

Approximate Entropy of Human Respiratory Movement During Eye-Closed Waking and Different Sleep Stages*

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Study objective: The breath-to-breath variability of respiratory parameters changes with sleep stage. This study investigates any alteration in the approximate entropy (ApEn) of respiratory movement as a gauge of complexity in respiration, by stage of consciousness, in the light of putative brain interactions.

Participants: Eight healthy men, who were between the ages of 23 and 29 years, were investigated.

Measurements and results: The signals of chest wall movement and EEG were recorded from 10:30 PM to 6:00 AM. After analog-to-digital conversion, the ApEn of respiratory movement (3 min) and EEG (20 s) were computed. Surrogate data were tested for nonlinearity in the original time series. The most impressive reduction in the ApEn of respiratory movement was associated with stage IV sleep, when the ApEn of the EEG was also statistically significantly decreased. A statistically significant linear relation is found between the ApEn of both variables. Surrogate data indicated that respiratory movement had nonlinear properties during all stages of consciousness that were investigated.

Conclusion: Respiratory movement and EEG signals are more regular during stage IV sleep than during other stages of consciousness. The change in complexity described by the ApEn of respiration depends in part on the ApEn of the EEG, suggesting the involvement of nonlinear dynamic processes in the coordination between brain and lungs.

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Key words: approximate entropy; complexity; EEG; respiration; nonlinear; sleep

Abbreviations: ANOVA = analysis of variance; ApEn = approximate entropy; D2 = correlation dimension; REM = rapid eye movement

The behavior of human physiologic systems is highly variable. Recently, mathematical techniques have been developed that may be useful for quantifying and describing the complex and chaotic signals that are characteristic of physiologic systems.

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Whereas much research in this area has been conducted in relation to the cardiac system, the same methods used in that research also show promise in relation to the respiratory system. Recent chaotic analyses of respiratory movement indicated a dependence of the correlation dimension (D2) on sleep stage,^{1,2} which is statistically significantly higher during rapid-eye-movement (REM) sleep than during

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stage I or IV sleep.^{1,2} These and other results led to the view that respiratory movement is a nonlinear deterministic process during waking^{1,3,4} and during sleep.^{1,2,5,6}

There is only scant evidence for brain-lung interactions based on (linear) spectral analyses of EEG

and respiratory signals. Pfurtscheller⁷ reported that EEG parameters changed synchronously with respiration and also with the rhythms of six beats per minute underlying heart rate variability. Sleep stage reportedly affects the breath-to-breath variability of respiratory parameters such as tidal volume or respiratory cycle. The variability of the breathing pattern increases during REM sleep and decreases during stage IV sleep.^{8,9} Higher centers in the brain are reported to affect breath-to-breath variability of the ventilatory pattern,⁹ the breathing pattern being more regular during deep slow-wave sleep (*ie*, stage IV sleep).

Respiratory disturbances have been observed during sleep in patients with different brain disorders.¹⁰ The EEG is usually used to evaluate sleep stages. The Kolmogorov entropy of the EEG during deep sleep is reportedly smaller than that during α rhythm sleep.¹¹ The EEG also has been viewed as a nonlinear deterministic process, with values of D2 differing with sleep stage^{12,13} and in the presence of brain disorders.¹⁴ Nonlinear characteristics of respiration during sleep may thus be important to further the understanding of these observations.

The term *approximate entropy* (ApEn) was developed as a measure of system complexity.¹⁵ A low value of ApEn indicates predictability and regularity in a time series, whereas a high value of ApEn indicates unpredictable and random variation. ApEn potentially can discriminate among a wide variety of systems, including deterministic, stochastic, and composite systems, while being applicable to noisy, medium-sized time series.^{15–19} This measure of complexity, however, apparently has not been used to evaluate changes in respiration during sleep. This study investigates changes in ApEn during four stages of consciousness (*ie*, eye-closed awake, REM, stage I, and stage IV sleep) and attempts to associate such alterations with brain function. While the term *complexity* encompasses several different concepts, it is restricted to the definition provided by Pincus¹⁵ in relation to ApEn herein.

