A Taxonomic Analysis of Sleep Stages

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Study Objectives: To study the structure of human sleep at the level of sleep stages. We applied taxonomic statistics to detect significant configurations (types) of different physiologic variables and their relationship to sleep stages.

Design and Statistics: Polygraphic sleep recordings from 32 subjects (normal sleepers as well as patients with insomnia, sleep apnea, or narcolepsy; n = 8 per group) were visually scored and submitted to a configural frequency analysis. The configural frequency analysis was computed with 3 continuous input variables: an electroencephalogram parameter, which represents the point of gravity of the EEG frequency distribution; the alpha slow-wave index, and the Rest Index, based on the presence or absence of phasic electromyographic activity. These variables were dichotomized for further analysis. The combination of 2 levels (+ or –) and 3 variables resulted in 2^3 patterns (+++ to – – –). The configural frequency analysis is a nonparametric χ^2-type multivariate statistic that identifies significant patterns or types.

Results: Each sleep stage contained 3 or 4 types. For non-rapid eye movement sleep stages 2, 3, and 4, types overlapped, whereas there was no overlap of types between stages 1 and 2. Types of rapid eye movement sleep did not overlap with those from stages 2, 3, and 4 but did overlap with wake and stage 1 types. The majority of observed types were significant in all 4 groups of subjects.

Conclusions: Sleep stages appear to be less homogenous than rule-based sleep scoring would suggest. Types were either restricted to one stage or overlapped with neighboring stages.

Keywords: Sleep stages, pattern analysis, configural frequency analysis (CFA), types, antitypes, taxonomy

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INTRODUCTION

VISUAL SLEEP STAGING IS STILL THE MOST WIDELY USED PROCEDURE TO ANALYZE SLEEP. IT ALLOWS ONE TO SUBDIVIDE SLEEP RECORDINGS INTO discrete states or stages, defined by coherent and recurrent patterns of one[1] or more[2] electrophysiologic signals. Based on this method, human sleep has been defined as an alternating sequence of 4 stages of non-rapid eye movement sleep (NREM stages 1 to 4), and rapid eye movement (REM) sleep.[3] Although there is unanimous acceptance of the existence of 2 different states of sleep, REM and NREM sleep, different conceptions of the structure of NREM sleep have been proposed. Based on quantitative electroencephalographic analysis during sleep, NREM sleep can be represented as a continuum instead of a staged process.[4,5] A continuous representation of NREM sleep allows one to model the sleep process by quantitative variables, such as the mean electroencephalographic (EEG) frequency or the power of different EEG frequency bands.[6,7,8] In contrast with this, the strongest point for sleep staging is that it allows the integration of a variety of electrophysiologic information from different recording channels into a reasonably small number of well-defined stages.

Sleep staging is confronted with 2 major difficulties: first, how to exactly delineate neighboring stages, and second, how to handle intrastate variability? Both points have an influence on the reliability of sleep studies.[9] Although rules for the definition of sleep states and stages have been developed,[2] the question of intrastate heterogeneity has been widely ignored. Exceptions consist of a few scattered proposals to subdivide the sleep-onset process into fine-graded steps,[10] to study differences between stage 2 sleep early and late in night-time sleep,[11] or to subdivide NREM and REM sleep into tonic and phasic segments.[12] Another approach to subdivide the NREM sleep process into meaningful subunits has been proposed by Terzano and coworkers.[13,14] These authors developed the concept of a cyclic alternating pattern (CAP), corresponding to different functional states of arousal-control mechanisms during NREM sleep.[15] In a recent study, Brandenberger et al[16] called into question the homogeneity of stage 2 sleep. These authors presented data that suggest that 2 types of stage 2 sleep can be differentiated, a quiet one, preceding slow-wave sleep, and an active one, preceding REM sleep.

Sleep staging is a rule-based procedure, which uses expert knowledge to define which combination of electrophysiologic patterns defines a sleep stage.[2] As an alternative, a statistical analysis could explore which pattern configurations, extracted from EEG, electromyogram (EMG), electrooculogram, or any other physiologic signal, are either typical, ie, occur more frequently, or atypical, i.e., occur less frequently, relative to one's expectation. The configural frequency analysis (CFA)[17] is a nonparametric taxonomic statistical analysis that allows one to identify over-representations (types) or underrepresentations (antitypes) in the frequency distribution of multiple variable classifications. This procedure examines the statistical significance of patterns of cell frequencies in cross-tabulated data and defines types or antitypes, depending on whether observed cell frequencies are greater or smaller than expected by the marginal distribution.

