



## EEG recurrence markers and sleep quality

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### ABSTRACT

**Objectives:** To show that EEG markers formed using the variable *percent recurrence* reliably quantified two related aspects of sleep quality, sleep depth and sleep fragmentation. As hypotheses, the depth marker would increase and the fragmentation marker decrease in patients where improved sleep quality occurred when assessed by polysomnography.

**Methods:** The patients (N = 20) had been diagnosed with obstructive sleep apnea during diagnostic polysomnography (dPSG), and had exhibited increased REM sleep (clinical indication of improved sleep quality) during subsequent polysomnography to titrate the pressure of a treatment device (cPSG). Percent recurrence was computed second-by-second from the EEG; sleep-depth and sleep-stability markers were obtained algorithmically. By assumption, the markers contained temporal information regarding the extent of deterministic (non-random) brain activity. Marker means were compared between the dPSG and the cPSG for NREM and REM sleep.

**Results:** Sleep depth was greater and sleep fragmentation was less during cPSG, as hypothesized ( $P < 0.05$ ). The effects occurred during NREM and REM sleep, but were greater during NREM sleep ( $P < 0.05$ ). At least one of the predicted changes occurred in 95% of the patients.

**Conclusions:** The factors generally regarded as responsible for subjective sleep quality were objectively quantified on the basis of dynamical changes in the EEG.

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### 1. Introduction

Human sleep and associated events are assessed on the basis of rules applied to simultaneously recorded physiological signals [1]. Three stages (N1, N2, N3) and particular arousal events (abrupt changes) are identified from the electroencephalogram (EEG), and a fourth stage (REM) is identified from the coordinated behavior of several signals including the EEG. The N3 stage is commonly regarded as deep sleep. The depth of sleep together with the rate of arousal events are determinants of sleep quality [2]. Loss of sleep depth and/or increases in arousal events produce non-restorative sleep, and are associated with various sleep disorders including obstructive sleep apnea (OSA).

Present methods for measuring the depth of sleep are problematical [3–7]. Determining the intensity of stimuli needed to wake a subject has been used to quantify sleep depth [3,4], but that method variably classified REM as the deepest level of sleep [5], intermittently deep [6], or as similar in depth to N1 and N2 sleep [6], depending on how the threshold

was measured. Delta power is a marker for sleep depth during non-REM (NREM) sleep [7], but no equivalent marker exists for REM sleep. Similarly, additional refinement of scoring arousals is needed [8]. We recently showed that a recurrence marker computed by algorithmic analysis of the EEG stratified all sleep stages, increased progressively with NREM sleep-stage depth (N1 < N2 < N3), and characterized sleep fragmentation caused by arousal events [9].

REM rebound (an increase in percent of overnight sleep that is staged as REM) occurs during recovery from chronic stress, including restorative sleep following sleep deprivation [10] and initiation of treatment for OSA using continuous positive airway pressure (CPAP) [11–14]. CPAP-associated REM rebound (CARR) is generally accepted to indicate deeper and less fragmented sleep [11–14]. We therefore expected an increase in recurrence in CARR patients and a decrease in the variability of the recurrence, compared with the corresponding values determined prior to initiation of CPAP.

Our goal was to evaluate the capability of the EEG-based recurrence variable *percent recurrence* to quantify sleep depth and sleep fragmentation. The first aim was to show that a recurrence depth marker increased in patients who experienced CARR (increased sleep depth). The second aim was to show in the same patients that a recurrence fragmentation marker exhibited a decreased rate of change (decreased sleep fragmentation).