MATERIALS AND METHODS

Subjects

The study was performed at the third Department of Internal Medicine, Tottori University, Yonago, Japan. Eight healthy men, aged between 23 and 29 years (mean [\pm SD] age, 24.6 \pm 2.1 years) and were nonsmokers, and who did not consume alcohol or caffeine on the day preceding the study, were investigated. They usually went to sleep around 11:00 PM and awoke at 7:00 AM. The protocol was approved by the local ethics committee. Informed written consent was obtained from all subjects.

Measurements

Monitoring started at 10:30 PM and was completed at 6:00 AM on the next day while the examinees were resting with eyes closed, lying in a darkened, sound-attenuated room. A chest band (Respiband; NonInvasive Monitoring Systems Inc; North Bay Village, FL) was applied around the rib cage at the level of the nipples to measure respiratory movement using an inductance plethysmograph (Respiomnograph; NonInvasive Monitoring Systems Inc). The EEG was recorded (Synafit 2100; NEC; Tokyo, Japan) at positions O1, O2, F3, F4, C3, and C4 according to the international 10–20 system. Surface electrodes at the outer canthi of both eyes recorded eye movements and submental electromyographic activity on the chin. Two independent neuroscientists each categorized the stage of consciousness at 30-s intervals on the EEG records, using the criteria of Rechtschaffen and Kales.²⁰ We analyzed the voltage change of both the EEG and the respiratory movement signals. From the eye-closed awake stage and from each sleep stage (*ie*, I, IV, and REM), three different epochs of artifact-free respiratory movement (3 min each) were selected for each subject. All subjects were right-handed. The C3 EEG position, which was referenced to the A2 position, was chosen²¹ for analysis. A low-pass filter that was set at 60 Hz and a time constant of 0.3 s were used for recording. The EEG signals used for analysis corresponded to 20-s artifact-free epochs within the 3-min spans selected to assess respiratory movement. The signals from respiratory movement and EEG were stored on a magnetic tape (model A-47 instrumentation tape recorder; Sony; Tokyo, Japan) and was digitized at sampling rates of 10 Hz (for respiratory movement) and 200 Hz (for EEG) with 12-bit resolution. The ApEn of respiratory movement was estimated for eight subjects and that of the EEG was estimated for 7 subjects because the EEG signal of one subject was not recorded on magnetic tape.

Linear Analyses

Periodic components of respiratory signals were estimated by means of the fast Fourier transform (MatLab; The MathWorks, Inc; Natick, MA). From the corresponding power spectra, the peak frequency and amplitude were calculated in each case.

Nonlinear Analysis

Computation Of ApEn: The ApEn is a measure of system complexity that was introduced by Pincus.¹⁵ It is computed as follows:

$$\text{ApEn}(m,r) = (N - (m - 1))^{-1} \sum_{i=1}^{N-(m-1)} \ln C_i^m(r) - (N - m)^{-1} \sum_{i=1}^{N-m} \ln C_i^{m+1}(r)$$

where C is the correlation integral.

Its derivation is outlined in the "Appendix." Entropy can be viewed as a measure of disorder, larger values conveying more disorder, randomness, or complexity.²²

We set the filter factor, *r*, to be 0.2 times the SD of the original data series.^{15,16} We used an embedding dimension of 2 (*ie*, *m* = 2).^{15,16} To embed the time series in state space,²³ we used a time lag, τ , of 11 (1.1 s) for respiratory movement and a time lag of 18 (0.09 s) for the EEG. These values were chosen as the average time lags that were determined for each time series as the lag at which the autocorrelation function first nears zero in

respiratory movement and 1/e in the EEG (see “Appendix”). ApEn was computed with a software package (MatLab; The MathWorks, Inc).

