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An original method for staging sleep based on dynamical analysis of a single EEG signal

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ABSTRACT

Background: The dynamical complexity of brain electrical activity manifested in the EEG is quantifiable using recurrence analysis (RA). Employing RA, we described and validated an originative method for automatically classifying epochs of sleep that is conceptually and instrumentally distinct from the existing method.
New method: Complexity in single overnight EEGs was characterized second-by-second using four RA variables that were each averaged over consecutive 30-sec epochs to form four-component vectors. The vectors were staged using four-component cluster analysis. Method validity and utility were established by showing: (1) inter- and intra-subject consistency of staging results (method insusceptible to nonstationarity of the EEG); (2) use of method to eliminate costly and arduous visual staging in a binary classifications task for detecting a neurogenic disorder; (3) ability of method to provide new physiological insights into brain activity during sleep.
Results: RA of sleep-acquired EEGs yielded four continuous measures of complexity and its change-rate that allowed automatic classification of epochs into four statistically distinct clusters ("stages"). Matched subjects with and without mental distress were accurately classified using biomarkers based on stage designations.
Comparison with existing methods: For binary-classification purposes, the method was cheaper, faster, and at least as accurate as the existing staging method. Epoch-by-epoch comparison of new versus existing methods revealed that the latter assigned epochs having widely different dynamical complexities into the same stage (dynamical incoherence).
Conclusions: Sleep can be automatically staged using an originative method that is fundamentally different from the existing method.

1. Introduction

Sleep macroarchitecture is conventionally characterized by visually analyzing multiple signals from brain and muscle in 30-s epochs and classifying them into stages according to standardized rules (American Academy of Sleep Medicine, 2007).The concept of sleep stage is fundamental for understanding sleep physiology (Kryger et al., 2010), and knowledge of visually determined sleep-stage distributions permits normal and pathological sleep to be distinguished (Chokroverty et al., 2005). Visual staging is about 80% reliable (Chokroverty et al., 2005; Ma et al., 2017). Computer-based ("automatic") staging is an alternative (Ma et al., 2017; Younes, 2017), but most proposed systems mimic the visual method and add additional unreliability (Boostani et al., 2017; Mariani et al., 2016).

Recurrence analysis (RA) is a technique for evaluating time-varying output signals from complex systems (Zbilut and Webber, 2006). Applied to the EEG (Carrubba et al., 2006, 2008a), RA quantifies the instantaneous amount of law-governed ("non-random") electrical activity in the brain (its functional "complexity"). We employed RA to detect non-time-linked evoked potentials (Carrubba et al., 2008b), demonstrate the existence of a human magnetic sense (Carrubba et al., 2007), detect changes in brain activity associated with multiple sclerosis (Carrubba et al., 2012a), identify alterations in brain activity caused by sensory transduction of electromagnetic fields (Frilot et al., 2013), and characterize sleep depth (Carrubba et al., 2012b). When RA values were combined with visual staging information to create sleep markers, individuals with mental health impairment were successfully classified (McCarty et al., 2014).

Here, employing four continuous recurrence variables computed from a single EEG signal, we described and validated a new method for

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Table 1
Demographic data for subjects with and without mental impairment.

	Normal Mental Health	Impaired Mental Health
N	34	34
Age (years)	57.6 ± 2.0	58.2 ± 2.0
BMI (kg/m^2)	25.6 ± 2.0	24.6 ± 0.6
Male/Female	12/22	12/22
MHI-5 (0-100)	81.9 ± 2.2	40.4 ± 1.5

N, number of subjects; BMI, body mass index; MHI-5, Mental Health Inventory-5. Normal, MHI-5 > 50; Impaired, MHI-5 < 50. Mean ± SD.

automatically staging sleep that is conceptually and methodologically distinct from the existing staging method. First we showed that recurrence variables captured the coarse- and fine-grained temporal activity of the sleep EEG, thereby permitting continuous quantitation on any desired time scale. Second we utilized cluster analysis to group 30-s sleep epochs, modeled as four-component vectors defined by the values of the RA variables, into four distinct clusters ("stages"). Third, we presented evidence for the validly and utility of the method by showing that the recurrence values of intra-subject stages differed consistently, that the method could replace visual staging for the purpose of classifying subjects as with or without mental illness, and that the method yielded insights into sleep physiology not otherwise observable.

