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Continuous EEG-based dynamic markers for sleep depth and phasic events

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ABSTRACT

Sleep architecture is characterized by classifying polysomnographic epochs into mutually exclusive stages. Notwithstanding the clinical importance of staging, it has the drawback of representing sleep as a discrete process. Metrics based on the electroencephalogram (EEG) are needed to supplement conventional sleep staging by allowing a description of sleep in terms of unitary, continuous markers. Traditional linear and nonlinear techniques for achieving this goal have not proved sufficient. Employing recurrence analysis, we developed a method for capturing and quantifying the dynamical states of the brain during sleep. The method yields markers for continuously determining sleep depth, for detecting sleep-specific phasic events, and for objectively defining potentially useful sleep markers and indices. Recurrence markers captured the coarse- and fine-grained temporal activity of the sleep EEG, thereby permitting continuous quantitation of brain electrical activity on any desired time scale. The markers were validated with respect to the tonic behavior (time scale of seconds) of the sleep EEG by establishing that they disambiguated the stages of sleep that are defined solely on the basis of EEG activity. Validation of the markers over time scales of milliseconds was achieved by showing that common types of sleep-EEG phasic events could be detected by recurrence analysis. The method was also used to define a generalized EEG arousal index that quantified previously unrecognized sleep-stage-dependent deterministic properties of brain electrical activity. Using nonlinear analysis that quantified the recurrence properties of the EEG, we described a novel method for producing dynamic markers of brain states during sleep.

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1. Introduction

Human sleep is commonly studied by analyzing simultaneously digitized signals from the brain, heart, skeletal muscle, and other physiological systems (Kryger et al., 2010). Sleep macro-architecture is characterized by analyzing the signals in 30-s epochs and classifying them on the basis of standardized rules into one of four mutually exclusive stages, either rapid-eye-movement (REM) sleep or progressively deeper stages of non-REM sleep respectively termed N1, N2, and N3 (American Academy of Sleep Medicine, 2007). Specific transient changes in the signals (phasic events) are incorporated into the definitions of the stages. Knowledge of sleep-stage distributions permits normal and pathological sleep to be distinguished (Chokroverty et al., 2005).

The concept of sleep stage is fundamental in understanding sleep physiology but has several limitations. Staging emphasizes the discontinuity of sleep, leading to its representation as a discrete process rather than as a continuous process which is actually the case. Additionally, phasic events in the electroencephalogram (EEG) are pictured as more or less distinct phenomena superimposed on the tonic EEG background, even though the events and the background must have a unitary cause because they are simultaneous outputs of the same system, the brain. Finally and perhaps most importantly, the non-REM sleep stages are defined in terms of the tonic/phasic behavior of the EEG, whereas REM sleep is defined in terms of the coordinated behavior of three signals, only one of which is the EEG. This fundamental difference prevents characterization of sleep stages in terms of a single, continuous, physiological variable. Consideration of these limitations suggested to us that a complementary perspective of sleep based on EEG metrics alone might increase the usefulness of sleep staging as an analytical tool and lead to new insights into sleep neurodynamics.

EEG metrics have traditionally been obtained by means of time averaging or spectral analysis (Thakor and Tong, 2004), but linear techniques are not well-suited for characterizing sleep EEG activity because it can change profoundly from second to second under the

influence of brain-wide interactions (both electrical and chemical) governed by nonlinear dynamical laws (Gazzaniga, 2000). Various model-based nonlinear techniques have been proposed for extracting information encoded in the EEG (Pradhan et al., 2012), but none have been validated for use in studying EEGs recorded during sleep. Recurrence analysis is a promising model-free approach for detecting tonic and phasic changes in the vigilant EEG induced by external stimuli (Carrubba et al., 2006, 2008). Our aim here was to describe and validate an extension of that approach to the study of the sleep EEG.

First we show that recurrence-based markers capture the coarse- and fine-grained temporal activity of the sleep EEG, thereby permitting continuous quantitation of brain electrical activity on any desired time scale. Second, we validate the markers by showing that they behave as expected when compared with the results of sleep staging, and that they can detect the common phasic EEG changes that occur during sleep. Third, we show that the markers can be used to objectively define a stage-dependent generalization of the conventional EEG arousal index.

2. Methods

2.1. Polysomnograms

Polysomnographic records (PSGs) of 7 attended overnight sleep studies were randomly selected from the patient database of our sleep disorders center. The PSGs had been recorded using commercial equipment (Respironics, Murrysville, PA, USA) controlled by proprietary software (Alice 5). All subjects had been referred for follow-up regarding suspected sleep disorders, mostly obstructive sleep apnea (OSA). The PSGs (800–900 30-s epochs) were staged independently by two board-certified sleep physicians according to standard rules (American Academy of Sleep Medicine, 2007). The staging consisted of assigning each epoch to wakefulness or to one of four rule-defined stages of sleep (N1, N2, N3, REM). Where disagreement occurred, stage classification was achieved by consensus (<8% of the staged epochs). The EEGs (six derivations) were analog-filtered to pass 0.3–109 Hz, sampled at 500 Hz, and analyzed offline; only results from derivation C4-M1 (International 10–20 System) are presented because they were representative of the results from the other derivations.

PSGs from 8 clinically normal subjects were obtained from the BIH/MIT database at PhysioBank (Goldberger et al., 2000; Ichimaru and Moody, 1999). The PSGs were staged by PhysioBank experts. The EEGs (two derivations) were sampled at 100 Hz; only results from Fz-Cz are presented.