The objective of the present study was to investigate the structure of sleep by means of the CFA. We applied the CFA to 3 continuously measured variables during sleep: (a) an EEG parameter (EEG-P), representing the distribution of EEG wave lengths,

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similar to other continuous EEG parameters[4,18]; (b) the alpha slow-wave index (ASI)[19]; and (c) the rest index (RI), based on the amount of phasic or transient EMG activity.[20] We selected these parameters because they are continuous, independent from staging rules, and belong to the standard of our sleep-analysis system. The EEG parameter describes the time course of EEG activity during sleep, which varies between low-amplitude fast waves in wakefulness and high-amplitude slow waves during deep NREM sleep. The ASI, which is based on the proportion of alpha to slow-wave EEG activity, recognizes fairly long arousals and intervening wakefulness.[19] Finally, the RI is a measure of motor rest or unrest, based on the presence or absence of transient EMG activity.[20,21]

Each of the 3 continuous variables EEG-P (E), ASI (A), and RI (R) was dichotomized, and the resulting cross-tabulation was tested for significant patterns of configurations. Significant configurations or types were matched with conventional sleep stages. This comparison allows us to (1) estimate the complexity (homogeneity vs heterogeneity) of sleep stages and (2) determine the degree of potential overlap between stages. If more than 1 significant configuration emerges from the same sleep stage, this stage seems to be heterogeneous. On the other hand, if a given configuration occurs in more than 1 stage, this indicates overlap between stages.

METHODS

Subjects and Procedures

The analysis was based on 32 all-night sleep recordings from 18 women and 14 men. The mean age was 50.1 ± SD 9.3 years (range: 35-70 years). The total sample consisted of 4 groups of 8 subjects each, namely control subjects without reported sleep disturbances (4 women, 4 men; mean age: 56.5 years; range: 36-70 years) and 3 groups of patients with the following International Classification of Sleep Disorders-defined sleep disorders: psychophysiological insomnia (5 women, 3 men; mean age: 48.4 years; range: 35-63 years); obstructive sleep apnea syndrome (OSA: 4 women, 4 men; mean age: 56.1 years; range: 40-68 years); and narcolepsy (5 women, 3 men; mean age: 52.1 years; range: 35-62 years).

Polygraphic sleep recordings were performed for 7.5 to 8 hours between 10:00 PM and 6:30 AM under standardized recording conditions in a clinical sleep lab. The following variables were continuously recorded: EEG (F1-A1, C3-A2, C4-A1, O2-A2), horizontal electrooculogram, chin EMG, heart rate, respiration (nasal/mouth flow, respiratory effort of abdomen and chest), oxygen saturation and EMG from right and left m. tibialis. For the present analysis, we used 1 EEG channel (C3-A2) and 1 EMG channel (chin EMG).

Digital sleep data were stored for later analysis, and sleep stages were visually analyzed in 30-second segments ("epochs") according to Rechtschaffen and Kales[2] criteria. In addition, 3 continuous parameters were computed from the recordings, A, a measure of the ratio of EEG alpha and slow-wave activity[19]; E, representing the point of gravity of the EEG frequency distribution (similar to Haustein)[4]; and R, a measure that is based on the momentary amount of phasic EMG activity.[20]

The variable A is defined as the ratio between alpha activity and the sum of activity in the delta and theta frequency ranges. This ratio is expressed as follows:

$$ASI = \frac{alpha}{delta + theta}$$

During a transition from wakefulness to sleep, the contribution of alpha decreases while that of the slow-wave frequency ranges increases.

E is a continuous variable that is defined for each 30-second epoch from the EEG frequency distribution. The amount of EEG activity in each frequency band is defined by an algorithm that combines zero crossing for low frequencies (< 4 Hz) and peak-to-peak detection for higher frequencies (> 4 Hz). The time portion per 30-second epoch was computed for each wavelength. E is defined by the following formula:

EEG parameter = (frequency × time portion) ÷ sum of all time portions

The values for parameter E are highest in waking and lowest in slow-wave sleep.

R was computed from the m. mentalis EMG. An EMG increase above a predefined threshold was scored as transient EMG activity. For each 30-second epoch, it was determined whether or not there was transient EMG activity. Based on this information, R was computed as a continuous variable between 0 and 1. As long as there is no transient EMG activity, the parameter value decreases by a certain constant amount per time unit, whereas it increases by a certain amount when transient EMG activity occurs. As a result, R reaches its lowest level during long time spans without transient EMG activity, and it reaches the upper level when a series of EMG transients occurs. The amount for a decrease was fixed at one third of that for an increase, to adjust for the different dynamics of EMG changes during descending (W → slow-wave sleep) and ascending (slow-wave sleep → W or S1) parts of the sleep cycle. The time course of R values can be graphically displayed as a time-dependent variable (see Figure 1). The computation of the 3 parameters was performed by a commercial sleep analysis software package (Leonardo; MKE, Willroth, Germany). Figure 1 represents a visually scored hypnogram in addition to the 3 continuous measures A, E and R.

Statistical Analysis

For each continuous variable (A, E, R), 1 value was computed for each 30-second epoch. Later, the continuous variables were transformed into binary variables by separating the total distribution of epoch-by-epoch values at the individual median. For a given variable and epoch, a plus (+) was assigned if the actual parameter value was above the median, and a minus (−) if the actual value was below the median for a given subject. The combination of the 3 binary variables (A, E, R) results in $2^3 = 8$ different patterns (+ + +, ..., − − −). The first sign relates to A, the second to E, and the third to R.