2. Methods and materials

2.1. Subjects

A total 149 clinically normal subjects were chosen from participants in the Sleep Heart Health Study (SHHS) who underwent overnight polysomnography in 2001 and 2003 (3295 participants) (Dean et al., 2016; Quan et al., 1997; Redline et al., 1998); de-identified EEG data and relevant covariate information were used (Sleep Heart, 2013). The subjects were 60.2 ± 9.3 years of age.

Another study cohort was formed from a SHHS dataset collected between 1995–1998 (6441 participants), which was searched to determine subjects for whom mental health status had been ascertained based on the Mental Health Inventory questionnaire (MHI-5). We arbitrarily regarded an MHI-5 score > 50 as indicating normal mental health and a score < 50 as indicating impaired mental health (Rumph et al., 2001). Two sub-cohorts were formed by randomly choosing 34 subjects who had MHI-5 scores less than 50 and matching them with 34 subjects with who had scores greater than 50 (Table 1).

The appropriate institutional review boards for human research where the data was collected approved all research-related procedures.

2.2. EEG measurements

Details regarding the EEG recording procedures were described elsewhere (Redline et al., 1998). Each EEG was about eight hours in duration, obtained during overnight sleep. EEGs recorded from C3–M2 and C4–M1were sampled at 125 Hz and provided as MAT files. We interpolated the signals to 500 Hz (our laboratory standard sampling frequency for the EEG) using a standard algorithm (Matlab, Mathworks, Natick, MA, USA), digitally filtered the signals to pass 0.5–35 Hz, and evaluated them using custom codes in a standard numerical computing environment (Matlab). The original SHHS investigators divided the sleep period into 30-second epochs and classified each one into mutually exclusive stages according to standard rules; wake (W), REM, light sleep (N1, N2), and deep sleep (N3, N4).

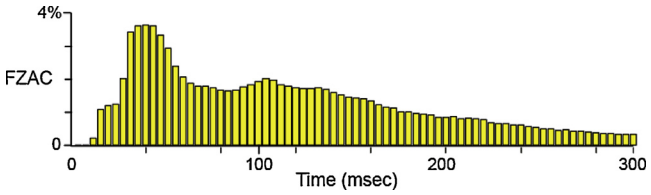

Fig. 2. Nonstationarity in the human EEG during sleep.