All EEG analyses were performed using a custom code after removing frequencies outside the 0.5–35 Hz band (Matlab, Math-Works, Natick, MA, USA). The EEGs recorded in Alice 5 were exported as CSV files; the PhysioBank EEGs were obtained as EDF files and converted into a Matlab-readable format. To standardize the scale for presentation of recurrence data (see below) the PhysioBank data was interpolated to 500 Hz (Matlab Resample command). Based on preliminary studies in which 500-Hz data was sub-sampled to 100 Hz and then interpolated to 500 Hz, we concluded that the recurrence values of the interpolated PhysioBank data were identical to those that would have been obtained had the data originally been sampled at 500 Hz. The sampling frequency is an important consideration in experimental studies that employ recurrence methods to test hypotheses, but sampling frequency was not a pivotal issue in defining the method described here or establishing its validity.

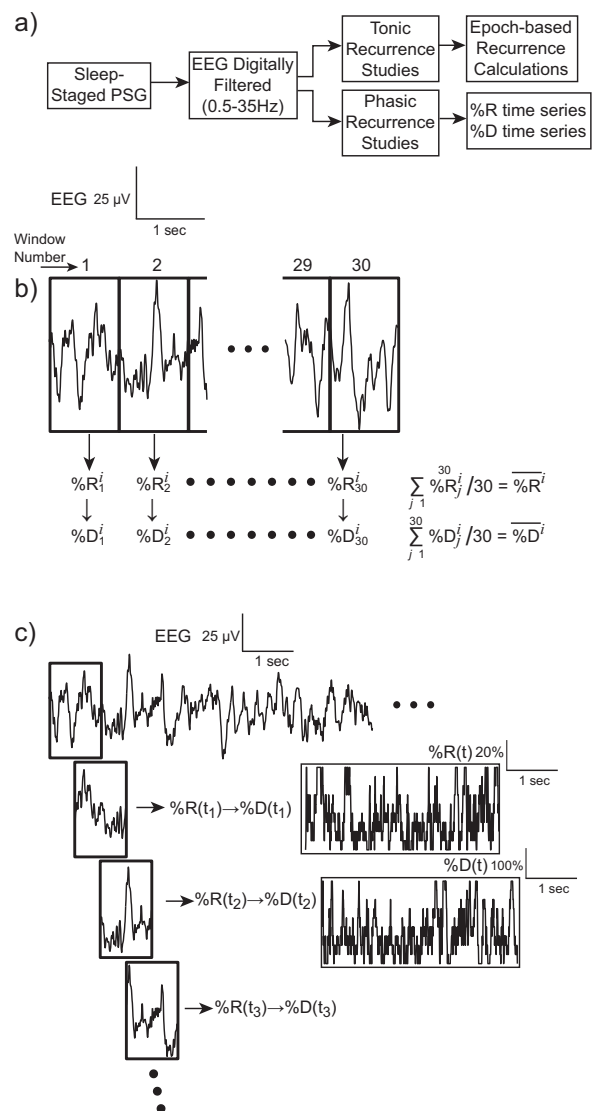The study was approved by the institutional review board for human research.

Fig. 1. Application of recurrence analysis to electroencephalographic signals (EEGs) recorded during sleep. (a) General description of the method for analyzing sleep EEGs. (b) For tonic studies, the recurrence variables percent recurrence (%R) and percent determinism (%D) are computed over successive one-second intervals. Averaging over the 30 values in a conventional sleep epoch allows the overnight range of the recurrence variables to be compared with the results of sleep staging. $\overline{\%R^i}$ and $\overline{\%D^i}$ are respectively the average percent recurrence (%R) and percent determinism (%D) for the ith sleep epoch. (c) Computation of %R(t) and %D(t) time series for use in extracting information regarding phasic changes in the sleep EEG. %R and %D are computed for overlapping time windows at a finer resolution (compared with (b)), resulting in time series for the variables that can be analyzed to detect phasic events.

2.2. Recurrence analysis

Pertinent mathematical details of recurrence quantification analysis (RQA) have been described (Zbilut and Webber Jr., 2006). Briefly, the signal together with time-lagged versions were embedded in a hyper-dimensional phase space using embedding conditions chosen and validated in earlier studies (see below). The trajectory of the state vector was represented graphically by plotting a point in two dimensions at the location addressed by (i,j) whenever the ith and jth state vectors were near (within 15% of the maximum Euclidean distance between any two states) (Eckmann et al., 1987). The plots were quantified using two variables. The first was percent recurrence (%R), defined as the number of points in the plot divided by the total number of point locations (places
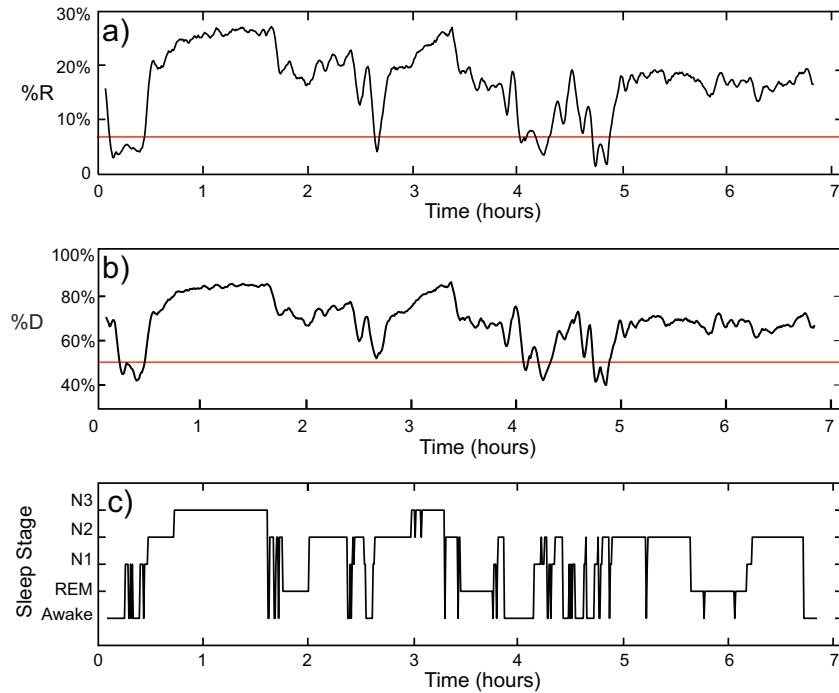
Fig. 2. Typical results for percent recurrence (%R) and percent determinism (%D) computed using successive 1-s intervals in an overnight sleep EEG (C4-M1). Subject diagnosed with obstructive sleep apnea. (a) and (b) For presentation, curves were smoothed using a Savitzky–Golay filter. The horizontal lines indicate the average values of the variables recorded from the subject during the epochs staged as wakefulness. Here and in subsequent Figures, sampling frequency, embedding dimension, delay time, line parameter, 500 Hz, 5, 5 points, 20 points, respectively. (c) Large-scale architecture seen in the conventional hypnogram, as determined by epoch-based sleep staging.