Surrogate Data Analysis

The purpose of surrogate data is to test for any nonlinearity in the original time series. Nonlinear indexes such as the ApEn are computed for several surrogate data series. Their values are compared with that assumed by the nonlinear index computed for the original data.²⁴ The lack of any statistically significant difference is interpreted as meaning that the original series originates from a linear process, since linear techniques are used to generate surrogate data that have general properties similar to those of the original series. By contrast, the demonstration of a statistically significant difference in ApEn between the original and surrogate data are in keeping with the presence of nonlinear dynamics in the original signal.

Several algorithms to generate surrogate data series have been designed.²⁴ The surrogate data series generated herein were constructed to have the same histogram and the same power spectrum as the original data. Their mean value and variance were identical to those of the original data. From the spectral aspect, this method of generating surrogate data is based on the amplitude adjusted Fourier transform method,²⁴ which yields the same distribution of amplitudes but randomizes the phases. Tentative surrogate data are obtained by inverse Fourier transform. Instead of using the data thus generated, the algorithm uses as surrogates shuffled versions of the original signal, where the shuffling is performed based on ranks of the inverse Fourier-transformed series. An iterative technique²⁵ is used to improve the match of the power spectrum, while maintaining an exact match of the histogram of the original data.

To test for a statistical significance of difference (*ie*, the σ of Theiler et al²⁴) in ApEn between the original and the surrogate data, 10 surrogate data series were generated to match each original signal. Let ApEn D be the ApEn of the original data, and let ApEn Si be the ApEn of the 10 surrogate series ($i = 1, \dots, 10$). The mean and SD of ApEn Si ($i = 1, \dots, 10$) are estimated as ApEn S and SD(ApEn Si). σ (Theiler et al²⁴) then is computed as follows:

$$|\text{ApEn D} - \text{ApEn S}| / \text{SD}(\text{ApEn Si}).$$

This statistic represents the number of SDs (σ) distant from ApEn D. It follows a Student *t* test distribution with 9 degrees of freedom ($\sim t_{9[1-\alpha/2]}$). For $\alpha = 0.05$, the critical value of *t* is 2.26. Accordingly, when the σ of Theiler et al²⁴ is > 2.26 , the null hypothesis is rejected at the 5% probability level, and the original data are considered to contain nonlinear features.

Statistical Analysis

The replicability of ApEn was assessed by intraclass correlation analysis from the three replicate measurements of ApEn (on three epochs of 3 min each), obtained from each subject during each stage of consciousness. The average values of ApEn of respiratory movement or EEG during a given stage of consciousness are presented as means ± 1 SD across subjects. A two-way analysis of variance (ANOVA) was used to assess any difference in the ApEn of respiratory movement among the four stages of consciousness. The Scheffé test was used for contrasts when multiple comparisons were performed. A global test of nonlinearity was carried out by a Wilcoxon matched-pairs signed rank test comparing ApEn values computed on the original data paired with the corresponding average ApEn values from the matching surrogate data series.^{24,25} A statistical software package (StatFlex;

ViewFlex; Tokyo, Japan) was used. Results were considered to be statistically significant if $p < 0.05$.

RESULTS

In order to facilitate the interpretation of the ApEn values of the respiratory movement and EEG signals, the ApEn values of a sine wave and a torus ($N = 1,800$) were estimated to be 0.001 and 0.095, respectively, as examples of regular (linear) signals. The ApEn of a series of uniformly random numbers ($N = 1,800$) was estimated to be 2.182.

As shown by intraclass correlation, the ApEn measurements were well-replicated among the three estimates obtained on separate 3-min epochs for each subject during each stage of consciousness. The intraclass correlation coefficients for respiratory movement were 0.450 ($p = 0.019$) during the eye-closed awake stage, 0.440 ($p = 0.021$) during REM sleep, 0.731 ($p < 0.001$) during stage I sleep, and 0.705 ($p < 0.001$) during stage IV sleep. For EEG signals, the intraclass correlation coefficients were 0.721 ($p < 0.001$) during the eye-closed awake stage, 0.727 ($p < 0.001$) during REM sleep, 0.791 ($p < 0.001$) during stage I sleep, and 0.825 ($p < 0.001$) during stage IV sleep.