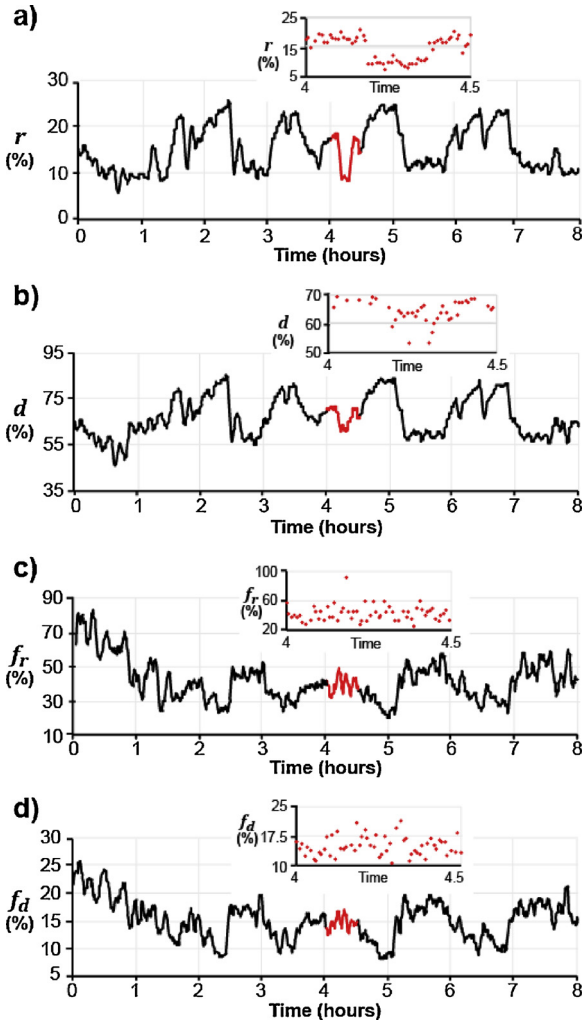

Fig. 3. Temporal behavior of recurrence measures of the sleep EEG from a typical subject. (a) and (b), EEG complexity. (c) and (d), EEG fragmentation (change in complexity) The curves typically consisted of about 900 points, one per epoch, and were smoothed using a Savitsky-Golay filter. The inserts depict the unsmoothed epoch-by-epoch values of the variables that occurred in the indicated 30-minute interval. Units for f_r and f_d are the means of the absolute values of the changes in depth that occurred over 1-sec intervals (see Methods).

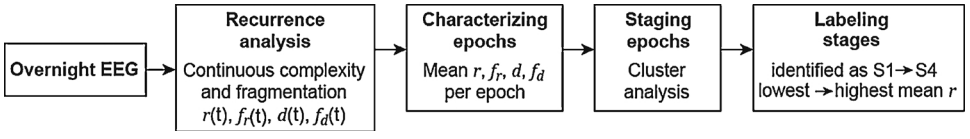

Fig. 1. Procedure for automatically grouping brain states occurring during sleep. The overnight EEG was converted into four recurrence time series that each characterized the dynamical complexity of the EEG. Each series was averaged epoch-by-epoch resulting in four recurrence measures per epoch. The epochs were algorithmically assigned to one of four groups labeled S1 to S4 based on the mean value of r.

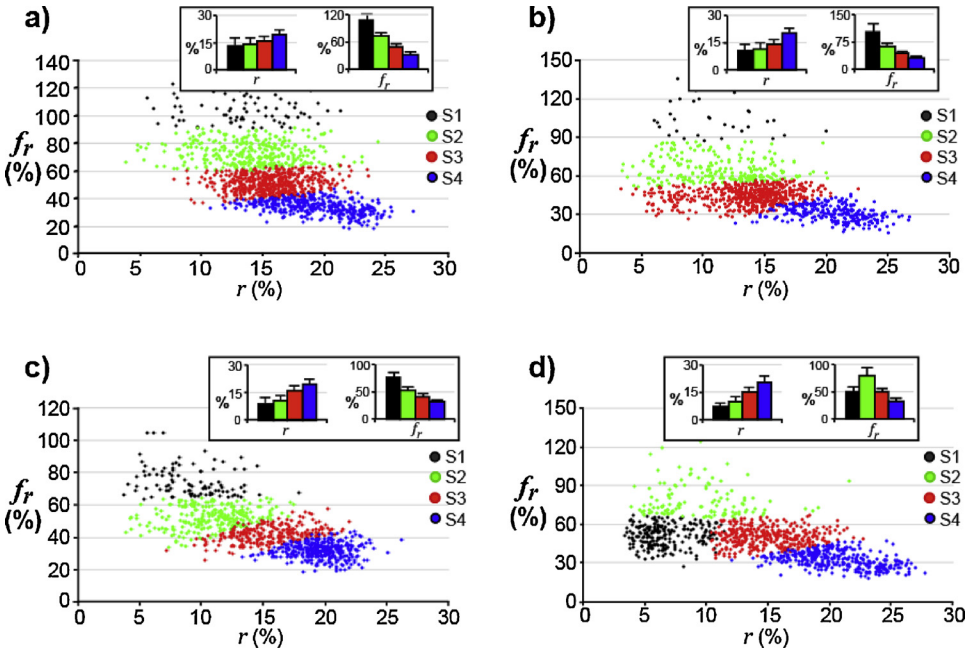

Fig. 4. Cluster formation in four typical subjects. Two-dimensional projections (r, f_r) from the four-dimensional cluster space (r, d, f_r, f_d) are shown. Individual epochs depicted as dots. Inserts show cluster mean ± SD.