where a point could have been placed). The second was percent determinism (%D), defined as the percentage points in the plot that formed diagonal lines (chosen on the basis of preliminary studies as ≥20 adjacent points). Both variables were interpreted to mean that higher values evidenced more law-governed activity in the EEG (less noise). Even so, they were only relative measures of law-governed activity because their numerical values depended on the choices of the embedding and other parameters. %R and %D were formally related (only a recurrent point can count towards %D), but we regarded them as equally relevant and mutually independent. Other RQA variables have been defined (Zbilut and Webber Jr., 2006) but were not employed here because in preliminary studies we did not find a benefit for analysis of sleep EEGs beyond that provided by using %R and %D.

We used an embedding dimension of 5 and a delay time of 5 points; the values were chosen based on modeling studies because the formal methods used to embed solutions of nonlinear equations (Abarbanel, 1994) have not been validated for application to the EEG. In the modeling studies, fully law-governed linear and nonlinear signals (signals generated by mathematical equations) having the same power spectrum as the EEG were added to baseline EEGs, and the embedding parameters that optimized their detection were identified (Carrubba et al., 2006). The values were subsequently employed in stimulus–response studies involving animal and human subjects, and shown to be effective for detecting stimulus-induced changes in the EEG (Carrubba et al., 2007; Marino et al., 2010).

2.3. Sleep EEG markers

Recurrence analysis was applied to both the tonic and phasic characteristics of the sleep EEG (Fig. 1). Our approach was based on the theory that the EEG signal is an instantaneous sum of electronically propagating contributions from numerous neuronal networks, each governed by nonlinear intra- and inter-network interactions. By hypothesis, the activities of at least some networks were affected by sleep depth, resulting in dynamical changes in the EEG that could be detected by recurrence analysis. To characterize the tonic background, consecutive 1-s intervals (500 points) of the EEG were embedded in phase space, and values for %R and %D were calculated as described above. The calculations were iterated in 1-s steps, thereby producing a series of values for %R and %D that continuously captured the dynamical activity in the overnight EEG.

Typical phasic events (transient changes) seen in the sleep EEG include arousals, sleep spindles, and K complexes (Kryger et al., 2010). To produce the fine-grained time series for %R and %D needed to detect the transient changes, the recurrence calculations were performed over time intervals smaller than one second, using a shifting window (Fig. 1c). For example sleep spindles were detected using a 30-point window (60 ms), with a one-point (2 ms) shifting window.