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## 2. Methods

### 2.1. Subjects

We reviewed consecutive records of patients who underwent attended overnight diagnostic polysomnography (dPSG) that was positive for OSA (apnea–hypopnea index (AHI)  $\geq 5$  events/hr), and who subsequently underwent overnight CPAP-titration polysomnography (cPSG) during which CARR (clinical indicator of increased sleep depth and improved sleep quality) was observed. CARR was defined as an increase in REM as a percentage of total sleep time of at least 20%. This threshold was higher than that used previously [11–14], but sufficiently low to ensure that an adequate number of patients were available for study after screening the database ( $> 500$  studies). Exclusion criteria included  $< 30$  minutes of REM sleep in any study, significant medical co-morbidities, current use of sleep-altering medications, and prior treatment for OSA. The study group consisted of the first 20 consecutive patients who met all the study criteria; the selected patients exhibited quite severe OSA (Table 1). Although CPAP treatment markedly reduced the AHI (clinical indicator of reduced sleep fragmentation), the patients still exhibited OSA (Table 1). The PSGs were staged by consensus between two sleep-medicine physicians, using standard rules [1], resulting in the assignment of every 30-sec epoch of the PSGs into one of five stages: REM, N1, N2, N3, or wakefulness after sleep onset (WASO). For purposes of simplifying the subsequent analysis (see below), the N1, N2, and N3 stages were combined into the NREM stage.

To estimate the recurrence values computed during wakefulness from EEGs of healthy individuals, eyes-closed vigilant EEGs were recorded from 20 clinically normal subjects. They were selected as a representative normal sample (median age 34 years, half of each gender), not as age and gender matches for the patients. The EEGs were analyzed similarly to those from the patients (see below). All experimental procedures were approved by the institutional review board for human research.

### 2.2. EEG measurements

PSGs (which included 6 EEGs) were recorded with commercial equipment (Respironics, Alice 5, Murrysville, PA, USA), using standard digital specifications and electrode montage (O1, O2, C3, C4, F3, F4, International 10–20 system) [15]. The EEGs were digitized at 500 Hz, and exported as CSV files for analysis.

Vigilant EEGs from normal subjects were recorded for 10 minutes in a dark isolation chamber (assumed reasonably sufficient for estimating normality) to mitigate the effect of irrelevant or random ambient stimuli. The electrode montage used (O1, O2, C3, C4, P3, P4, referenced to linked ears) was chosen in accordance with the standard practice for recording EEGs in our research laboratory. The EEGs were digitized at 500 Hz, and stored as ASCII files for analysis. The recurrence values were averaged over all electrodes and all subjects to provide estimates of recurrence and its variability in normal awake subjects (the cognitive state where the variables have their extreme values).

**Table 1**

Characteristics of the sleep patients. BMI, body mass index. AHI, apnea–hypopnea index. dPSG, diagnostic polysomnogram. cPSG, CPAP polysomnogram. (Mean  $\pm$  SE).

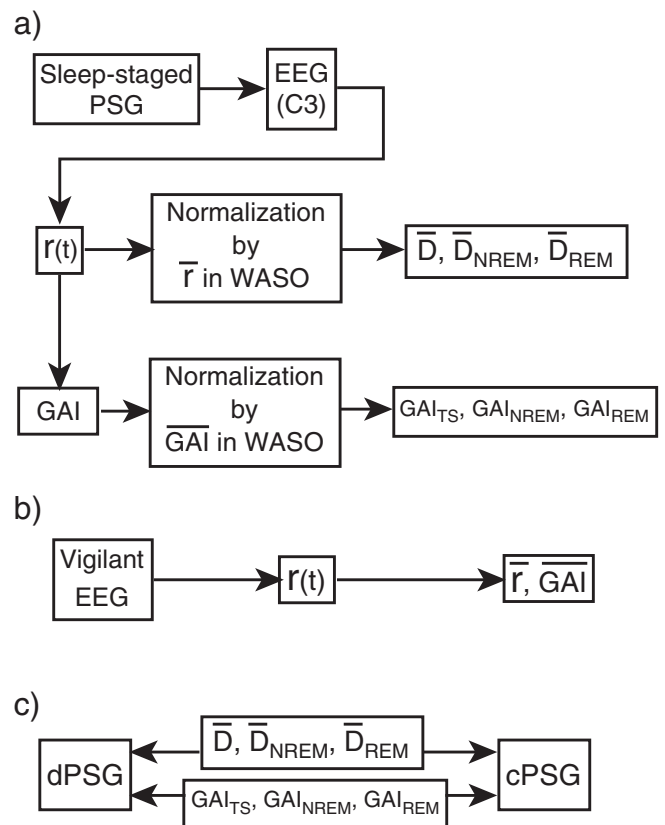
Number of patients	20
Age (years)	46.5 $\pm$ 3.1
BMI (kg/m <sup>2</sup> )	47.4 $\pm$ 2.0
Male/Female (%)	67/33
AHI (events/hr)	100.6 $\pm$ 6.1 (dPSG)
	16.1 $\pm$ 3.1 (cPSG)

