{M} \right) \Big) + 2$$

where $\alpha = N \Big(\sum_i \ln \left(x_i / M \right) \Big)^{-1}$.

The relative likelihoods of each model is given by the following Akaike weights [22]

Akaike weights Exponential=

$$\frac{e^{-AIC_{\rm exp}/2}}{e^{-AIC_{\rm exp}/2} + e^{-AIC_{\rm power-law}/2}} \quad (26)$$

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Akaike weights Power-law=

$$\frac{e^{-AIC_{\text{power-law}}/2}}{e^{-AIC_{\text{exp}}/2}+e^{-AIC_{\text{power-law}}/2}} \quad (27)$$

The sum of the Akaike weights for exponential and power-law distributions is always 1. Following Edwards et al. [22], in Table I we calculate Akaike weights for the pooled data using bounded ranges of (i) [3min, 14min] for children and (ii) [2min, 14min] for adults. Hence, the value of M in Eqs. 24 - 26 is $M = 2$min for adults and $M = 3$min for children.

F. Database

We analyze hypnograms of adults and children of three age-matched groups: healthy, obstructive sleep apnea (OSA) and central sleep apnea (CSA). Groups of adults include: 48 healthy participants (age: 50.9 $\pm$ 9.4 years), 29 participants with OSA (age: 53.4 $\pm$ 8.0 years) and 25 participants with CSA (age: 50 $\pm$ 10 years). The children groups include: 40 healthy children (age: 6.7 $\pm$ 1.9 years), 18 OSA children (age: 6.9 $\pm$ 2.7 years), 73 CSA children (age: 6.7 $\pm$ 2.6 years) and 10 CSA children treated with CPAP (age: 8.3 $\pm$ 3.1 years).

Hypnograms of all groups were scored in 30s epochs and contain the following stages: wakefulness, rapid-eye-movement (REM) sleep, and non-rapid-eye-movement (NREM) sleep stages.

Healthy and OSA adults data were recorded within the EU-project SIESTA [30], whereas adults CSA data were collected at the St. Vincent's University Hospital Sleep Disorders Clinic [31]. All children data were recorded at Beijing Children's Hospital and scoring was performed following the AASM guidelines [32].

G. Statistical analysis

In our analyses, statistical significance of p<0.05 indicates that the correlation is significantly different from zero. Significance of the favored probability distribution is measured by Akaike weights probability likelihood (see Eqs. 26-27).

III. Results

A. Probability distributions of wake bout durations in healthy and apnea subjects

An important characteristic of sleep regulation is the cumulative probability distribution of sleep and wake bout durations. As has been shown for humans [14], [15] and other species [16], [19], sleep bout durations follow an exponential distribution whereas wake bout durations follow a power-law distribution that emerges during the early postnatal period [17], [33]. Furthermore, it has been shown that OSA preserves the power-law distribution for arousals and the scaling exponent α can be used to distinguish between healthy and OSA subjects [15]. Since the main contributor to the power-law organization of arousals is sleep inertia [14] and the related sleep-restoring current [20], we hypothesize that the absence or delay of such current is due to the GAP in CSA patients which abolishes the power-law, and causes wake bout durations to follow an exponential distribution similar to sleep (compare Eq. 2b to Eq. 4a).