An EEG arousal is an abrupt shift of EEG frequency (identified by an expert) lasting at least 3 s that occurs after at least 10 s of sleep (American Academy of Sleep Medicine, 2007). The arousal index (number of arousals per hour) is a measure of sleep fragmentation, which is a clinically validated determinant of excessive daytime sleepiness. To illustrate a potential application of a recurrence marker, we defined a generalized arousal index based on %R, and validated its association with sleep depth. Let x_i be the value of %R in the ith second of a normalized (to 100%) %R time series. Following the definition of an arousal, we defined a generalized arousal as $(x_{i-2} + x_{i-1} + x_i)/3 - (x_{i-3} + x_{i-4} + \ldots + x_{i-12})/10$, counted each instance where the generalized arousal was >|25%|, and computed the resulting generalized arousal indices (number of events per hour) for each sleep stage.
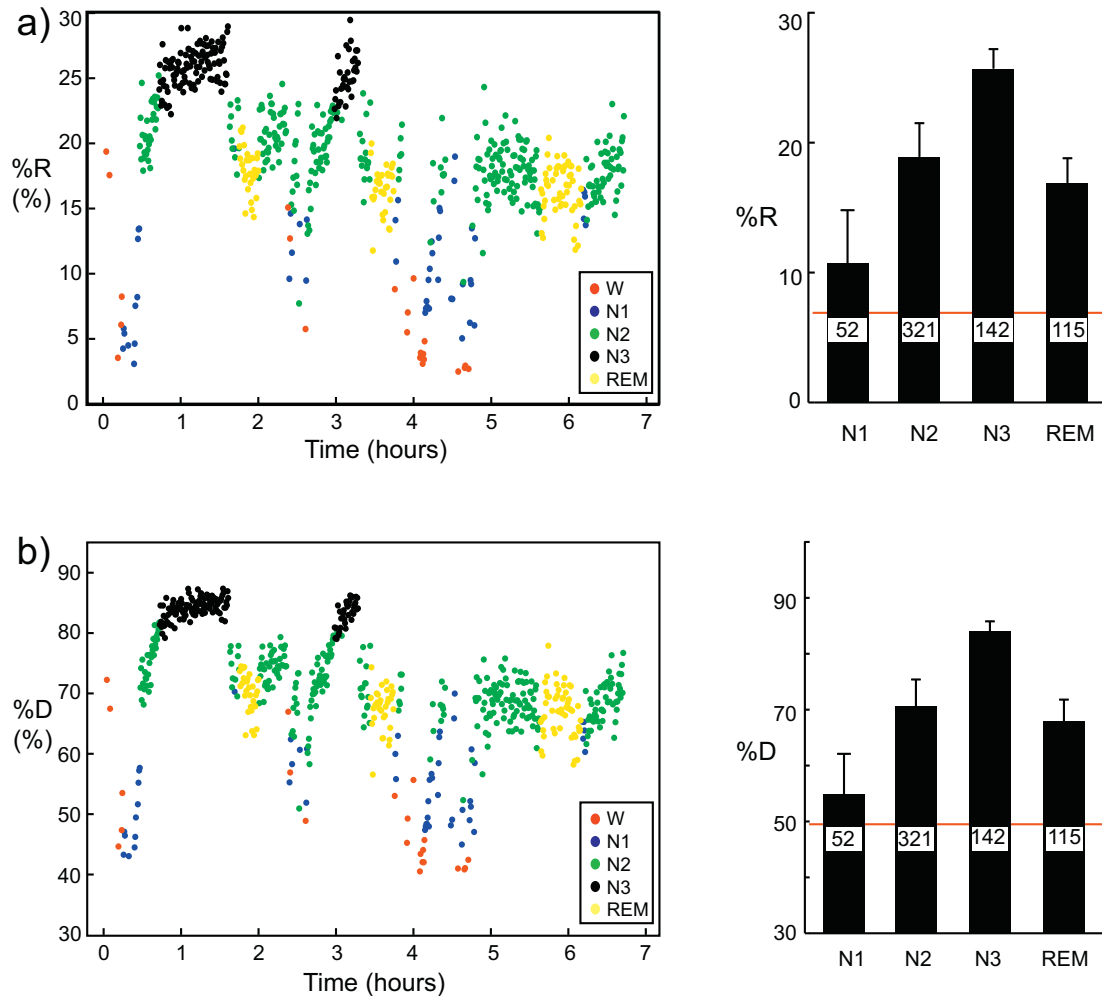
Fig. 3. Percent recurrence (%R) and percent determinism (%D) computed using successive 1-s intervals in an overnight sleep EEG (C4-M1) from a subject with obstructive sleep apnea. (a) Recurrence variables averaged epoch by epoch and color-coded by sleep stage (determined by PhysioBank experts). Each point represents the average value of the recurrence variable for one 30-s EEG epoch. (b) Mean ± SD and stage-specific number of sleep epochs. Wakefulness values 6.9 ± 5.0 (22), 49.3 ± 9.4 (22) for %R and %D, respectively. All means were disambiguated from each other and from wakefulness (horizontal line) ($P < 0.05$, t test).

3. Results

3.1. Tonic EEG states during sleep

When the law-governed activity in overnight sleep EEGs was examined using recurrence analysis at a resolution of 1 s, second-by-second changes in the recurrence variables superimposed on a cyclic background were seen (Fig. 2). In each subject, the complexity of the EEG recorded during sleep decreased as evidenced by increased values of %R and %D above the average level associated with wakefulness (Fig. 2a and b). In contrast to the conventional hypnogram (Fig. 2c), the recurrence hypnograms were rich in dynamic detail and provided a continuous numerical marker for sleep depth.

When the 1-s values of the variables were averaged epoch by epoch, the recurrence representation of sleep EEGs from subjects with and without sleep disorders exhibited the expected sleep architectures (Figs. 3 and 4). If the recurrence variables reliably captured sleep-specific physiological information, we would expect that averaging epoch by epoch and coding each average value by clinical sleep stage would reproduce the well-known macro-architectures of normal and disordered sleep, and this result was consistently observed. In Fig. 3, for example, the recurrence hypnograms consisted of 2 cycles of deep sleep in which epochs having

the highest recurrence values were usually scored as N3 sleep, wake and N1 had the lowest recurrence values, and N2 epochs were intermediate. For non-REM sleep, agreement between the range of recurrence values and the independently scored sleep stage was consistently greater than 90%. REM sleep was not disambiguated at this level of certainty, but in some cases the mean values of the recurrence variables for REM were pair-wise different from all non-REM stages, and from wakefulness ($P < 0.05$) (Fig. 3).

Similar results were found in clinically normal subjects (Fig. 4). The macro-architecture of normal sleep consists of 4–5 cycles of deep sleep, which was what we observed when the epoch-averaged values of the recurrence variables were color-coded by the sleep stage that had been assigned by the PhysioNet experts (Fig. 4). Again, agreement between the range of recurrence values and non-REM stage was consistently greater than 90% and, as was observed in the subjects with sleep disorders, the REM distributions of %R and %D overlapped the corresponding distributions of stages N1 and N2. In some cases the mean values of the recurrence variables of REM from normal subjects were pair-wise different from all non-REM stages, and from wakefulness (Fig. 4).