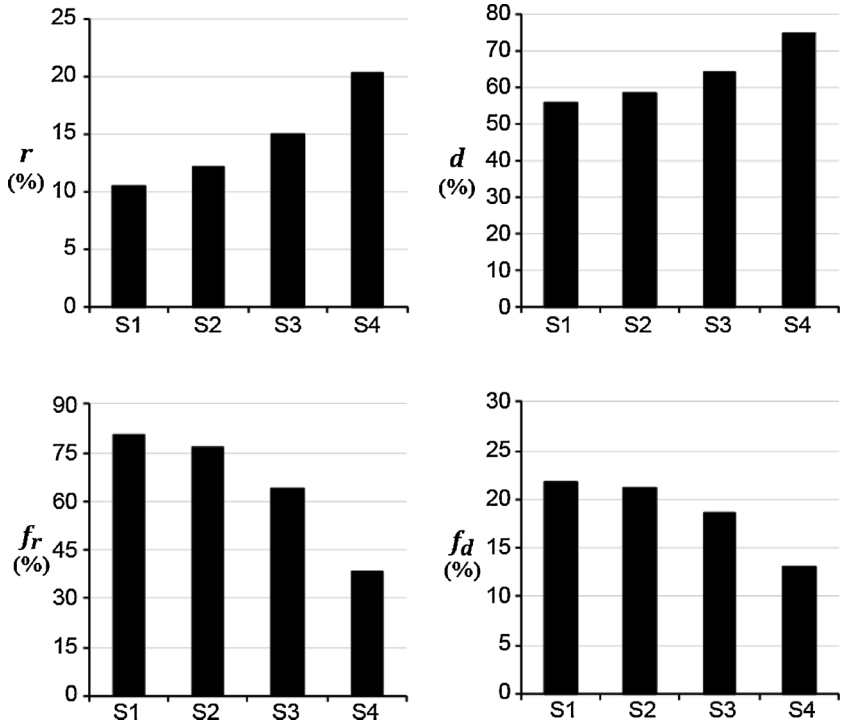

Fig. 5. Means of recurrence variables in the normal cohort as a function of group. N = 149. For each variable, the mean in a given group differed pair-wise from the other means (S1 vs. S, S3, or S4; S2 vs. S3 or S4; S3 vs. S4) ($P < 0.05$). Error bars not resolved at indicated scale.

2.3. Recurrence analysis

Recurrence analysis imposes no restrictions on the statistical properties of signals produced by complex systems (Frilot et al., 2015).The computational details of RA applied to the EEG have been provided (Frilot et al., 2015). Briefly, 5-component groups of numbers ("vectors") were formed that consisted of the EEG amplitude at time t and four earlier times identified by successive time lags of 10 ms. Following standard practice (Heath, 2000), the path in a five-dimensional mathematical hyperspace of all such vectors obtainable from one second of the EEG (480 vectors, given our choices of sampling rate, vector dimension, and delay time) was interpreted to indicate the presence of law-governed activity in the EEG. The amount of lawful activity in each second of EEG was quantified using the variables percent recurrence ("r"), defined as the percent of the vectors that were near other vectors (and hence were recurrent), and percent determinism ("d"), defined as the percent of the recurrent vectors that were adjacent to at least one other recurrent vector (a measure of the

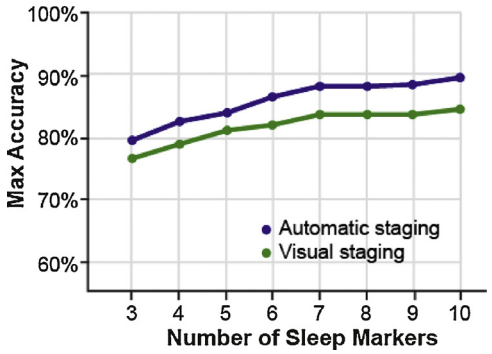

Fig. 6. Determination of number of sleep markers needed for maximum classification accuracy of subjects with or without mental impairment as a function of sleep-staging method. Each point is the mean of five replicate determinations. Accuracy did not increase when more than 10 markers were employed. Across the 3–10 range accuracy was greater using automatic grouping (binomial theorem, $P < 0.05$).