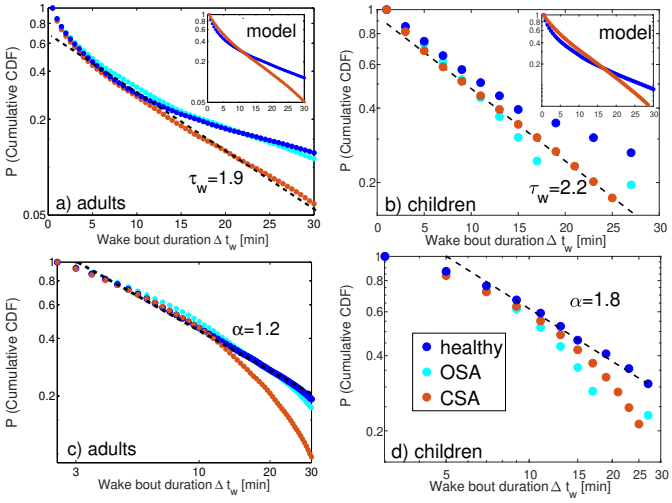

Fig. 4. **Cumulative probability distributions (cumulative CDF) of wake bout durations for healthy (blue curves), central apnea (orange) and obstructive apnea (cyan) patients.** Adults (left column, plots a) and c)) and young children (right column, plots b) and d)) show qualitatively similar results: healthy adults and children, as well as adults and children with obstructive sleep apnea (OSA) show power-law distributions. In contrast, for adults and children with central sleep apnea (CSA) the distribution of arousal durations is exponential. For the sake of clarity, the upper panel shows semi-logarithmic plots and the lower panel shows the corresponding distributions on a double-logarithmic plot (a straight line on a log-log plot is indicative of a power-law, whereas a straight line on a semi-log plot suggests an exponential distribution). The power-law distributions for healthy participants and OSA patients can be attributed to the 'sleep restoring current' from sleep-promoting neurons (SPN) that 'kicks in' at the time of arousal initiation [20]. However, for CSA patients there is a delay between arousal generation and the response of SPN in triggering such current because of a GAP in excitability thresholds (Fig. 2). As a result, wake bout durations in CSA show an exponential distribution. Power-law exponents α as well as characteristic time constants τ_w are presented in Table I. Power-law vs. exponential distribution was probed by Akaike weights information analysis [22] of the pooled data of each group. If the obtained Akaike weight is higher for the exponential distribution than for the power-law distribution, the underlying process is more likely to be exponential and vice versa (see Table I for a list of Akaike weights for all groups). The insets in a) and b) show the results of model simulations with parameters that were determined from the empirical data (see Methods and Materials). Clearly, an exponential distribution is observed if $GAP > 0$ (orange dots) whereas the distribution is a power-law for $GAP = 0$ (blue dots). Note that MLE is not affected by the choice of binning [21]. Model results are obtained by pooling the data from 100 simulations for each group with GAP = 0 (healthy adults and children), GAP = 9.3 mV (CSA adults) and GAP = 7.7 mV (CSA children).

Figure 4 shows the cumulative CDF of wake bout durations for adults (left column) and children (right column). While the distributions of healthy and OSA subjects are very similar and reminiscent of a power-law (close to straight lines in the log-log plot of Fig. 4c,d), CSA patients have wake bout distributions that decay exponentially (straight lines in the log-linear plot of Fig. 4a,b). This observation is supported by quantifying the Akaike weights [22]. Akaike weights information analysis shows that for healthy and OSA subjects, data is best fit by a power-law whereas for CSA exponential fits have higher Akaike weights (Table I). Model results are shown in the insets of Fig. 4a,b, simulating healthy sleep with GAP = 0 and CSA with GAP > 0 and reproducing the power-law and exponential distributions, respectively.

Another argument in favor of our hypothesis that CSA is caused by absence or delay of a sleep-restoring current, is

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TABLE I
AKAIKE WEIGHT ESTIMATION FOR THE DISTRIBUTIONS OF WAKE BOUT DURATIONS.

Group	Akaike weights Power-law	Akaike weights Exponential	favored distribution	α	τ_w
healthy adults	0.971	0.029	power-law	1.2	
OSA adults	0.995	0.005	power-law	1.3	
CSA adults	0.042	0.958	exponential		1.9
healthy children	0.943	0.057	power-law	1.8	
OSA children	0.990	0.010	power-law	1.8	
CSA children	$< 10^{-5}$	1.000	exponential		2.2
CSA+CPAP children	0.011	0.989	exponential		2.0

Significance tests for power-law and exponential distributions are performed by using Akaike weights [22] of relative likelihoods of the arousal distributions shown in Fig. 4. A comparison of the Akaike weights for power-law vs. exponential distribution for each group suggests which distribution is better represented by the data (e.g., higher Akaike weight for the power-law is indicative for an underlying power-law distribution). The Akaike weights are based on Akaike's information criterion using each models' log likelihood [20] (see Methods and Materials). Based on Eq. 29 and on the values of τ_w, we estimate GAP = 9.3 mV for our group of OSA adults and GAP = 7.7 mV for the OSA children. Age is not significantly different among the adults (age: 50±10 years) and among the children groups (age: 7±2 years). Note that the Akaike weights are not affected by the choice of binning.

that treatment of CSA children by continuous positive airway pressure (CPAP) does not affect their wake bout distribution. Specifically, the corresponding Akaike weights of the wake bout durations suggest an exponential distribution with a high probability of $P = 0.989$ (see Table I). Since we hypothesize that for CSA patients the sleep promoting neurons have higher excitability threshold, treatment with CPAP may have positive effect on their ventilation but will not affect neuronal signalling between sleep- and wake-promoting neurons. As a result, the GAP remains above 0 with similar values for both CSA children with and without CPAP treatment (this is also confirmed by the empirically obtained τ_w values that are very similar for both groups, see Table I).