The relationship between the recurrence variables and sleep stage can be clearly seen in Figs. 5 and 6 which show the results for all epochs obtained from the seven subjects diagnosed with
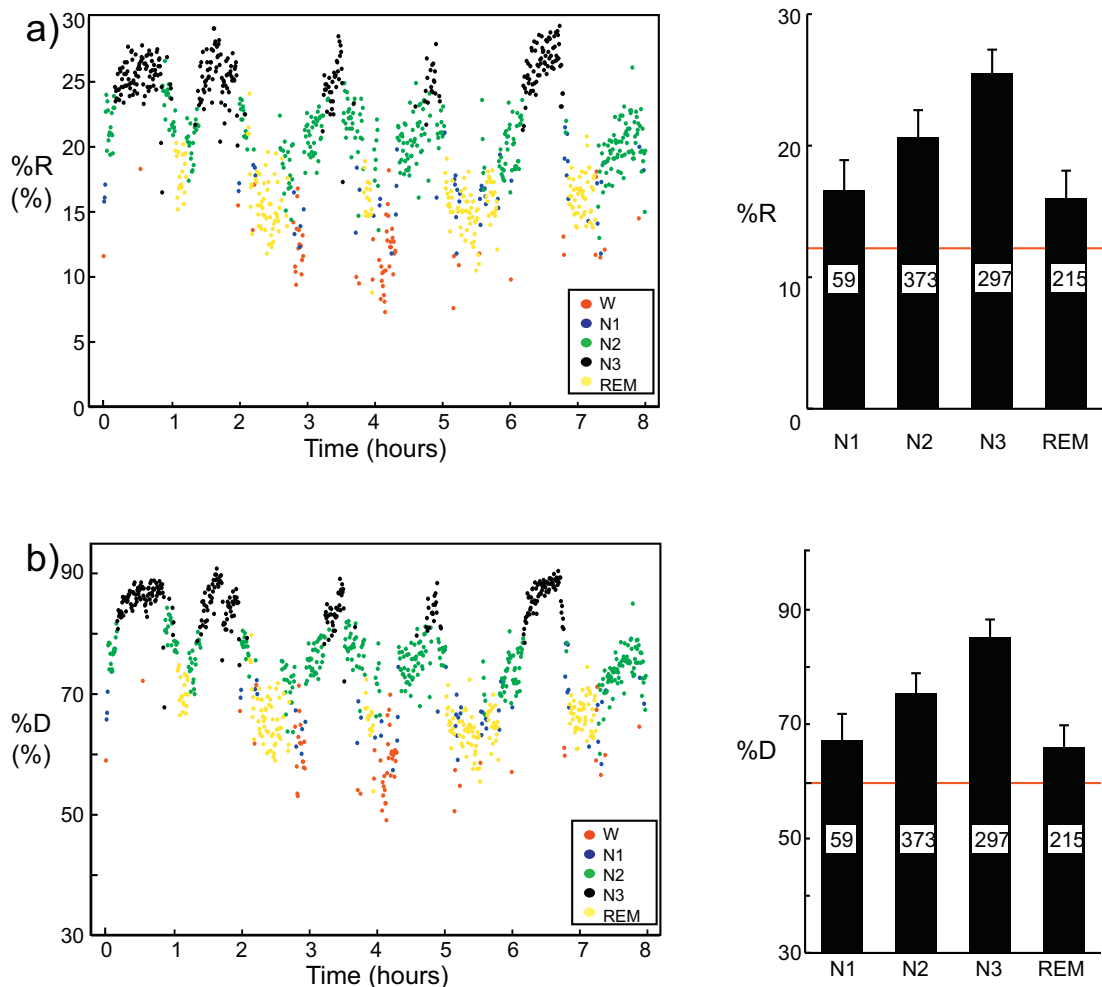
Fig. 4. Percent recurrence (%R) and percent determinism (%D) computed using successive 1-s intervals in an overnight sleep EEG (Fz-Cz) from a clinically normal subject. (a) Recurrence variables averaged epoch by epoch and color-coded by sleep stage (determined by PhysioBank experts). Each point represents the average value of the recurrence variable for one 30-s EEG epoch. (b) Mean ± SD and stage-specific number of sleep epochs. Wakefulness values 12.2 ± 2.6 (66), 59.7 ± 5.4 (66) for %R and %D, respectively. All means were disambiguated from each other and from wakefulness (horizontal line) ($P < 0.05$, t test).

sleep disorders. In each case when the recurrence variables were averaged per epoch and sorted by stage, the values fell into ranges that matched the sleep scoring, with epochs having higher values corresponding to deeper sleep. In general, the values for the REM epochs overlapped the values for stages N1 and/or N2, as expected. Similar results (Figs. 5 and 6) were found in clinically normal subjects (data not shown).

3.2. Tonic events during sleep

Arousals, sleep spindles, and K complexes, which are characteristic phasic events seen in the sleep EEG, were readily detectable by recurrence analysis (Fig. 7). Under the hypothesis that the recurrence variables also captured fine-grain structure in the sleep EEG, we would expect to observe systematic changes in the recurrence time series that corresponded to the phasic events. Their time scales differed, necessitating the use of different analysis-window widths and time shifts. The phasic events were detected using a range of widths and shifts; typical results are shown in Fig. 7 (window of 60 ms, shift of 2 ms).

3.3. Generalized arousal index

Different rates of abrupt EEG changes (objectively defined arousals) occurred during different sleep stages, as evidenced by

the GAI (Fig. 8), thereby showing that the index was sleep-stage specific. The physiological relevance of the conventional arousal index has been demonstrated in clinical studies, but the identification of individual arousal events is based on a subjective rule. In contrast, the GAI was defined objectively using the recurrence variable %R. For each subject, the %R-based GAI decreased monotonically with increasing sleep depth as assessed by sleep stage. As expected, the GAI during REM sleep was comparable to the value of the index in stages N1 and N2. The ability of the GAI to capture sleep-stage-specific dynamical activity raised the possibility that the index could be useful in basic research involving sleep physiology and/or in clinical studies, but neither those issues nor the relative sensitivity of a GAI based on other recurrence variables were addressed here.