In the next step, a sleep stage and an (A, E, R) pattern were assigned to each epoch of the sleep recording. Finally, the frequency of occurrence of the 8 patterns was tabulated for each sleep stage and analyzed by CFA.[17,22] The CFA is a test procedure for the analysis of multidimensional contingency tables. It computes the probability of whether a given pattern could be expected to occur by chance, according to the margin frequency distributions of the binary variables A, E, and R pattern, or whether it is

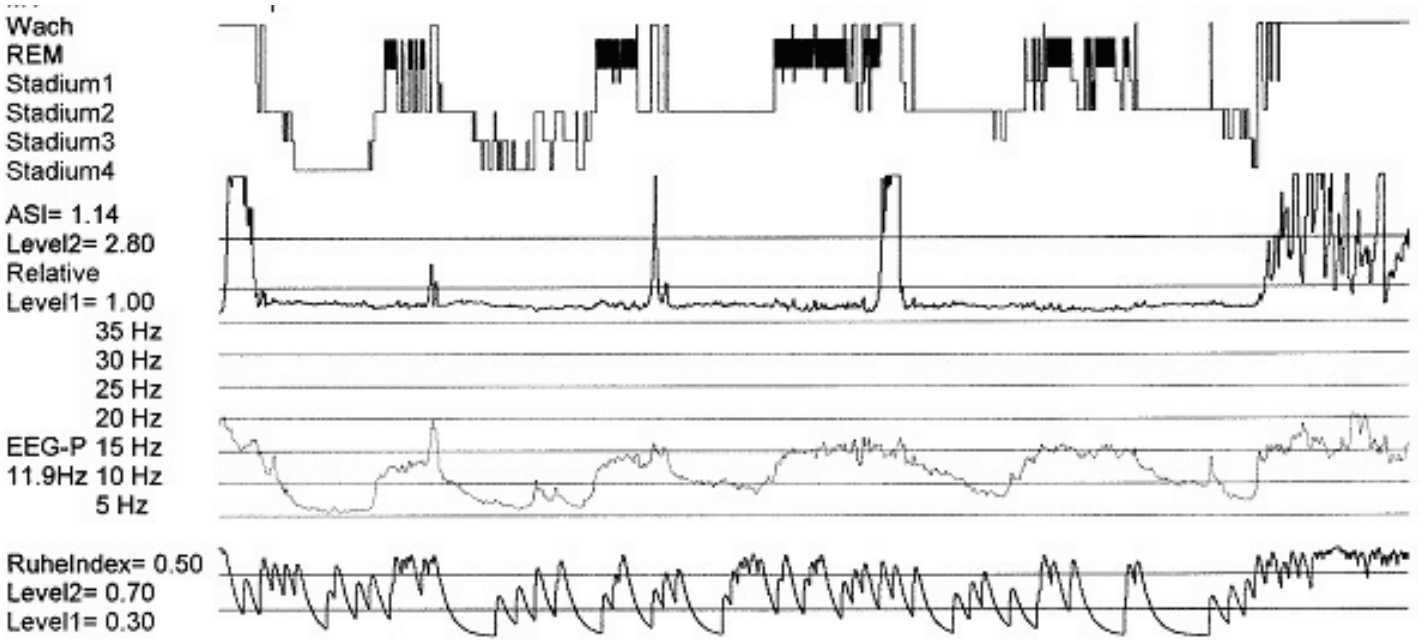

Figure 1—Visually scored hypnogram (top), with Alpha Slow-Wave Index (ASI)(A: upper panel), electroencephalogram parameter (EEG) (E: middle panel) and Rest Index (Ruhe Index) (R: lower panel). REM refers to rapid eye movement sleep.

significant, i.e., overrepresented, for a given sleep stage. If more than 1 pattern becomes significant for a given sleep stage, this suggests that the stage contains different identifiable substages. The CFA allows one to define types, by a statistical probability above the chosen level of significance, as well as antitypes, which occur less frequently than expected by chance. In the present case, the prediction CFA was performed with the configurations A, E, R as predictors and with visually scored sleep stages as criteria.[23,24] For CFA statistical testing, we used the Fisher exact test for 4-fold tables.[23] The level of significance α was set at .05, and the Holm method[25] was applied to adjust α for multiple testing.

RESULTS

The analysis was based on 32 polysomnographic recordings with a total of 28,086 epochs. The distribution of sleep stages was 8.8% (n = 2484 epochs) for Stage 1, 46.9% (n = 13,182) for Stage 2, 7.5% (n = 2113) for Stage 3, 2.1% (n = 587) for Stage 4, and 16.5% (n = 4,625) for REM sleep. The remaining epochs were scored as awake (17.7%, n = 4972 epochs), movement time (0.3%, n = 79), or undefined (0.2%, n = 44 epochs). There was no definition of types for movement time and undefined. Table 1 shows the absolute and Table 2 the relative frequencies of the 8 combinations of binary values for A, E, and R per sleep stage for all 32 sleep recordings. The margin frequencies show that the patterns $+++$ (n = 6410, 22.8%) and $---$ (n = 5501, 19.6%) were the most frequent, whereas the pattern $-+-$ (n = 1893, 6.7%) was least frequent.

Those patterns identified by the CFA as significant for the total sample of 32 recordings are marked in Table 2.