B. Calculating the increase in excitability threshold of sleep-promoting neurons

According to our hypothesis the delay ('GAP') between excitation of cortical neurons (caused by an arousal) and SPN (triggering the sleep-restoring current) in CSA affects arousal and wake bout distributions (as shown above) but should not alter the statistics of sleep bouts. Indeed, in Fig. 5 we show that the probability distributions for sleep bout durations are exponentials for all groups (healthy, OSA and CSA) with similar characteristic time constants τ_s. Notably, τ_s is larger for children than for adults, consistent with an overall deeper sleep during childhood [19], [34]. Because the distinction between sleep and arousal/wake is at the level of the cortex (through analysis of scalp EEG), these results indicate that the excitability threshold $\Delta_{\rm cortex}$ does not change with CSA, and therefore a GAP > 0 is caused by higher excitability threshold $\Delta_{\rm SPN}$ (see also Eq. 1). The excitability threshold of the cortex can be calculated from the characteristic time constants τ_s and the level of neuronal noise σ (see Methods and Materials Eqs. 12-13), and [20],

$$\Delta_{\rm cortex} = \sigma \cdot \sqrt{\tau_s}, \tag{28}$$

with $\sigma = 25/\sqrt{\langle \text{sleep bout durations - } M_s \rangle}$ [23] and $\tau_s = \langle \text{sleep bout durations - } M_s \rangle$ [20], where $\langle \text{sleep bout durations - } M_s \rangle$ is the average over all sleep bout durations beyond the shortest sleep bout duration M_s as considered within the exponential distribution [20].

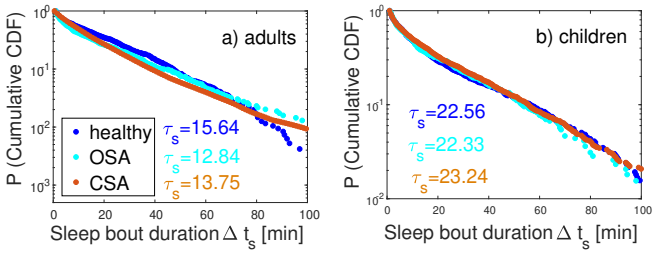

Fig. 5. **Cumulative probability distributions of sleep bout durations for healthy (blue curves), central apnea (orange) and obstructive apnea (cyan) patients.** All groups show exponential distributions, with lower characteristic time constants for a) the adults as compared to b) the children groups. The similarity in sleep bout distributions among the three groups of adults and among the children groups shows that sleep periods are not affected by the GAP and suggests that the cortical excitability thresholds $\Delta_{\rm cortex}$ (Fig. 2) are similar. In fact, $\Delta_{\rm cortex}$ is approximately 25 mV [23] which allows to determine the neuronal noise level σ for adults and children using Eq. 28. For example, CSA adults with $\tau_s = 13.8$ min have $\sigma = 25/\sqrt{13.8} = 6.7$, and CSA children with $\tau_s = 23.2$ min have $\sigma = 25/\sqrt{23.2} = 5.2$.

The value of GAP can be calculated by considering the dynamics of the WPN voltage in the range $0 < V \leq GAP$ as a simple Wiener process (Eq. 4a), and we determine the value of GAP as a function of neuronal noise σ and the characteristic time constant of arousals τ_w in CSA (for detailed analytical derivations see Methods and Materials Eqs. 5-11),

$$GAP = \sigma \cdot \sqrt{\tau_w}. \tag{29}$$

with $\sigma = 25/\sqrt{\langle \text{sleep bout durations - } M_s \rangle}$ [23] and $\tau_w = \langle \text{wake bout durations - } M_w \rangle$, where $\langle \text{wake bout durations - } M_w \rangle$ is the average over all wake bout durations of the exponential distribution within [1min, 10min] (i.e., $M_w = 1$min) and [4min, 10min] (i.e., $M_w = 4$min) for adults and children, respectively.