4. Discussion

4.1. Tonic background

We adopted a nonlinear viewpoint regarding the perceptive, integrative, and cognitive activities of the brain, and developed a method that quantitated sleep as a dynamical process (Fig. 1). The key element in the method was the development of RQA for application to physiological signals (Zbilut and Webber Jr., 2006). The method consisted of an algorithm that imported
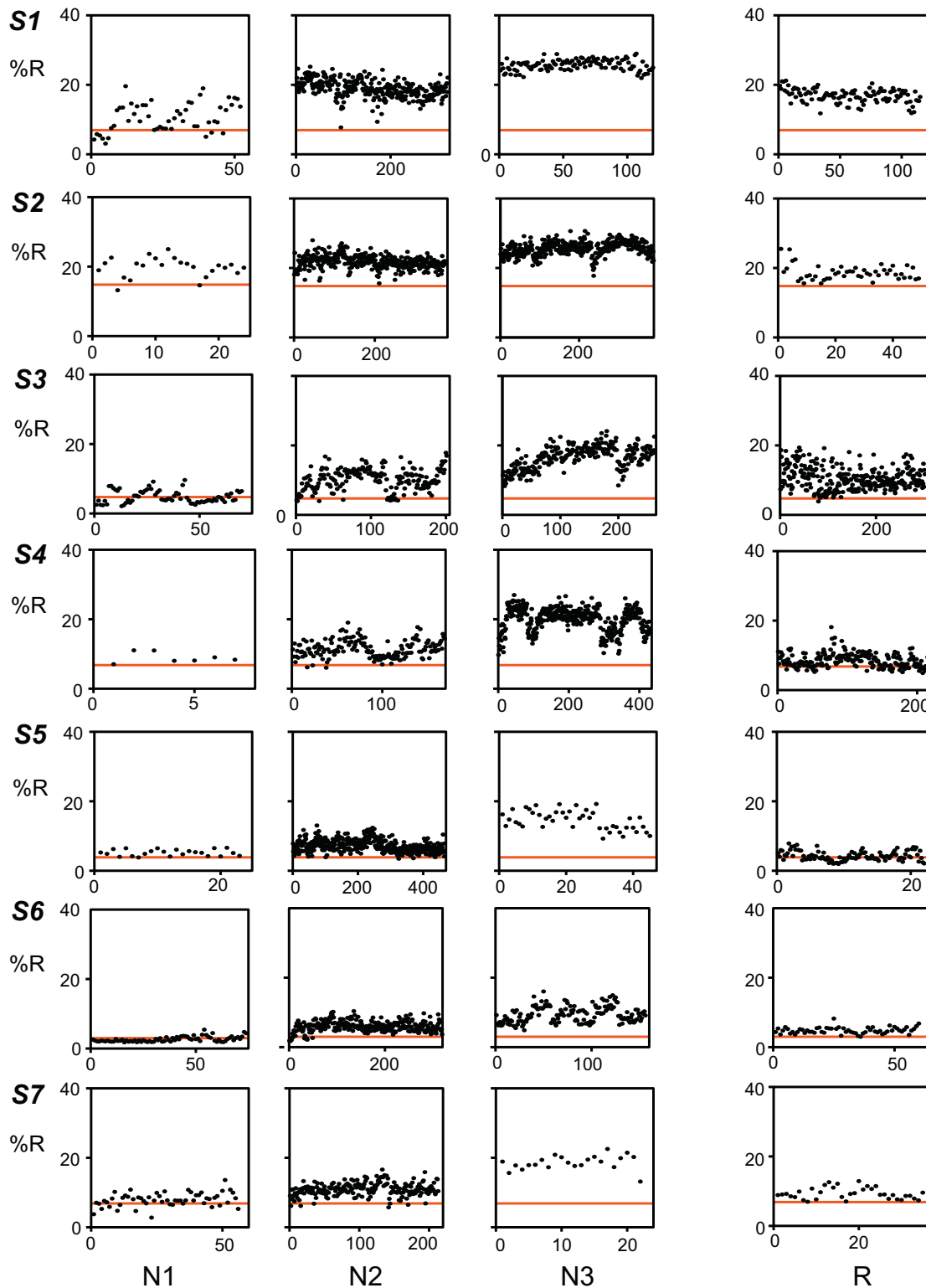
Fig. 5. Sleep-stage dependence of percent recurrence (%R) in seven subjects (S1–S7) diagnosed with sleep disorders. C4-M1 derivation. %R was computed over 1-s intervals, averaged epoch by epoch, and the epochs were grouped by stage. Each point represents the average value of one epoch. For each box, the abscissa is the epoch number in chronological order for the respective stage. The wake results (horizontal lines depicting the subjects' average values) were used as a reference to characterize sleep depth.