### 2.3. Recurrence analysis

All EEGs were digitally filtered to pass 0.5–35 Hz and evaluated using recurrence analysis in a standard numerical computing environment (Matlab, Mathworks, Natick, MA, USA). The signal-processing techniques were developed to study nonlinear physical systems and subsequently extended to physiological signals [16,17], including the vigilant and sleep EEGs [9,18–20]. Briefly, at time  $t$  a 5-component vector was formed that consisted of the EEG amplitude at  $t$  and four earlier times identified by four successive lags of five points (10 msec). The next vector in the sequence was at  $t + 10$  msec and consisted of the EEG at that time,  $t$ , and the values 10, 20, and 30 msec earlier. The sequence of all such vectors obtainable from 1 sec of the EEG (480 vectors, given our choices of sampling rate, vector dimension, and number of lag points) formed a path (in a mathematical space) that is conventionally interpreted to be a result of the deterministic (non-random) activity in the EEG. By hypothesis, the EEG determinism increased and its variability decreased as a consequence of CPAP treatment.

The determinism was quantified second by second using the recurrence variable *percent recurrence* ( $r$ ), defined as the percent of the 480 vectors in the path that were near other vectors [17]. The Euclidean norm was used for measuring distance, and vectors were identified as *near* if they were within 15% of the distance between the two vectors that were furthest apart. These choices (and those for dimension and lag) were previously found to be useful for quantifying deterministic activity in the EEG [9,18,19].

Approximately 60 sec  $\times$  60 min  $\times$  8 hrs = 28,800 values of  $r$  were computed for a typical eight-hour overnight EEG, resulting in the time series  $r(t)$ . For the vigilant subjects, 60 sec  $\times$  10 min  $\times$  6 derivations  $\times$  20 subjects = 72,000  $r$  values were averaged to obtain the mean value of recurrence in normal subjects during wakefulness ( $\bar{r}$ ).



**Fig. 1.** Experimental design. a) Computation of recurrence markers from overnight sleep EEGs. b) Computation of recurrence markers from vigilant EEGs. c) Statistical design.

## 2.4. Experimental design

The macroarchitecture of recurrence in the sleep EEG exhibits ultradian cycles that vary between minimum values of  $r$ , which occur during WASO, and maximum values which occur during N3 sleep [9]. To permit direct intra- and inter-subject comparisons,  $r(t)$  from each PSG was normalized by the mean  $r$  of WASO ( $\bar{r}_{WASO}$ ) and multiplied by 100 to permit the normalized value ( $D(t)$ ) to be expressed as a percent (labeled *recurrence-based sleep depth*),  $D(t) = 100r(t)/\bar{r}_{WASO}$ . The average value of  $D(t)$  was computed for the entire overnight sleep study ( $\bar{D}$ ), and separately for NREM and REM stages ( $\bar{D}_{NREM}$ ,  $\bar{D}_{REM}$ ) (Fig. 1a).