The mean (\pm SD) intrasubject coefficients of variation of the ApEn for respiratory movement during each stage were $8.0 \pm 5.2\%$ (eye-closed awake stage), $6.6 \pm 4.5\%$ (REM sleep), $7.2 \pm 3.2\%$ (stage I sleep), and $5.7 \pm 5.2\%$ (stage IV sleep). For the ApEn of the EEG, intrasubject coefficients of variation were $1.9 \pm 1.0\%$ (eye-closed awake stage), $2.3 \pm 2.0\%$ (REM sleep), $4.1 \pm 2.1\%$ (stage I sleep), and $3.0 \pm 2.5\%$ (stage IV sleep). By comparison, the intersubject coefficients of variation of the ApEn for respiratory movement during each stage were 9.8% (eye-closed awake stage), 8.0% (REM sleep), 13.3% (stage I sleep), and 12.4% (stage IV sleep). For the ApEn of the EEG, the intersubject coefficients of variation were 3.6% (eye-closed awake stage), 5.2% (REM sleep), 8.8% (stage I sleep), and 8.0% (stage IV sleep).

The mean (\pm SD) values of ApEn for respiratory movement (original data) were 1.39 ± 0.14 during the eye-closed awake stage, 1.48 ± 0.12 during REM sleep, 1.37 ± 0.18 during stage I sleep, and 1.13 ± 0.14 during stage IV sleep (Fig 1). The ApEn of respiratory movement is found to differ with statistical significance among the four stages of consciousness ($p < 0.0001$ [ANOVA]). The ApEn was significantly lower during stage IV sleep than during the eye-closed awake stage ($p < 0.01$), stage I sleep ($p < 0.01$), or REM sleep ($p < 0.001$). A global test of nonlinearity comparing ApEn values between pairs of original and surrogate data series found the

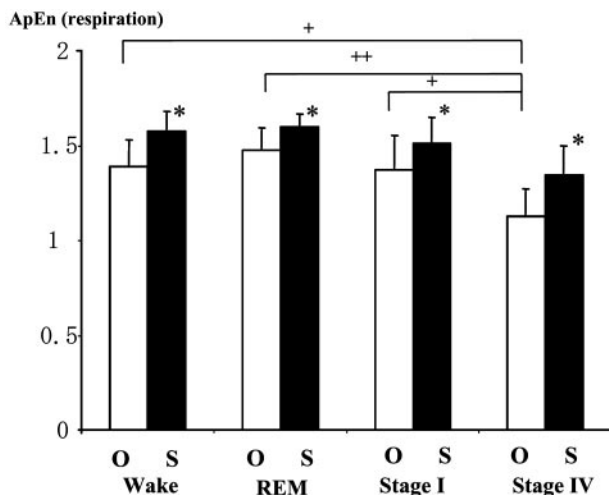


FIGURE 1. ApEn of original (O) and surrogate (S) data in respiratory movement during different stages of consciousness in eight subjects ($p < 0.0001$ [ANOVA]). Values are given as the mean \pm SD. + = $p < 0.01$ (Scheffé test); ++ = $p < 0.001$ (Scheffé test); * = $p < 0.01$ (from comparison with ApEn of original data using Wilcoxon matched-pairs signed rank test).

difference to be statistically significant for respiratory movement during each stage of consciousness ($p < 0.01$ in each case) [Fig 1].