The values for τ_w can be obtained from Fig. 4a,b with $\tau_w = 1.9$ min for CSA adults and $\tau_w = 2.2$ min for CSA children, and the neuronal noise can be calculated from $\Delta_{\rm cortex}$ and τ_s (Fig. 5 and Eq. 28). Therefore, with $\tau_w = 1.9$ and $\sigma = 6.7$ (CSA adults), $GAP = 6.7 \cdot \sqrt{1.9} = 9.3$ mV, and with $\tau_w = 2.2$ and $\sigma = 5.2$ (CSA children), $GAP = 7.7$mV. In Fig. 6 we show that the values of GAP as calculated by Eq. 29 are in good agreement with the results of our model simulations and

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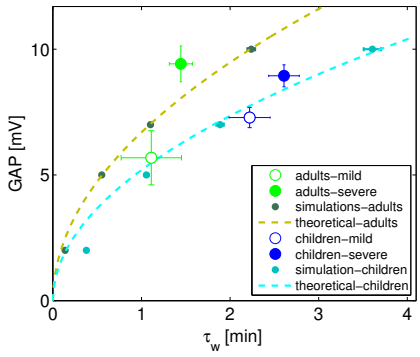

Fig. 6. **Estimating GAP from the characteristic time constant of the exponential distribution of wake bout durations for CSA.** The dashed lines show the relationship between GAP as a function of the characteristic time constant τ_w according to Eq. 29. The curve for adults (dashed olive green line) has a steeper slope as compared to the children (cyan) because of higher values of the neuronal noise σ (group averages: $\sigma_{\text{adults}} = 6.7$ vs. $\sigma_{\text{children}} = 5.2$ – see Methods and Materials, Eq. 17). Results of our model simulations with different values of GAP (dark green and dark cyan filled circles for adults and children, respectively) are in good agreement with the theoretical prediction of Eq. 29. For the empirical data of CSA subjects we distinguish participants (adults green/children blue) with mild CSA (CA index$\leq$4; open circles) and severe CSA (CA index$>$4; filled circles). We note that adults with mild CSA have significantly lower values of GAP than adults with severe CSA (Mann-Whitney U test: $p < 0.05$). There is no difference in the characteristic time τ_w between mild CSA and severe CSA within the adult or children groups, however, children have significantly higher τ_w values than adults (Mann-Whitney U test: $p < 0.01$). Shown are mean and standard error of the group averaged data for GAP and τ_w. Deviations between theoretical curves and empirical data are mainly due to differences in σ (there is a variation of σ within each group while for the theoretical lines we consider only the group average values).

the empirical analysis of sleep data from CSA children and adults. The steeper slope of the theoretical curve for CSA adults is due to the higher values of the neuronal noise level σ. Moreover, it can be seen that subjects with more severe CSA tend to have larger GAP values.

C. Introducing a new parameter to evaluate severity of central sleep apnea

On the practical side, the GAP value (Eq. 29) could be used to evaluate the CSA severity. From the WPN voltage fluctuations in the interval $0 < V < GAP$ we can derive a measure of 'energy dissipation' to characterize sleep/wake transitions in CSA patients. We call this measure CSA_{GAP} index, and we calculate it by

$$\text{CSA}_{\text{GAP}} \text{ index} = \sigma^2 \cdot \text{GAP} \tag{30}$$

with $\sigma = 25/\sqrt{\langle \text{sleep bout durations - } M_s \rangle}$ [23] and GAP can be calculated by Eq. 29 (for exact analytic derivation, see Methods and Materials Eqs. 18-23).

In Fig. 7a we show that the CSA_{GAP} index increases with CSA severity (as quantified by the CA index) and is a superior marker for CSA severity than a common measure using the number of arousals per night [35](cp. Fig. 7a and b). Moreover, the CSA_{GAP} index is better correlated with the CA index than the GAP values alone, indicating that the neuronal noise level plays an important role in CSA.