Table 2
Epoch-level comparison between automatic and visual staging of the normal cohort (155,089 epochs).

Automatic Stage	Number of Epochs	Visual Stage (% of Automatic Stage)			
		W	REM	Light Sleep	Deep Sleep
S1	23,765	66	15	19	0
S2	32,317	43	23	34	0
S3	51,202	17	25	55	3
S4	47,805	2	6	52	40

persistence of the recurrence). Both variables quantified the complexity of the signal in the sense that higher values indicate less complexity (Zbilut and Webber, 2006). Both r and d were minimal during wake and maximal during deep sleep (Carrubba et al., 2012b; Wang et al., 2013), indicating that they could be interpreted as measures of sleep depth. The variables were computed second by second, resulting in chronological sequences ($r(t)$, $d(t)$) that consisted of approximately 28,800 points for a typical 8-hr EEG.

Additional recurrence variables were employed to characterize the rates of change of $r(t)$ and $d(t)$ (their first derivatives), labeled "fragmentation variables." The fragmentation occurring at the ith second in $r(t)$ ("f_r") was defined as $|\{(r_i - r_{i\text{-}1})/\Delta t\}/r_{i\text{-}1}|$, where $\Delta t = 1$ s; fragmentation in $d(t)$ ("f_d") was similarly defined as $|\{(d_i - d_{i\text{-}1})/\Delta t\}d_{i\text{-}1}|$. Because f_r and f_d were defined in terms of absolute values of change, they did not depend on whether the fragmentation resulted in an increase or decrease in complexity. Both variables were expressed as a percent change.

The second-by-second values of r, d, f_r, and f_d were averaged over successive 30-s epochs, resulting in approximately 900 epochs for a typical overnight period of sleep, each characterized by two measures of sleep depth and two of fragmentation.

2.4. Cluster analysis

The RA-characterized epochs were grouped automatically using cluster analysis, a method for identifying clusters of data in a dataset based upon attributes that make the individual items of data in a group similar to one another. No prior knowledge is required regarding which items belong in which group; the number of groups ("k") is chosen by the user rather than fixed by the clustering algorithm (Cluster Analysis, 2011). For a given k, the algorithm combines the multiple measures of each item (here, an EEG epoch), thereby characterizing it by a single number, iteratively estimates the group means, and assigns each item to the group for which the item's mathematical distance to the group mean is a minimum. Whether the groups formed for any particular k are objectively meaningful is an empirical question.

In preliminary studies involving different choices of k, we found that the epochs formed statistically independent groups for k's at least as high as 6. Here we arbitrarily chose $k = 4$, which was sufficient for achieving our purposes. The four automatically determined groups were defined to be the sleep states S1 to S4 based on increasing mean r (decreasing complexity). The overall procedure is summarized in Fig. 1.

2.5. Discriminant analysis

Linear discriminant analysis (DA) is a method for finding a combination of features ("markers") that best separates data into two classes. We previously reported that markers formed by combining RA-characterized epochs of the sleep EEG and visual-stage information accurately classified subjects with psychological distress (McCarty et al., 2014). Here, we evaluated the validity of automatically grouping brain states during sleep by determining whether the grouping information (S1–S4) could replace the visual-stage information (Wake, REM, light sleep, deep sleep) and yield comparable classification accuracies.

Using DA, The four epoch-level recurrence values from the subjects in the MHI-5 cohort were combined with the four group designations determined by cluster analysis to produce sixteen sleep markers (Kim et al., 2013), and the number of markers and the particular combination that yielded the best binary classification of the 68 subjects was determined. Accuracy was calculated as the ratio of true positive and negative classifications to the total number of subjects, expressed as a percent, using clinical diagnosis as ground truth. For control purposes, the entire process was repeated using corresponding markers formed using visual-stage information.