In order to eliminate interindividual variation, the data in Figure 2 were expressed as a percentage of the mean ApEn value across the four stages. The percentage change of respiratory ApEn during each stage then was obtained by subtracting 100% (Fig 2). ApEn is seen to be invariably below average during stage IV sleep, while it is invariably above average during REM sleep. The percentage change in ApEn was found to differ with statistical significance among the four stages of consciousness ($p < 0.0001$ [ANOVA]). Contrasts show similar results as for the

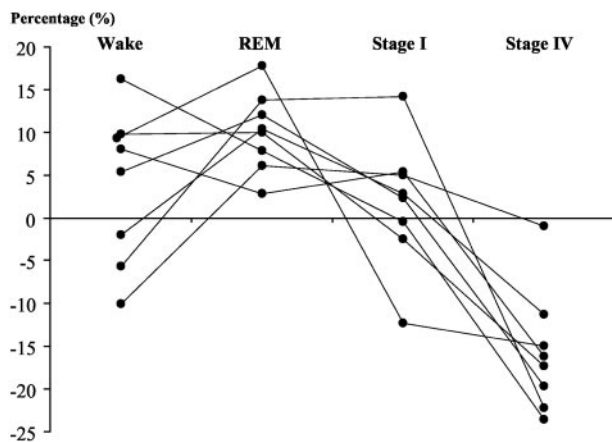


FIGURE 2. Percentage change in mean ApEn during different stages of consciousness (eight subjects; $p < 0.0001$ [ANOVA]).

original data. In accordance with the presence of nonlinear features in respiratory movement, only a weak relationship between peak power frequency and ApEn was found ($r = 0.299$; $p = 0.005$) [Fig 3]. The mean peak frequency of respiratory movement was 0.282 ± 0.052 Hz (eye-closed awake stage), 0.285 ± 0.053 Hz (REM sleep), 0.284 ± 0.049 Hz (stage I sleep), and 0.279 ± 0.035 Hz (stage IV sleep). No statistically significant difference in the peak frequency of respiratory movement was found among the four stages.

Values of ApEn for the EEG signals are compared in Figure 4 among the four stages of consciousness ($p < 0.0001$ [ANOVA]). Again, contrasts indicate that the ApEn of the EEG during stage IV sleep is lower than during other stages of consciousness ($p < 0.01$ in each case) [Fig 4].

The σ test of Theiler et al²⁴ was performed for each data series separately to test for nonlinearity (Fig 5). The mean (\pm SD) values of the σ test of Theiler et al²⁴ for respiratory movement (original data) were 9.0 ± 5.4 during the eye-closed awake stage, 5.6 ± 2.8 during REM sleep, 6.8 ± 3.8 during stage I sleep, and 11.9 ± 7.0 during stage IV sleep. Evidence for nonlinearity in the respiratory signals is present in 21 of 24 series during the eye-closed awake stage and during REM sleep, and in 23 of 24 series during stages I and IV sleep. Whereas only 8 signals of respiratory movement failed the test, all 76 other series showed nonlinearity (Fig 5).

Figure 6 shows that the ApEn of respiratory movement is linearly related to the ApEn of the EEG ($r = 0.494$; $p = 0.0001$).

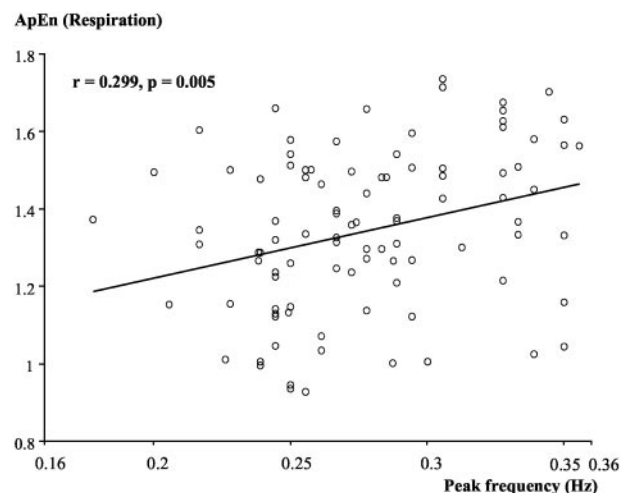


FIGURE 3. Linear regression between the ApEn of respiration and the peak frequency of signal from eight subjects. There is a weak relationship between the peak power frequency and the ApEn ($r = 0.299$; $p = 0.005$).