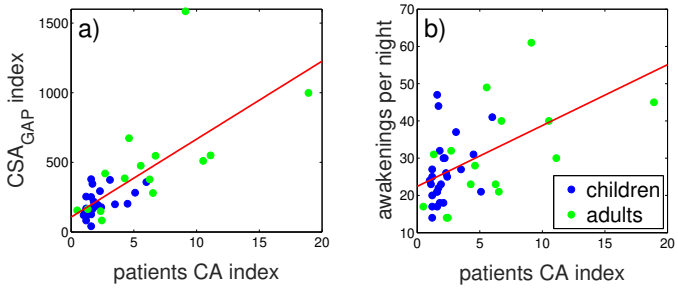

Fig. 7. **Comparison of clinical measures to evaluate CSA severity.** (a) Our CSA_{GAP} index as calculated by Eq. 23 for each subject (pooled data of children and adults) shows a very good correlation with an expert scoring of CSA severity quantified by the CA index (Spearman's rank correlation coefficient $\rho = 0.75$ ($p < 10^{-7}$)) (separately for children (blue filled circles): $\rho = 0.58$ ($p < 10^{-2}$), and for adults (green filled circles): $\rho = 0.78$ ($p < 10^{-3}$)). (b) The number of awakenings per night is considered to be a good indicator for CSA severity [35] and yields $\rho = 0.48$ ($p < 10^{-2}$) (children: $\rho = 0.40$ ($p < 0.05$), and adults: $\rho = 0.58$ ($p < 10^{-2}$)). These results suggest that the CSA_{GAP} index is a robust parameter (as it is valid for both children and adults) as well as a more sensitive measure of CSA severity than the number of awakenings per night.

IV. Discussion

We have conducted a systematic analysis of sleep data from healthy participants and patients with OSA and CSA, and we show that wake bout durations for healthy adults and healthy children as well as adult and children with OSA follow a power-law distribution. In contrast, we find that wake bout durations of CSA patients (adults as well as children with and without CPAP) decay exponentially. We propose a mechanism for this change in CSA wake bout distributions caused by the absence of the sleep restoring current at the transition from sleep to wake/arousal. Specifically, for CSA, the sleep restoring current occurs only after some delay due to higher excitability threshold of sleep promoting neurons (that trigger the current) as compared to the excitation of cortical neurons (that lead to arousal). The difference in these excitability thresholds ('GAP') is directly related to the delay between arousal generation and arousal attenuation, and when assuming a GAP in our biased diffusion model, we can reproduce the empirically-found exponential arousal distributions.

The GAP values can be estimated for individual subjects based on their arousal statistics throughout the night, and we suggest a clinical measure ('CSA_{GAP} index') of CSA severity that correlates very well with the manual CSA scoring provided by sleep clinicians. Since arousals during sleep can be determined simply by actigraphy [36], our method may be used to diagnose CSA (through the distribution of arousal/wake bout durations) and to monitor CSA treatment and progression (through the CSA_{GAP} index) in home environment on a daily base.

Generally, the findings by Lo et al. of a power-law probability distribution of wake-bout durations in healthy subjects [14], [16] as well as in OSA subjects [15] strongly indicate that arousals and short awakenings during sleep have physiological origin rather than being just random (external) perturbations (in which case one would expect exponential distributions). Moreover, the coexistence of scale-invariant (i.e., arousal distributions) and scale-specific (i.e., sleep distributions) pro-

cesses as output of a single sleep regulatory mechanism suggests that sleep (or brain dynamics during sleep) can be considered a self-organized criticality (SOC) system [15], [37]. As we show for CSA subjects, the power-law distribution of arousal durations is lost making sleep-stage transitions in CSA more random and diminish the SOC characteristics of the sleep process.

Our work provides a simple method to discriminate between OSA and CSA based on their arousal/wake bout durations. This discrimination is important, since OSA and CSA show similar clinical manifestation (i.e., sleep-disordered breathing) but their underlying pathology is very different and may require different treatment. Basic characteristics of sleep and wake bout distributions of OSA are similar to those of healthy participants (Fig. 4, Table I, and Appendix Fig. A1) suggesting that endogenous sleep regulation is largely unaffected in OSA. On the contrary, the alterations in arousal statistics of CSA patients imply that sleep-promoting centers do not show normal activity and their response to arousals is delayed. Therefore, CSA may be characterized not only by higher apneic threshold but also by higher excitability threshold of sleep-promoting neurons (SPN). Indeed, future studies of CSA could investigate abnormalities in excitability threshold also in other neuronal brain centers that are, for example, related to metabolic or cardiac regulation, as CSA is often associated with high incidence of cardiovascular disorders [38] and obesity [39].

Patients with sleep-disordered breathing sometimes show apnea of mixed type, i.e., apnea episodes begin as CSA and end as OSA [40]. In this case we expect a deviation from the power-law statistics of arousal durations towards an exponential distribution. However, further research has to show whether CSA and mixed apneas can be discriminated based on the analysis of hypnograms alone.

Currently, the standard treatment strategy of CSA focuses on the induced breathing problems and application of continuous positive airway pressure (CPAP) [41] sometimes in combination with supplementary CO_2 [9]–[11]. However, even in the presence of CPAP and CO_2 arousability remains high, leading to low sleep quality [10]. Moreover, we have found a GAP$>$0 even in CSA children treated with CPAP (see Fig. 4 and Table I). Our results suggest to combine supplementary CO_2 inhalation with administration of eszopiclone. Eszopiclone is a sedative agent that has been shown to lower the excitability threshold of GABAergic neurons [42], and therefore could effectively decrease the GAP leading to simultaneous SPN response to cortical excitation and reduce arousability.