2.6. Statistics

Pair-wise means tests were performed using the Mann-Whitney U test or the Wilcoxon signed-rank test, depending on whether the data consisted of matched pairs. When the data consisted of repeated measures, the Bonferroni correction was used. The probability that the apparent increased subject classification accuracy obtained using the new method could be explained by chance was evaluated using the binomial theorem. For clarity of presentation, the overnight $r(t)$ and $d(t)$ curves were smoothed using a cubic 119-point Savitzky-Golay filter (Sgolayfilt, Matlab).

3. Results

3.1. EEG nonstationarity

EEGs were recorded for 7–8 h from each of ten randomly selected clinically normal sleeping subjects, and the first zero of the autocorrelation function (FZAC) was determined second-by-second. The calculated values (~28,000 /subject) were divided into 4-ms bins, averaged, and normalized. The resulting histogram (Fig. 2) indicated that the statistical properties of the sleep EEG changed drastically from second to second, indicating that the EEGs were highly nonstationary.

3.2. Characterizing sleep EEGs

The time dependence of the four recurrence variables that described the sleep EEG—two that measured dynamical complexity (r and d) and two that measured its fragmentation (f_r and f_d)—revealed ultradian architecture consisting of 2–5 relative maxima/minima and associated fine structure; the results for a representative subject are shown in Fig. 3.

The smoothed curves for r and d were similar (Fig. 3a and b) but differed at the single-epoch level (inserts, Fig. 3a and b), indicating that the two variables captured different physiological aspects of the EEG