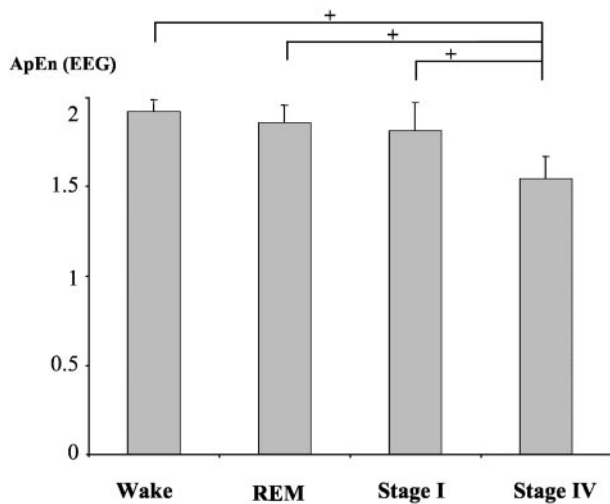


FIGURE 4. ApEn of original data in EEG during different stages of consciousness in seven subjects ($p < 0.0001$ [ANOVA]). Values are given as the mean \pm SD. + = $p < 0.01$ (Scheffé test).

DISCUSSION

Nonlinear analyses of respiratory movement and EEG signals during eye-closed awake and different sleep stages reveal a most impressive reduction in

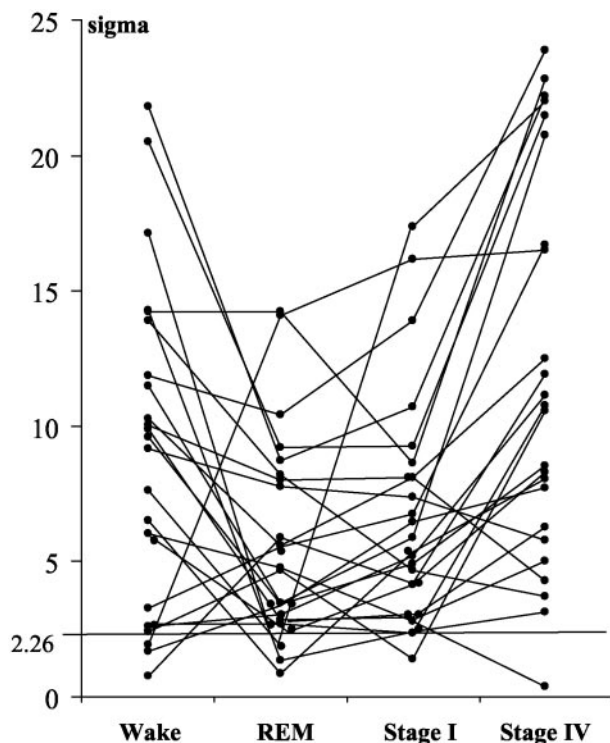


FIGURE 5. Documentation of nonlinearity in respiratory movement using σ by Theiler et al²⁴ to test the significance of difference in ApEn during each stage of consciousness between the original and the surrogate data (see text). For $\alpha = 0.05$, the critical value of t is 2.26.