The significant patterns or types for the 4 groups of subjects are summarized in Table 3. As can be seen, the majority of significant pattern-to-stage relationships applies to all 4 groups of subjects. An identical pattern-to-stage relationship was found for all 4 groups in 11 cases, for 3 groups in 2 cases, for 2 groups in 5 cases, and for 1 group in 2 cases. Given the limited sample size of only 8 sleep recordings per group, this suggests a rather stable pattern-to-stage relationship, largely independent of the specific pathology of the diagnostic groups.

Table 1—Absolute Frequencies of AER Combinations for Visually Scored Stages of 32 Sleep Recordings

AER pattern	Wake	S1	S2	S3	S4	REM	MT	UND	Sum
+ + +	3081	1009	983	2	0	1286	38	11	6410
+ + -	830	320	614	3	0	970	7	2	2746
+ - +	179	217	1928	96	14	186	8	2	2630
+ - -	40	72	2460	422	140	94	3	0	3231
- + +	641	489	781	1	1	1094	11	9	3027
- + -	163	168	744	19	0	788	7	4	1893
- - +	30	155	1960	272	93	126	2	10	2648
- - -	8	54	3712	1298	339	81	3	6	5501
Sum	4972	2484	13,182	2113	587	4625	79	44	28,086

Configural frequency analysis was used to defined types of activity—A refers to alpha slow-wave index; E, electroencephalogram parameter; R, Rest Index; S1, Stage 1 sleep; S2, Stage 2 sleep; S3, Stage 3 sleep; S4, Stage 4 sleep, REM, rapid eye movement sleep. UND refers to undefined; MT, movement time.

Stage wake was characterized by a single pattern ($+++$) with high values for A, E, and R in all 4 groups. One additional pattern ($++-$) with a low R value became significant for patients with insomnia and narcolepsy, and 1 ($-++$) with low A for patients with OSA.

Stage 1 sleep exhibited 2 significant patterns for all groups, 1 with high values in all 3 variables ($+++$) and 1 with a low value for A but high values for E and R ($-++$). This suggests 2 types of Stage 1 sleep, 1 with more alpha activity ($+++$) and 1 with less alpha ($-++$). An additional Stage 1 pattern with a low value for R ($++-$) became significant only for control subjects and patients with insomnia.

Stage 2 sleep turned out to be heterogeneous, with 4 significant

Table 2—Relative Frequencies (Percentages) of AER Combinations for Visually Scored Stages of 32 Sleep Recordings From The Whole Sample of Subjects

AER pattern	Wake	S1	S2	S3	S4	REM	MT	UND	Sum
+ + +	10.97[a]	3.59[a]	3.50	0.01	0.00	4.58[a]	0.14	0.04	22.82
+ + -	2.96[a]	1.14[a]	2.19	0.01	0.00	3.45[a]	0.02	0.01	9.78
+ - +	0.64	0.77	6.86[a]	0.34	0.05	0.66	0.03	0.01	9.36
+ - -	0.14	0.26	8.76[a]	1.50[a]	0.50[a]	0.34	0.01	0.00	11.50
- + +	2.28[a]	1.74[a]	2.78	0.00	0.00	3.90[a]	0.04	0.03	10.78
- + -	0.58	0.60	2.65	0.07	0.00	2.81[a]	0.02	0.01	6.74
- - +	0.11	0.55	6.98[a]	0.97[a]	0.33[a]	0.45	0.01	0.04	9.43
- - -	0.03	0.19	13.22[a]	4.62[a]	1.21[a]	0.29	0.01	0.02	19.59
Sum	17.70	8.84	46.93	7.52	2.09	16.47	0.28	0.16	100

Configural frequency analysis was used to defined types of activity—A refers to alpha slow-wave index; E, electroencephalogram parameter; R, Rest Index; S1, Stage 1 sleep; S2, Stage 2 sleep; S3, Stage 3 sleep; S4, Stage 4 sleep, REM, rapid eye movement sleep. UND refers to undefined; MT, movement time.
[a]$\alpha \leq .05$.

patterns in all 4 groups. All 4 patterns had a low value for E in common. Two patterns had a high value for A ($+--$ and $+--$) and 2 had a low value ($---$ and $---$), whereas the value for R was twice positive and twice negative. Interestingly, none of the Stage 2 patterns overlapped with Stage 1 patterns in any of the 4 groups of subjects.

The main pattern for Stage 3 sleep, valid for all 4 groups, was $---$. One additional pattern ($+--$) became significant for 3 groups (insomnia, OSA, narcolepsy), and 1 other ($---$) for 2 groups (OSA, narcolepsy). All 3 patterns were characterized by a low value for E, and 2 of them by an additionally low value for A or R, respectively.

Stage 4 sleep displayed the same pattern configuration as Stage 3. Again, the pattern $---$ was typical for all 4 groups, whereas the remaining 2 patterns were significant for either 2 groups ($+--$: OSA and narcolepsy) or only 1 group ($---$: insomnia).