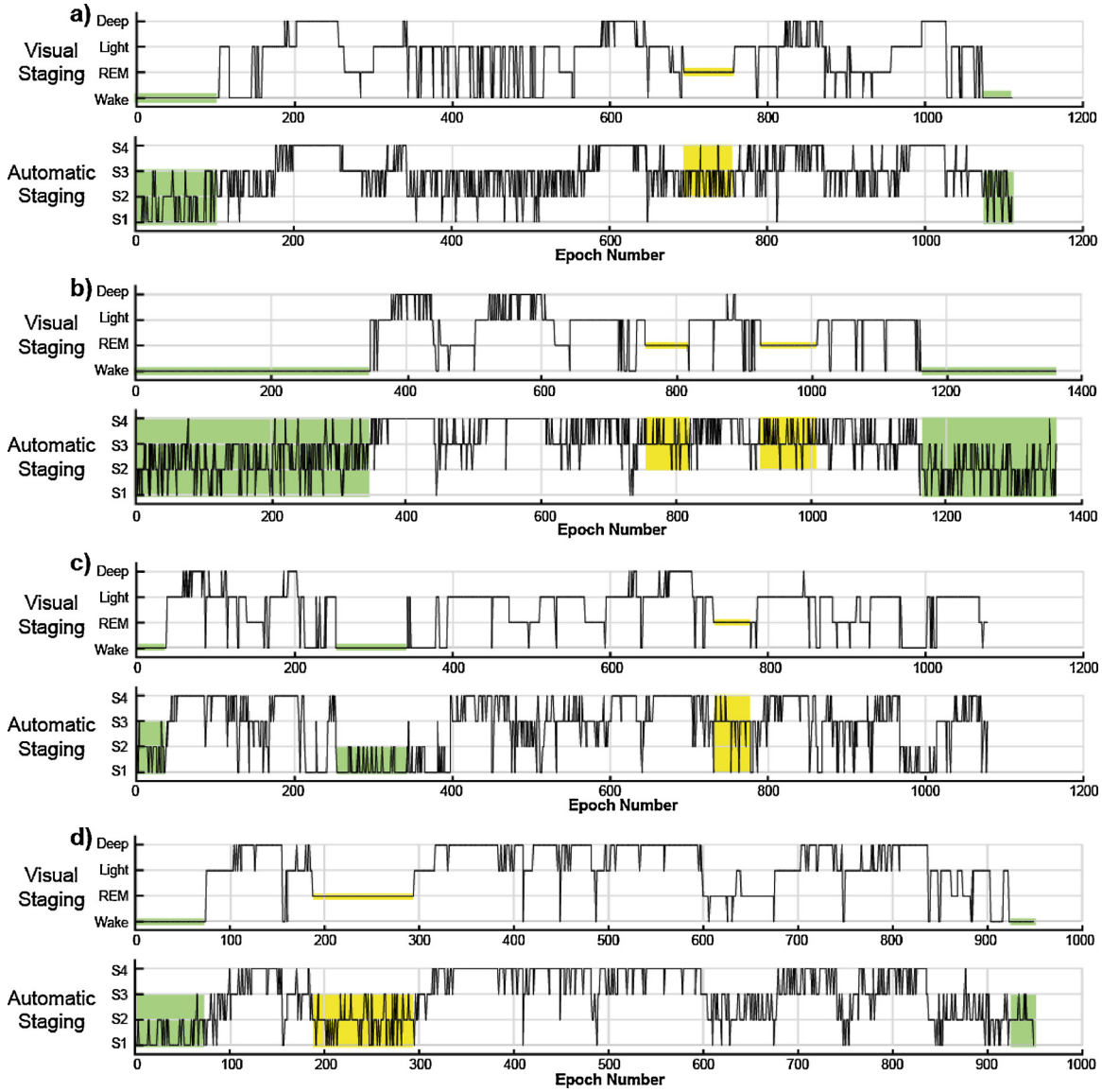

Fig. 7. Four typical visual-stage hypnograms and their corresponding brain-state hypnograms (a–d). Sleep-period intervals of W (green) and REM (yellow) in which no change in stage was observed were found to consist of 2–4 groups of brain states (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 3
Recurrence values of W epochs as a function of location in the sleep cycle. DSP, during sleep period. Mean ± SD. For both data sets, *P < 0.001 compared with Pre-sleep and with Post-sleep. Wilcoxon signed-rank test with Bonferroni correction for repeated measures.

Wake Period	Time (min)	Recurrence Variables (%)			
		r	d	f_r	f_d
a) Normal subjects (N = 149)					
Pre-sleep	56.7 ± 40.3	10.7 ± 4.1	55.4 ± 7.0	73.0 ± 17.5	20.7 ± 3.1
Post-sleep	13.3 ± 18.4	10.7 ± 3.0	56.2 ± 5.5	73.0 ± 17.9	20.8 ± 3.2
DSP	60.7 ± 46.0	*15.1 ± 2.9	*64.6 ± 5.5	*51.9 ± 11.7	*16.7 ± 2.2
b) MHI-5 Subjects (N = 68)					
Pre-sleep	50.1 ± 36.7	12.7 ± 3.2	61.4 ± 5.5	55.8 ± 9.0	17.3 ± 2.0
Post-sleep	11.9 ± 25.3	13.5 ± 7.0	62.7 ± 7.8	52.8 ± 13.5	3.6 ± 16.8
DSP	52.9 ± 44.4	*16.5 ± 2.8	*68.4 ± 4.5	*43.6 ± 6.0	*1.6 ± 14.5

during sleep. The smoothed curves for f_r and f_d (Fig. 3c and d) commonly exhibited relative minima during intervals of sleep when the depth variables were relative maxima. As with the complexity variables, the fragmentation variables resembled one another over broad time scales but differed at the level of single epochs (inserts, Fig. 3c and d).

3.3. Staging EEG sleep states

When 30-sec EEG epochs were automatically assigned to one of four clusters based on a computational combination of their recurrence values, a consistent geometrical pattern occurred comprising the spatial separation of epochs into distinct groups; results for representative subjects are shown in Fig. 4, which depicts one of the possible two-dimensional projections from the four-dimensional computation space. The groups thus formed ("stages") were labeled S1 to S4 based on increasing mean r (increasing signal recurrence, equivalent to decreasing signal complexity).

3.4. Validation

If automatic grouping of RA-characterized EEG epochs occurring during sleep created stages that actually were well-defined physiological entities, we expect the recurrence variables to differ consistently between the groups, and reproducibly so from subject to subject, indicating that the staging was insusceptible to the nonstationarity of the EEG; that result was observed (Fig. 5).