sleep-related data obtained under standardized conditions using commercially-available equipment and, over time scales relevant to sleep, computed recurrence metrics for complexity of brain electrical activity. The validity of the metrics was established by structuring the calculations in relation to standard sleep-staging

and showing that the metrics could be interpreted as a marker for sleep depth at the time scale of a 30-s epoch. This result implied the potential usefulness of the metrics for other applications where, presently, there is no gold-standard for comparison (Figs. 2–4).
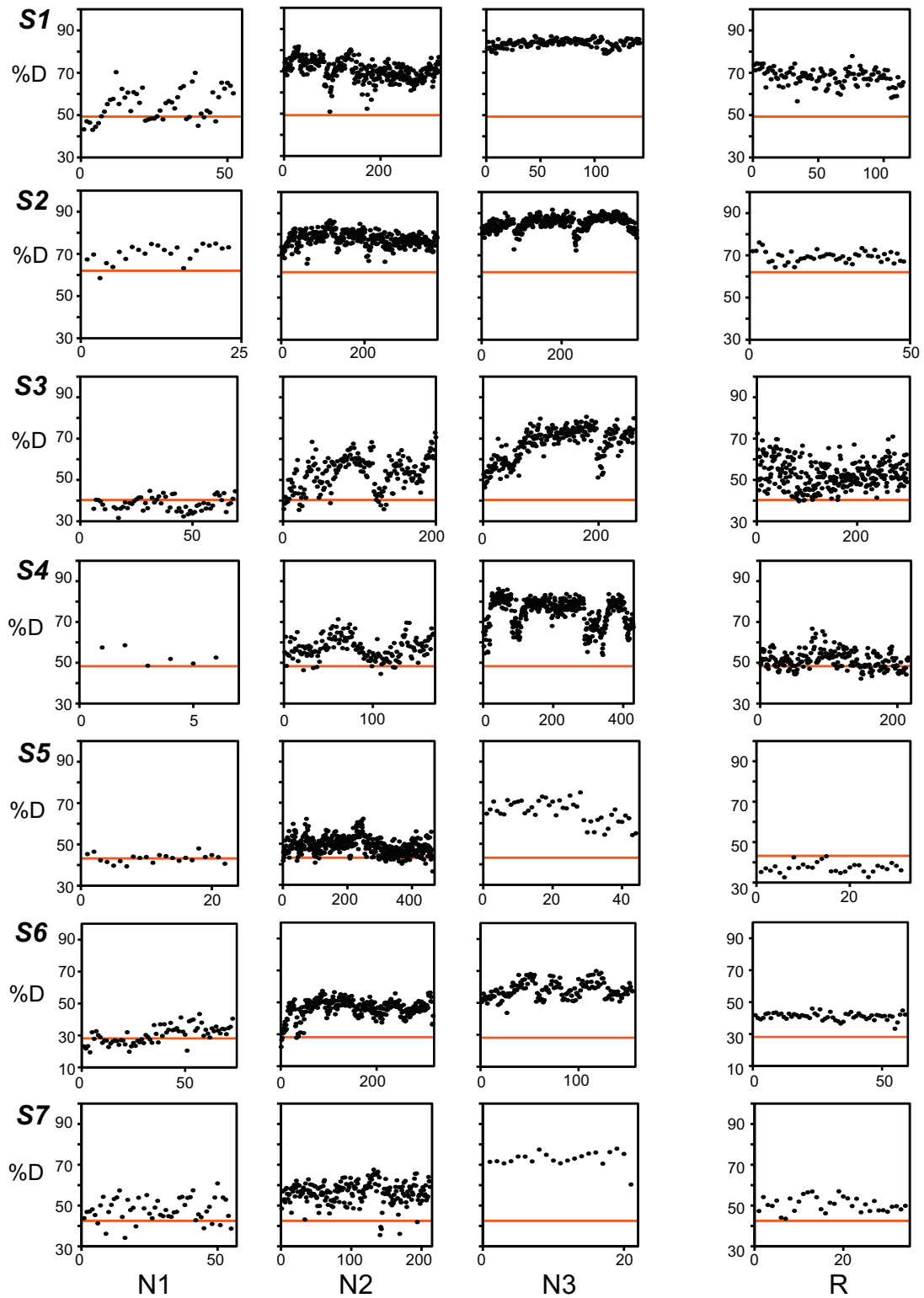
Fig. 6. Sleep-stage dependence of percent determinism (%D) in seven subjects (S1–S7) diagnosed with sleep disorders. C4-M1 derivation. %D was computed over 1-s intervals, averaged epoch by epoch, and the epochs were grouped by stage. Each point represents the average value of one epoch. For each box, the abscissa is the epoch number in chronological order for the respective stage. The wake results (horizontal lines depicting the subjects' average values) were used as a reference to characterize sleep depth.