REM sleep was characterized by 4 significant patterns. All 4 had a high value for the EEG parameter E. Two of these were also high for A, whereas R was either high or low ($+++$ and $++-$). The remaining 2 patterns were low for A but differed for the R value ($-++$ and $-+-$). The latter 2 patterns were significant for all 4 groups whereas the other 2 patterns were significant for 3 groups each ($+++$ for controls, OSA, and narcolepsy; $++-$ for controls, insomnia, and OSA). Representative examples for each type are shown in Figure 2.

Overall, 76.8% of all epochs fitted into significant patterns. The value was highest for Stage 3 (86.2%) and lowest for Stage 1 (68.3%) sleep. The 4 subject groups differed only slightly in the total number of epochs fitting into significant AER patterns. The percentage was highest for OSA (80.3%) and lowest for patients with narcolepsy (74.5%).

Beside types, the CFA also allows one to define antitypes. Antitypes are those patterns that occur significantly less frequently than would be expected according to the margin frequencies. In the present analysis, a pattern was accepted as an antitype only if its probability was less than 0.05 and if this was the case in all 4 groups. Using this criterion, 20 patterns could be defined as

Table 3—Significant AER Patterns for Wake as well as Different Sleep Stages for Control Subjects

AER	Wake	S1	S2	S3	S4	REM
+ + +	CON	CON				CON
	INS	INS				
+ + -	INS	CON				CON
		INS				INS
+ - +			CON			
			INS			
+ - -			CON			
			INS	INS		
- + +		CON				CON
		INS				INS
- + -						CON
						INS
- - +			CON		INS	
			INS			
- - -			CON	CON	CON	
			INS	INS	INS	

Configural frequency analysis was used to defined types of activity—A refers to alpha slow-wave index ; E, electroencephalogram parameter; R, Rest Index; S1, Stage 1 sleep; S2, Stage 2 sleep; S3, Stage 3 sleep; S4, Stage 4 sleep, REM, rapid eye movement sleep. CON refers to controls; INS, patients with insomnia.

antitypes (see Table 4). The combination of 8 AER patterns and 6 stages (wake, Stage 1, Stage 2, Stage 3, Stage 4, REM) results in a total of 48 pattern-to-stage combinations. Of these 48 fields, 20 include types of at least 1 group (see Table 3) and of 20 antitypes (see Table 4). The remaining 8 fields are neutral, ie, they may either hold this status in future studies with larger samples or they may shift in the direction of types or antitypes. The percentage of epochs in fields with antitypes was quite low across all 4 groups of subjects, namely 1.6% for wake, 5.1% for Stage 1, 18.0% for Stage 2, 1.2% for Stage 3, 0% for Stage 4 and 10.5% for REM sleep.

DISCUSSION

The present results call attention to the structural complexity of sleep stages. The statistical analysis revealed that visually scored sleep stages are not homogeneous units but, rather, agglomerations of different significant patterns, called types, that in the present study were based on a set of 3 physiologic variables representing aspects of the momentary EEG and EMG activity. The decomposition of sleep stages into types by the prediction CFA resulted in fairly comparable solutions for the various diagnostic groups. This is in agreement with the experience gained from clinical sleep research, which shows that sleep recordings from different diagnostic groups can be analyzed with the same scoring system.

Heterogeneity of Sleep Stages

Sleep stages contained more than 1 type, indicating a physiological heterogeneity of sleep stages. The least-complex stages were wakefulness and Stage 4; the most complex were Stage 2 and REM sleep. Each of the latter 2 sleep stages was composed of 4 different types, which did not significantly overlap between these 2 stages.