On average, epochs assigned to S1 exhibited the lowest values of r and d and highest values of f_r and f_d, and epochs assigned to S4 exhibited highest r and d, lowest f_r and f_d. The means of the epochs assigned to S2 and S3 had intermediate values of all four variables (Fig. 5). Because the groups were labeled S1 to S4 based on increasing mean r, it was necessarily a minimum in S1 and a maximum in S4. An increase with group number also occurred in mean d even though it was not definitionally constrained. Both f_r and f_d were also not constrained and both decreased with group number. For each variable, the mean in a given group was pair-wise different from all the other means ($P < 0.05$). The cohort-level statistical significance of the recurrence means was also manifested at the level of the individual subject; of the 149 subjects × 6 stage comparisons (S1 vs S2, S3, S4, and S2 vs S3, S4, and S3 vs S4) × 4 variables = 3576 separate nonparametic-test pair-wise comparisons (Mann-Whitney U), more than 96% were significant ($P < 0.05$).

We evaluated the utility of automatic staging by comparing the classification accuracy it facilitated with that achieved using staging based on the visual method. Twenty subjects with no mental impairment (MHI-5 > 50) and 20 subjects with impairment (MHI-5 < 50) were randomly selected from matched subject sub-cohorts (Table 1), and their epoch-level recurrence values were combined with automatic grouping information to produce sixteen sleep markers (four variables x four stages) that were used in a discriminant analysis to classify subjects as with or without mental impairment. Maximum classification accuracy was determined using all possible combinations of the sleep markers, taken 3 to 16 at a time. For both staging methods, accuracy did not increase when more than 10 markers were employed (Fig. 6). *Post hoc* analysis based on the binomial theorem suggested that the accuracy achieved using automatic staging was greater than that found using visual staging.

3.5. New sleep-physiology insights

We asked whether the EEG in sleep epochs assigned to a specific visual stage exhibited similar dynamical activity. If so, the epochs in each of the automatic stages would be expected to map mostly to one or possibly two visual stages. The results of epoch-level staging comparisons of each of the 155,089 epochs in the 149 normal subjects revealed that the visual stages W and REM were dynamically inhomogeneous (Table 2).

We expected that automatic staging would be more sensitive than was possible using the existing rule-based classification method. As hypothesized, transitions between brain states occurred more often than transitions between visual sleep stages. For all subjects studied, about 24% of the automatically grouped EEG epochs were singlets (preceding and succeeding epochs in different groups), compared with 4% in the visually-staged hypnograms. Similar differences in frequency were observed for doublets (9% compared with 2%) and triplets (4% compared with 1%). Typical examples of comparisons between the two methods are shown in Fig. 7, where the mappings of W- and REM-staged sleep epochs to automatic stages are highlighted

We evaluated whether the dynamical incoherence in wake (W) was related to the timing of the sleep cycle. The W epochs were divided into three periods depending on whether they occurred before sleep onset (the first non-W epoch) ("pre-sleep"), during the sleep period ("DSP"), or after it ended ("post-sleep"). In both study cohorts, we found that DSP epochs exhibited significantly less complexity and less fragmentation compared with epochs in the pre- and post-sleep periods (Table 3), as hypothesized.

4. Discussion

We described an original objective method for staging sleep that is fundamentally different from the existing subjective staging method. Our method is based on four continuous recurrence variables computed from a single EEG signal. The signal thus characterized is divided into epochs that are algorithmically assigned to one of four groups ("stages") by means of cluster analysis. In a test group of 149 subjects, the method yielded reliably consistent changes in each of the variables as a function of stage (Fig. 5), indicating that the stages were well-defined physiological entities, which is the purpose of staging. The usefulness of the method was demonstrated by showing that, for the purpose of classifying subjects as with or without mental illness, the staging results could be used to replace the staging results obtained using the existing staging method (Fig.6). Our method also yielded insights into sleep physiology not otherwise observable (Fig. 7, Table 3), thereby further demonstrating its usefulness. We did not address the issues of using stages shorter than 30 s or more than four groups

In summary, we algorithmically defined brain dynamical activity in terms of four physiologically based variables readily computable from a single EEG derivation, and showed that human sleep could validly be characterized naturally in terms of four statistically distinct groups of similar states (stages).

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