4.2. Phasic events

The recurrence markers identified the common EEG phasic events occurring during sleep in the sense that the markers changed whenever arousals, sleep spindles, or K complexes occurred (Fig. 7). This result suggested that experimentally useful objectively-defined functional EEG changes could be defined even in the absence of predefined visual patterns (see GAI below). We did not address the possible use of markers as the basis of an algorithmic system for automatically identifying the phasic changes in the EEG. Our more limited purpose was to further validate the markers by showing that they behaved as
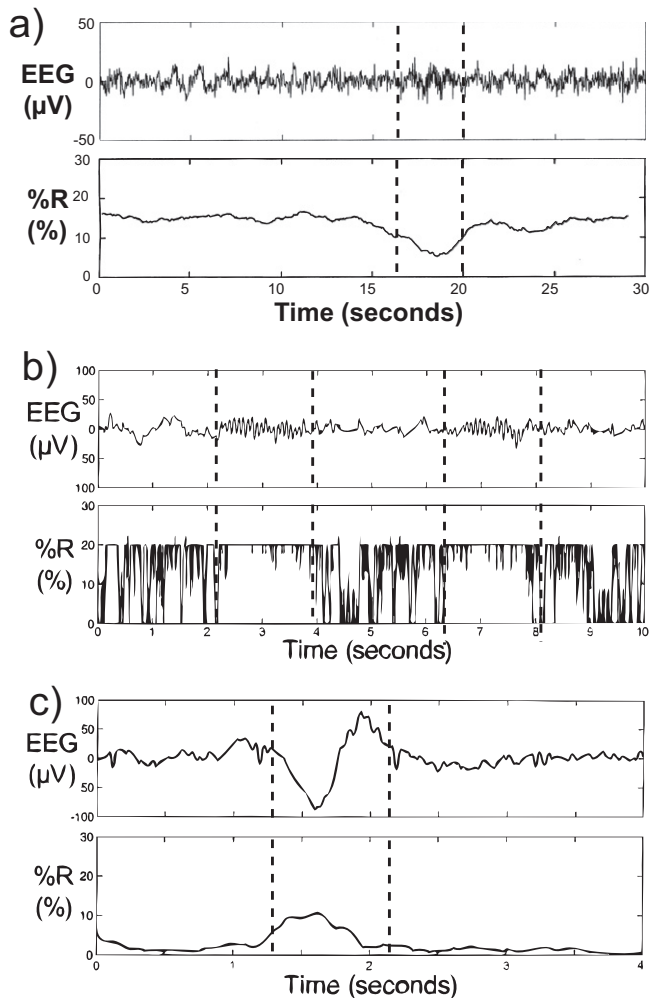
Fig. 7. Detection of sleep phasic events using recurrence analysis (60 ms computational window, 2 ms shift). (a) Top, EEG showing the location of an arousal detected by an expert scorer. Bottom, %R time series averaged over 2 s (2 ms shift). (b) Top, EEG showing sleep spindles. Bottom, %R time series averaged over 200 ms (2 ms shift). (c) Top, EEG showing a K complex. Bottom, %R time series averaged over 330 s (2 ms shift).
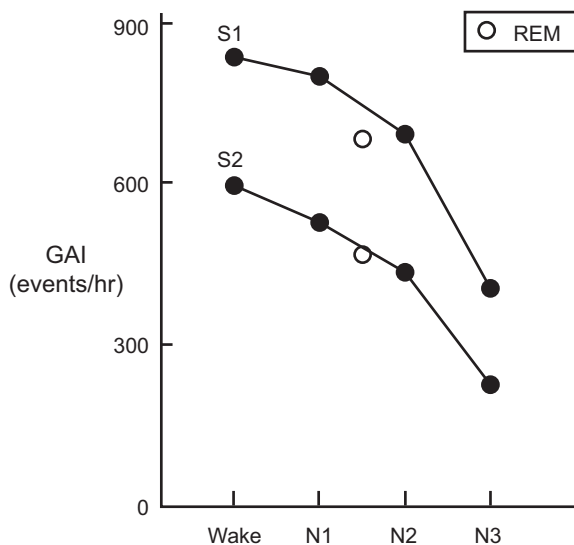

Fig. 8. Generalized arousal index (GAI) in two randomly chosen subjects (S1 and S2) as a function of sleep stage. An event was defined as a change >|25%| in %R averaged over 3 s, compared with the average over the preceding 10 s. %R computed from C4-M1.

expected under the hypothesis that they were relevant to sleep dynamics.

4.3. Potential applications of recurrence analysis

The two-process model of sleep regulation posits that sleep propensity rises during waking and declines during sleep (process S) (Borbély, 1998). The marker for S during sleep is the occurrence of visually detected low-frequency EEG changes (delta waves). Numerical calculation of the marker during wakefulness is commonly based on spectral analysis (Rusterholz et al., 2010). That choice, however, confounds distinctly different physiological states. During delta-wave sleep the brain is a true low-frequency oscillator (evidenced visually by the waves). In wakefulness, delta is a mathematical abstraction, not an ontological oscillator. Recurrence analysis of the EEG offers the possibility of overcoming the problem of combining actual and conceptual elements because it characterizes the pattern in the EEG, not its spectral content.

Use of the GAI is another potential application of recurrence analysis of the sleep EEG. An arousal is an abrupt change in the EEG during sleep, as assessed by an expert scorer on the basis of visual inspection of the EEG. Increased incidence of arousals results in fragmented sleep leading to excessive daytime sleepiness (EDS) (Bonnet et al., 2007). The GAI, an algorithmic generalization of the arousal concept, may lead to stronger associations with EDS because the GAI detects all abrupt EEG changes (regardless of whether they are visually recognizable). We broadly validated the %R-based GAI by showing that it was related to sleep depth. The actual relationship between GAI and EDS or other sleep disorders as well as the usefulness of other recurrence variables (Zbilut and Webber Jr., 2006) remains to be studied.

4.4. Limitations

Sleep staging and the recognition of phasic events are non-algorithmic tasks because they contain irreducible elements of human judgment. Consequently the decisions have an intrinsic inter-rater variability. Many computer-based algorithms have been proposed as alternatives to human decision-making for determining the values of sleep variables, but without notable impact because the computer can do no better than the expert, whose judgment is the gold standard. Even if algorithmic performance eventually matched human performance, a serious question would remain regarding whether that were any real benefit, considering the prolixity of the algorithms and the cost of the implementing equipment. These comments apply equally to our method, perhaps suggesting that it is primarily a tool for use in conjunction with sleep staging rather than a potential replacement. We are also skeptical regarding the potential use of the method described here as a basis for automatic detection of known phasic events. We showed that recurrence analysis can detect the events, but we did not address whether it does so more effectively than methods previously proposed for that purpose.

4.5. Conclusion

Based on nonlinear analysis that quantified the recurrence properties of the EEG, we described a novel method for producing dynamic markers, at any desired time scale, of the functional states of the brain during sleep.

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