Wakefulness was characterized in all 4 groups by type AER/

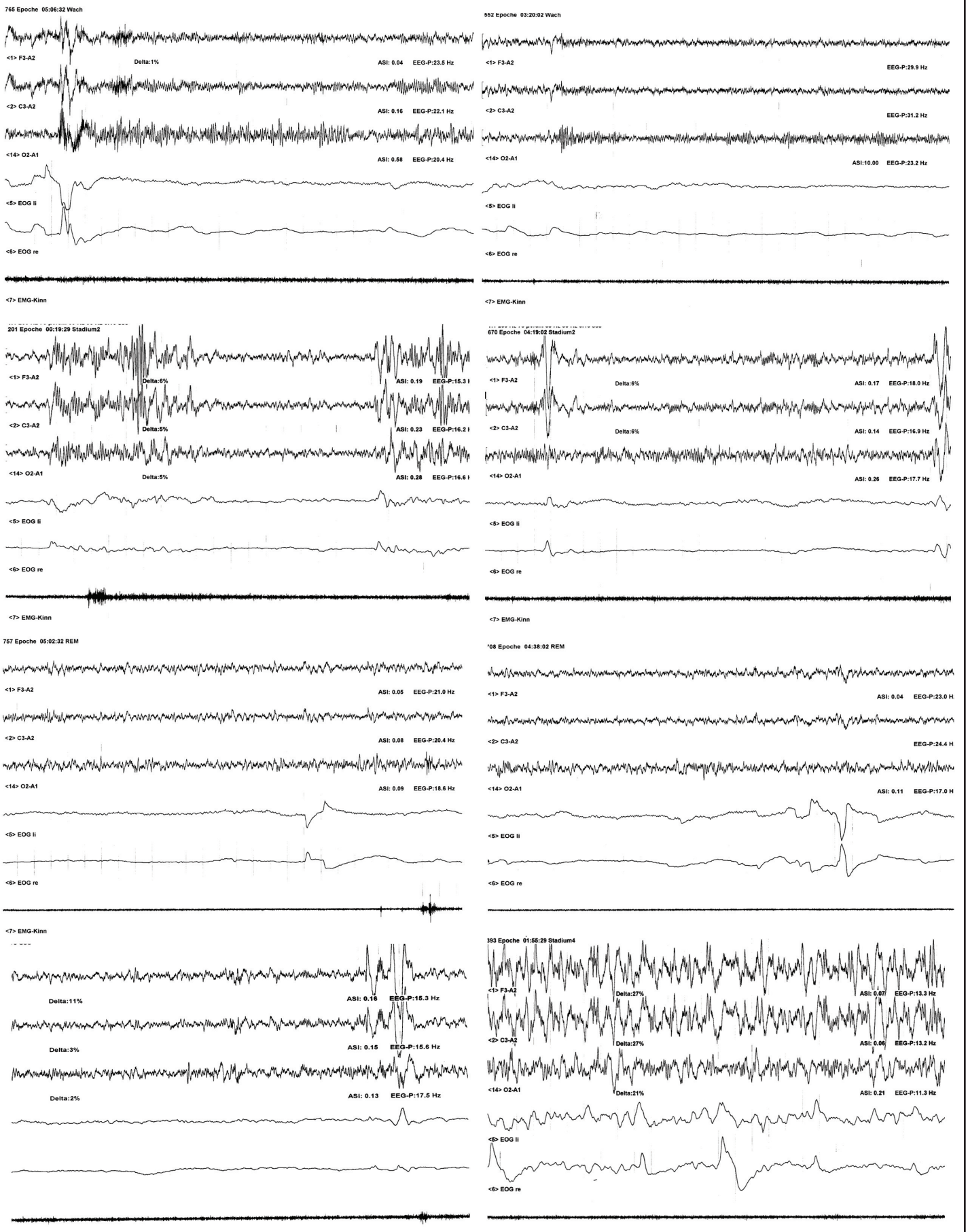

Figure 2—Sample representations of polygraphic recordings for each type. Each 30-second epoch contains 3 channels of electroencephalogram (F3, C3, C4), 2 electrooculogram (EOG), and 1 electromyogram (EMG) chin recording (from top to bottom).

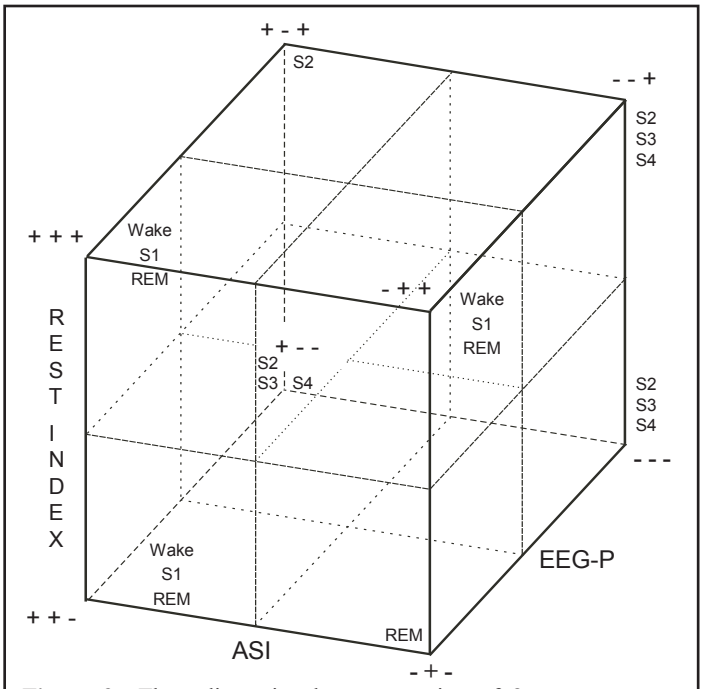

Figure 3—Three-dimensional representation of 8 pattern-to-stage combinations. The 3 axes - A (Alpha Slow-Wave Index [ASI]); the proportion of electroencephalogram (EEG) alpha to slow-wave activity E (EEG-P), mean EEG frequency; and R (Rest Index), a proportion of phasic electromyogram (EMG) activity - were bisected at the median. The resulting cube contains 8 compartments corresponding to the 8 possible combinations of the three binary variables. REM refers to rapid eye movement sleep; S1, Stage 1; S2, Stage 2; S3, Stage 3; S4, Stage 4 sleep.

+++, with high values for all 3 parameters. The additional occurrence of patients with insomnia and narcolepsy on the neighboring type ++−, and of patients with OSA on type AER/−++, needs replication with larger samples before they can be taken for granted.