A recurrence marker for fragmentation in sleep depth was created by generalizing the conventional definition of EEG arousals [1]. The ratio of the mean of  $r(t)$  for 3 sec (one value per second) to the mean of  $r(t)$  for the preceding 10 sec (ten values) was determined, and the process was repeated using successive steps of 3 sec, resulting in a time series of approximately 28,800 ratios for an overnight EEG. Whenever the ratio increased by more than 100% the change was counted as an arousal, and the hourly rate of arousals, termed the *generalized arousal index* (GAI) was determined for WASO, NREM and REM sleep separately, and for total sleep (all epochs in the PSG between lights out and lights on except for WASO epochs). The latter three values were normalized by the value for WASO and expressed as a percent

( $GAI_{NREM}$ ,  $GAI_{REM}$ ,  $GAI_{TS}$ ) (Fig. 1a). Preliminary studies showed that the results for  $D$  and  $GAI$  did not depend on the electrode derivation. Consequently, only results from C3 were presented here.

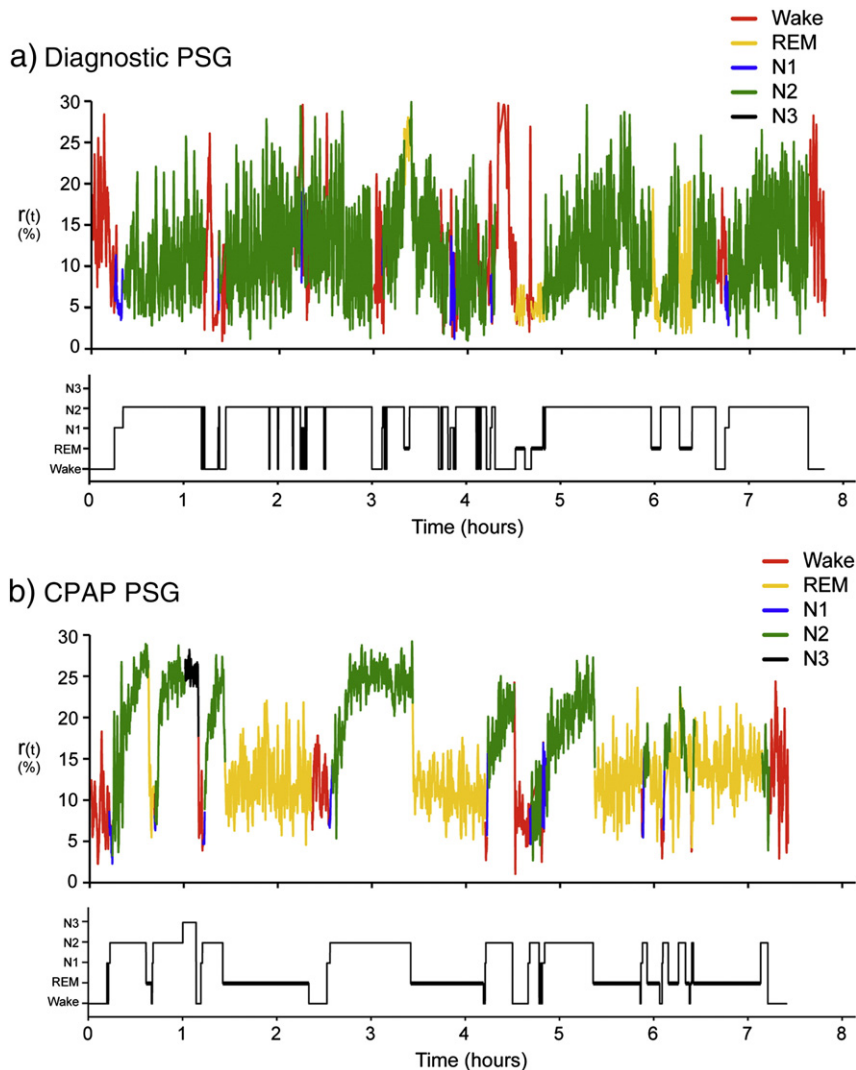
Both  $\bar{r}$  and  $\overline{GAI}$  during wakefulness were estimated from the vigilant EEGs (Fig. 1b).