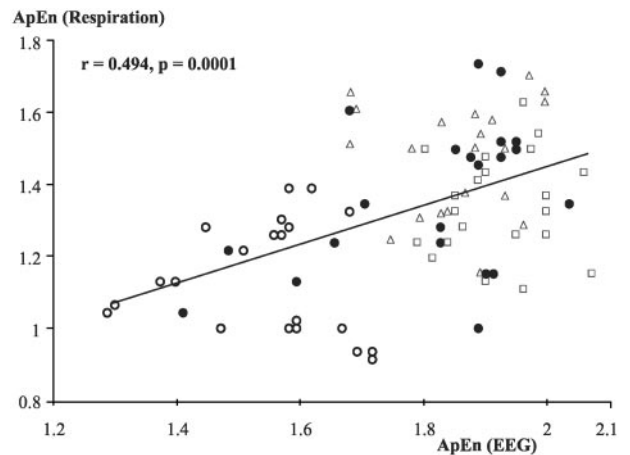


FIGURE 6. Single linear regression between the ApEn of respiratory movement and the ApEn of EEG (original data) in seven subjects. Note the statistically significant correlation ($r = 0.494$; $p = 0.0001$). \square = eye-closed awake stage; \triangle = REM sleep; \bullet = stage I sleep; \circ = stage IV sleep.

ApEn during stage IV sleep (*ie*, slow-wave deep). Both respiratory movement and EEG signals are more regular during this stage than during other stages of consciousness. This increased regularity of the respiratory rate during slow-wave sleep (stage IV) compared to lighter stages of non-REM sleep and to REM sleep in itself is not a new finding. In an extensive review, Phillipson²⁶ offers as an explanation the fact that respiration then is coordinated solely by the “metabolic respiratory control system.” The “monotonous regularity of the rate and depth of breathing” during stage IV sleep also was commented on by Sullivan.²⁷

These earlier findings are extended herein to an end point of deterministic chaos, the ApEn, which also indicates the presence of nonlinear dynamics in the signals of respiratory movement. Indeed, the analysis of surrogate data yielded evidence of nonlinearity during all four stages for respiratory movement. Although a weak significant linear relationship was found between ApEn and the peak power frequency (Fig 3), there was no significant difference in peak power frequency among the four stages of consciousness, despite the significant changes in ApEn. These results suggest that ApEn provides useful information on respiration signals during sleep beyond that available from the power spectrum. The intersubject variability of the percentage change in ApEn was somewhat larger during the eye-closed awake stage (SD, 8.9%) than during REM sleep (SD, 4.6%), stage I sleep (SD, 7.6%), or stage IV sleep (SD, 7.2%) [Fig 2]. This could be related to behavioral control in respiration during waking. In addition, some individuals had different patterns of ApEn during sleep, notably during stage I. The transition from waking to light sleep also may influence the value of ApEn in stage I sleep in some cases. The

classification of sleep stages from the EEG used currently, which is based on (linear) spectral analyses, is admittedly artificial. Further work could investigate whether the variability in ApEn seen during different stages of consciousness could be used as a tool for a more refined classification of sleep stages.

For the study of brain-lung interaction, we examined the relationship between the ApEn of the EEG and that of respiratory movement during different stages of consciousness. We found a statistically significant linear relation between the ApEn of the two variables (Fig 6). The difference in ApEn found between the original and surrogate data for respiratory movement during all four stages of consciousness suggests that the relationship found between the brain and lungs is, at least in part, nonlinear. If a reduced ApEn can be interpreted as reflecting a less complex (in the sense of more regular) system, then the result suggests that a reduction of complexity in the EEG may be associated with an increased regularity of breathing during deep stage IV sleep.

An alternative explanation for the linear relationship between the ApEn of respiratory movement and the EEG signals is that an independent third system may affect both the lungs and the brain.²⁶ Brainstem systems, including that of the cholinergic system, for instance, may affect both respiration and the cortex independently.²⁸ Work by Lieske et al²⁹ on brainstem slices containing the pre-Bötzinger complex suggests that a single medullary network may underlie multiple breathing patterns.