Whereas Stage 1 sleep and stage wake had type AER/+++ in common, Stage 1 sleep displayed AER/−++ as a second type in all 4 groups. This shows that a reduction of alpha and a shift to EEG slow-wave activity, resulting in a low value for parameter A, is typical of a significant proportion of stage 1 epochs. The additional pattern AER/++−, characterized by low phasic EMG activity, again was significant only for patients with insomnia and control subjects. This may indicate fewer stage 1 movement arousals near the onset of sleep for the control and insomnia groups compared with patients in the OSA and narcolepsy groups.[26] The present results underline the position of Stage 1 as a transitional stage that shares the same AER types with stage wake but with different proportions of these types (see Table 2).

As opposed to the noticeable overlap of types in stages wake and 1, Stage 2 was characterized by 4 new types. All Stage 2 types had a low value for parameter E in common, indicating a definite shift to lower EEG frequencies. The other 2 parameters, A and R, were either high or low. The presence of 4 AER types in all diagnostic groups suggests that Stage 2, which occupies about 50% of total sleep time, is a broadly defined heterogeneous sleep state.[27] In an early study, Sträle (see Lairy[11]) differentiated between 3 Stage 2 EEG patterns with the following characteristics: (1) epochs with fewer than 4 sleep spindles, as well as moderate delta activity; (2) epochs with fairly low-voltage mixed-frequency EEG with 4 to 8 spindles; and (3) Stage 2 epochs with a maximum amount of slow activity. Sträle observed a specific chronologic distribution of the different types with a preference for the second type of Stage 2 later in the night. A specific chronologic distribution with increasing sleep-spindle activity during sleep, and a reciprocal relationship with EEG slow-wave activity, was later evaluated more systematically by others using digital data-analysis techniques.[28] Comparing the present types of Stage 2 with those defined by Sträle, his type c may correspond with the types AER/−−+ and – – –, which differ only in phasic EMG activity. In future studies, it would be of interest to analyze the relationship of the present types of Stage 2 sleep with autonomic and hormone data, since Brandenberger et al,[16] who analyzed such data, presented evidence for a quiet type of Stage 2, preceding slow-wave sleep, and an active type that precedes REM sleep.

Table 4—Patterns Recognized by the Configural Frequency Analysis as Antitypes

AER	Wake	S1	S2	S3	S4	REM
+++			X	X	X	
++-			X	X	X	
+-+						X
+--	X	X				X
-++			X	X	X	
-+-				X	X	
--+	X					X
---	X	X				X

Configural frequency analysis was used to defined types of activity—A refers to alpha slow-wave index ; E, electroencephalogram parameter; R, Rest Index; S1, Stage 1 sleep; S2, Stage 2 sleep; S3, Stage 3 sleep; S4, Stage 4 sleep, REM, rapid eye movement sleep. Patterns recognized as antitypes for a given stage are marked by an X.

Molinari and Foulkes'[12] distinction between tonic and phasic NREM sleep corresponds with the 4 types in sleep Stage 2 of the present analysis, 2 of them with phasic EMG activity (AER/+−+ and −−+) and 2 without (AER/+−− and – – –). Thus, Stage 2 seems to be a composite state with consistently low-frequency background EEG (low parameter values for E) activity, but fluctuations of the alpha to slow-wave ratio (parameter A either + or –), and of tonic versus phasic EMG activity (parameter R either + or –).[29]

The type AER/– – – continued into deep NREM sleep and was the core type for all 4 groups in sleep Stages 3 and 4. As opposed to the group of healthy controls, all 3 patient groups had an additional significant pattern (AER/+−−) in Stage 3, which persisted in patients with OSA and narcolepsy even in stage 4. This finding, which awaits confirmation, suggests that patients with sleep disorders (as opposed to healthy persons) have a significant subset of epochs in Stages 3 and 4, with a high EEG alpha to slow-wave ratio (parameter A +). An analysis of the chronologic sequence of appearance of types is also needed to evaluate whether the AER types +−− and −−+ in deep NREM sleep (see Table 3) represent transitional patterns that may be located preferentially near the onset or the end of slow-wave sleep.

REM sleep turned out to be a complex state with 4 types. In contrast with the AER types of NREM sleep, all AER types of REM sleep had a high value for parameter E in common, indicating a high-frequency EEG. Whereas the two types with low

R represent tonic REM sleep, the 2 types with high R represent phasic REM sleep.[12] Two of the 4 types in REM sleep occurred in all patient groups, indicating prototypes of REM-sleep patterning (AER/$-++$ and $-+-$).

Type AER/$+++$ was significant for 3 groups (controls, insomnia and OSA), sparing the group of patients with narcolepsy. A closer inspection of frequency distributions of the different types in REM sleep showed that, in contrast with the other 3 groups, in patients with narcolepsy, type $+++$ was clearly more frequent than type $++-$, suggesting a higher rate of phasic EMG activity in REM sleep of narcoleptic patients. This is in agreement with results by Geisler et al,[30] who found higher rates of phasic EMG activity in narcoleptic patients than in healthy controls.

In summary, the present results suggest that sleep stages are not homogeneous units but represent an aggregation of different substates or types. Additionally, the analysis showed that the basic structure of sleep, defined by types, is similar for normal sleepers and for patients with different sleep pathologies. This is in line with the clinical experience that sleep stages, as defined for normal adult sleepers,[31] are also used routinely for the analysis of patients with sleep disturbances. Future studies will show whether the observed differences between diagnostic groups are actually valid or whether they merely resulted from limited sample sizes in the 4 groups.