Our analysis may also shed light on the ontogeny and phylogeny of mammalian sleep in general and sleep regulation during early maturation in particular. As has been shown for fetal sheep [33], infant mice [18] and rats [17], wake bouts initially follow an exponential distribution and a power-law distribution emerges during the early postnatal period. Therefore, sleep in mammals during the prenatal and early postnatal periods could be influenced by not yet fully developed sleep promoting neuronal centers in the brain as reflected by higher excitability thresholds and manifested in $GAP > 0$. In the course of maturation, SPN excitability thresholds normalize resulting in $GAP = 0$. Since CSA is common in preterm and newborn infants and during infancy in general [4], and there is an age-related decrease in CSA that is thought to be related to maturation of the central nervous system [43], GAP as obtained from wake bout durations could be used to monitor maturation and in turn help to determine a marker of biological age for premature babies and infants.

The stochastic model of sleep arousals presented in this paper is based on competing excitatory vs. inhibitory neuronal inputs. This concept of modeling the competition between opposing/competing regulatory mechanisms (e.g., sympathetic vs. parasympathetic tone) has been successfully used in earlier works on cardiac dynamics [44], [45] and human gait [46] to obtain the scaling behaviors commonly observed in physiological signals under neural regulation [47]. Introducing a time delay between excitation and inhibition (for example due to different excitability thresholds in wake- and sleep-promoting neurons ('GAP') in case of CSA) can lead to the alteration or even breakdown of the scaling behavior. It needs to be shown in future studies whether this sensitivity to time delays is a general property of complex systems with competing regulatory dynamics.

V. Conclusions

Central sleep apnea (CSA) is a common sleep disorder in younger children and in the elderly, and it is particularly frequent in chronic heart failure patients. Little is known about the pathogenesis of central sleep apnea (CSA), and there is no definite treatment strategy for CSA. In this work, we investigate the underlying neuronal mechanism of CSA by studying sleep data from adults and children. We find that the sleep/wake statistics of CSA patients is very different from those of healthy subjects and even patients with obstructive sleep apnea (OSA), and we show that this difference may be due to neuronal malfunctioning in CSA that increases the excitability threshold of GABAergic neurons. We anticipate that our methodology on deriving the difference in excitability thresholds based on simple and vastly available sleep/wake recordings can improve medical diagnostics (e.g., distinguishing between CSA and OSA) as well as offers new strategies and monitoring of pharmacological treatment of CSA patients.

Appendix A
Histograms of wake bout durations

Because of the delay between arousal generation and SPN excitation, which results in lack of an arousal-attenuating current, CSA patients have more intermediate length arousals compared to healthy subjects and even patients with OSA (Fig. A1). Specifically, we find that for CSA adults, arousals of 1-2 min duration are increased by a factor of 1.5 as compared to healthy and OSA subjects. Moreover, for CSA children intermediate arousals (duration 6.5-9 min) are increased by a factor of 2.5 (Fig. A1).

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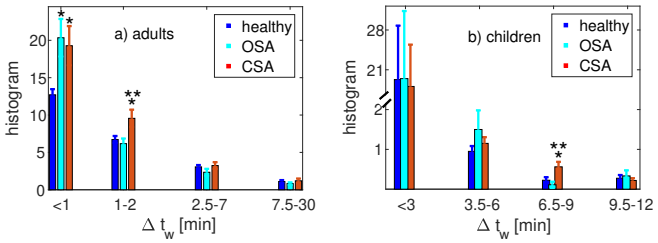

Fig. A1. **Histograms of wake bout durations.** (a) Adults and (b) children with central sleep apnea (CSA, red lines) have more arousals of intermediate length (between 1-2 min for CSA adults and 6.5-9 min for CSA children) as compared to healthy participants (blue) and subjects with obstructive sleep apnea (OSA, cyan). This may be because of the difference in excitability thresholds between cortical neurons and VLPO neurons ('GAP'; Fig. 2). Shown are the pooled arousal and wake bout durations for each group. Note the large number of very short arousals (duration < 1 min in adults) in OSA and CSA due to the apnea [48]. Group differences are statistical significance if $p < 0.05$ (Mann-Whitney U test): $*$ compares OSA or CSA to healthy; $**$ is for the comparison CSA to OSA.

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