We found no report on ApEn applied to respiration in relation to sleep. This nonlinear index was mostly used in relation to the heart. A decrease in ApEn, that is an increase in regularity, was associated with the presence of cardiac disease. The heart rate during quiet sleep is more regular in infants who have experienced one or more episodes of aborted sudden infant death syndrome than in matched healthy infants, as evidenced by low ApEn values in the aborted-sudden infant death syndrome group.³⁰ On the other hand, high ApEn values with more tidal volume irregularity have been reported in association with respiratory failure. Engoren³¹ reported a statistically significant difference in the ApEn of respiration between patients with respiratory failure who either succeeded (low ApEn) or failed (high ApEn) in being weaned from mechanical ventilation. Given that high ApEn values may relate to respiratory failure, whereas low (rather than high) ApEn values may indicate cardiac disease, one may speculate that the pulmonary system differs from the cardiac system. This may be so perhaps because respiration is partly under behavioral control, whereas the cardiac system has little voluntary control. This difference may result in the differing changes in ApEn of respiratory and cardiac disease on complexity

and/or regularity. In endocrinology, the values for the ApEn of growth hormone secretion or aldosterone secretion were reportedly higher in patients with acromegaly³² or primary aldosteronism³³ than in healthy subjects. Since the pathologic mechanism may differ with each organ system and/or each disease, the values assumed by ApEn in the presence of disease may differ accordingly.

Before assessing ApEn in patients who are ill, it is important to know how ApEn may vary under usual conditions in clinical health. Our study shows relatively large changes in the ApEn of respiratory movement with sleep. Any change in ApEn in patients who are ill will need to account for such changes, which occur naturally in healthy persons. For instance, it will be important to specify the sleep stage during which ApEn is estimated. This may be particularly pertinent in cases of patients with different brain disorders who also exhibit respiratory disturbances,¹⁰ notably since nonlinear indexes such as D2 have been shown to be affected by brain disorders.¹⁴

Breathing regularity is reportedly increased with anesthesia or vagotomy, as gauged by the Kolmogorov entropy of the flow-volume respiratory-phase space.³⁴ The entropy of respiration was decreased during anesthesia compared to waking.³⁴ The ApEn values of the EEG also are decreased with anesthesia.^{35,36} Anesthesia not only causes deep sleep, but also strongly affects the autonomic nervous system.³⁷ These results are in keeping with our demonstration, without external factors, that the values of ApEn are statistically significantly lowered during deep sleep (*ie*, stage IV sleep) in healthy subjects.

The results obtained herein suggest that ApEn contributes information in terms of nonlinear features of respiratory signals beyond that available from linear approaches such as the power spectrum. ApEn and other indexes of nonlinear dynamics thus offer themselves as new, added tools for the study of respiration and how it may relate to the brain, to sleep, and to the autonomic nervous system.

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APPENDIX

Computation of the ApEn

The ApEn was introduced by Pincus¹⁵ as a measure of system complexity. It is derived from the correlation integral $C_i^m(r)$, which represents the number of points within a distance r from the i th point when the signal is embedded in an m -dimensional space:

$$C_i^m(r) = (N - (m - 1))^{-1} \sum_{j=1}^{N - (m - 1)} \Theta(r - |\mathbf{x}_i - \mathbf{x}_j|)$$

where $\Theta(t)$ is the Heaviside function (if $t \geq 0$, $\Theta(t) = 1$; if $t < 0$, $\Theta(t) = 0$) and \mathbf{Xi} and \mathbf{Xj} are vectors constructed from the time series $[x(1), x(2), \dots, x(N)]$ as

$$\begin{aligned}\mathbf{Xi} &= \{x(i), x(i + \tau), \dots, x(i + (m - 1)\tau)\} \\ \mathbf{Xj} &= \{x(j), x(j + \tau), \dots, x(j + (m - 1)\tau)\} \\ &(i, j = 1, 2, \dots, N - (m - 1)\tau)\end{aligned}$$

where τ is the time lag at which the serial correlation between consecutive samples becomes negligible. The ApEn statistic is defined as follows:

$$\begin{aligned}\text{ApEn}(m, r) &= \Theta^m(r) - \Theta^{m+1}(r) \\ \Theta^m(r) &= (N - (m - 1))^{-1} \sum_{i=1}^{N - (m - 1)} \ln C_i^m(r).\end{aligned}$$

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