Spatial Representation of Sleep Trajectory

The types from Table 3 can also be depicted as 8 compartments of a cube, with the axes A, E, and R, bisected ($+$/–) on each side (see Figure 3). In this figure, Stages wake and 1 are represented in the left upper, left lower, and right upper front compartments. The NREM stages 2 to 4 are distributed over the 4 rear compartments. Whereas Stage 2 is represented in all 4 rear compartments, Stages 3 and 4 are both localized in the right upper, right lower, and left lower rear compartments. The 4 REM sleep types are localized in the 4 front compartments of the cube.

Whereas Stages wake and 1 form a triangle at the front of the cube, Stages 3 and 4 form a triangle in the rear of the cube. The 2 spared positions, namely left upper rear corner and right lower front corner, are uniquely occupied by a singular Stage 2 ($+-+$) and REM sleep ($-+-$) pattern, respectively. The 3-dimensional representation of stages and patterns allows one to allocate each epoch of the recording to a spatial position and to display the trajectory of the NREM-REM sleep cycles.

The 3-dimensional representation of types shows apparent similarities to Hobson's 3-dimensional AIM model,[32] with the 3 dimensions of low versus high activation (A), internal versus external orientation (I), and aminergic versus cholinergic modulation (M). If the 2 models were placed to coincide, the present variables of A, E, and R would correspond with the dimensions of internal/external (I), low/high activation (A), and aminergic/cholinergic modulation (M), respectively. The assumed compatibility suggests that both models represent basic dimensions of sleep organization. This being the case, one would expect a comparable outcome should the present input variables be replaced by other physiologic measures such as autonomic variables.

A special feature of the CFA is that it defines not only types, but antitypes as well. The interpretation of antitypes warrants some caution, since the independence of types and antitypes has been questioned.[33] However, Netter[24] has emphasized that types and antitypes can be interpreted independently if the data are embedded not in 2 × 2 but in larger r × c tables. The distribution of antitypes was quite obvious in the present analysis. Stage wake contained 3 antitypes (AER/$+--$, $--+$, and $---$). Two of them were also significant for Stage 1. All 3 antitypes had a low value for E, i.e., low EEG frequency, which is quite untypical of these stages. In contrast, Stages 2, 3, and 4 showed 4 antitypes, all with a high value for E. Finally, all 4 antitypes observed in REM sleep (AER/$+-+$, $+--$, $--+$ and $---$) were characterized by a low value for E, again indicating a low-frequency EEG, which is untypical of REM sleep. In summary, the observed antitypes represent those patterns of physiologic input variables that are very unlikely to occur in these states.

Sleep as a Continuum Versus Sleep Staging

The present analysis began with 3 continuous physiologic variables (A, E, and R), which were then split into dichotomous entities for further statistical analysis by the CFA technique. This back projection of continuous variables into discrete states or stages touches upon a crucial question of sleep research, namely, how best to describe the sleep process as such. In the era of analog signal recording, sleep staging was the single most reasonable and economic procedure for analyzing sleep data.[1,2] With the introduction of digital data recording and storage, alternative solutions became available. Today a wealth of algorithms is available, allowing any kind of signal analysis (from microscopic to macroscopic) of sleep data. Sleep staging was driven by the concept that sleep can be subdivided into different states (REM and NREM) and stages within NREM sleep, implying specific regulatory mechanisms.[31] Many recent computerized procedures for sleep analysis represent hybrid systems, first separating the sleep process into NREM and REM sleep states, then analyzing NREM sleep as a Continuum.[18]

The results of the present statistical analysis shed light on the following 3 aspects of sleep structure: (1) Sleep stages are constituted by discrete substates (types); (2) The substates or types overlap between Stages wake, 1, and REM and between NREM Stages 2, 3, and 4, without significant overlap between these 2 clusters of states; (3) although normal sleepers and sleep disorder patients displayed basically the same structure of substates, there appeared some specific group differences, which still need confirmation.

The present analysis has various limitations and thus can only constitute a first step in the direction of a taxonomic classification of sleep. First, the 3 input variables of A, E, and R were selected from a pragmatic point of view, since the continuous variables were computed on a routine basis in our lab and, thus, were available for all subjects. Additionally, because A and E are both EEG-derived parameters, the information content of these 2 variables may overlap to a certain extent. Other continuous variables might be used in future studies. Second, dichotomization of the input variables at the individual median admittedly coarsens their distribution. Due to this methodologic restriction, variability within each variable is largely reduced. This may have contributed to the substantial overlap of patterns in sleep stages 2, 3, and 4. Trisecting the input variables as an alternative procedure, which would allow a finer grading of the input variables, has the disadvantage of resulting in 27 different patterns for only 3 variables. In this case, a very large number of sleep recordings would be needed

for statistical testing.

The taxonomic analysis of multiple physiologic processes in sleep uncovered stable pattern configurations beyond the level of sleep stages. Thus, the CFA represents an analytic procedure that allows one to study the internal structure of sleep stages and transitions between stages.

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