The paired  $t$  test was used to compare means of the depth and arousal markers between the dPSGs and cPSGs (Fig. 1c). The unpaired  $t$  test was used to compare  $\bar{r}$  and  $GAI_{TS}$  from the vigilant subjects with the corresponding values from WASO in the PSGs. Tolerances shown for means were standard errors. For clarity of presentation, the overnight  $r(t)$  was smoothed using a cubic 59-point Savitzky-Golay filter (Sgolyfilt, Matlab).

## 3. Results

The second-by-second variation of brain electrical activity as reflected in  $r(t)$  differed profoundly as a consequence of treatment with CPAP (Fig. 2). In the dPSG,  $r(t)$  typically varied over its entire range regardless of sleep stage (Fig. 2a). In the cPSG, however,  $r(t)$  was bounded with the highest mean value occurring in N3, lowest in wake, and intermediate in N2 and REM (Fig. 2b). The hypnograms in the dPSGs and cPSGs effectively were averages of the temporal changes in  $r(t)$ .

After normalizing  $r(t)$  using the patient's  $\bar{r}$  from WASO (to control for intra- and inter-patient variability in recurrence), mean depth of



**Fig. 2.** Recurrence ( $r(t)$ ) in the EEG (C3) from an overnight sleep study (color-coded by stage) of a patient who exhibited REM rebound: a), b) diagnostic and CPAP PSGs, respectively. The corresponding hypnograms are shown.

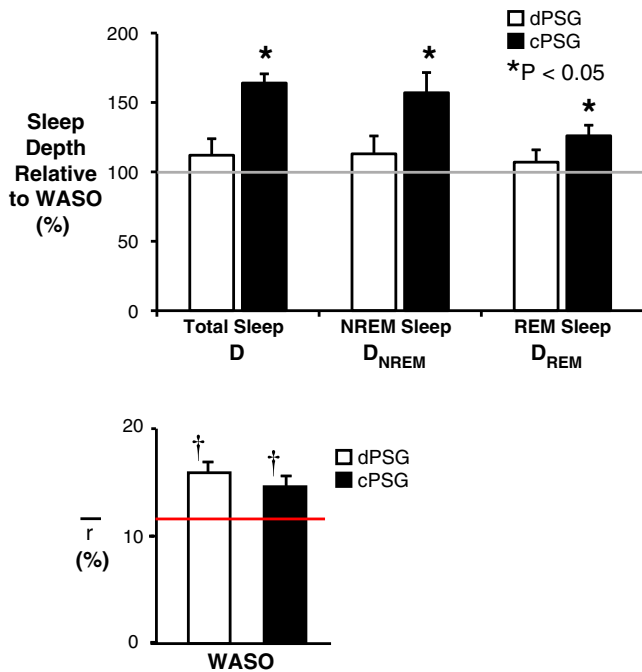
total sleep (all sleep stages) increased significantly in the cPSGs, compared with the dPSGs, as hypothesized,  $164 \pm 10\%$ ,  $112 \pm 5\%$ , respectively ( $P < 0.05$ ) (Fig. 3). Increases occurred in both NREM (44%) and REM (19%) sleep; the increase during NREM was greater than the increase during REM ( $P < 0.05$ ). WASO was higher in the dPSGs and cPSGs, compared with the corresponding value in the EEGs of clinically-normal awake subjects ( $P < 0.05$ ) (Fig. 3).

The normalized GAI during total sleep was significantly reduced in the cPSG study,  $65 \pm 14\%$ , compared with  $37 \pm 6\%$  in the dPSG ( $P < 0.05$ ) (Fig. 4). The effect occurred during both NREM and REM sleep. GAI during WASO was higher in both the dPSGs and cPSGs, compared with the corresponding value in the EEGs of clinically-normal vigilant subjects ( $P < 0.05$ ) (Fig. 4).

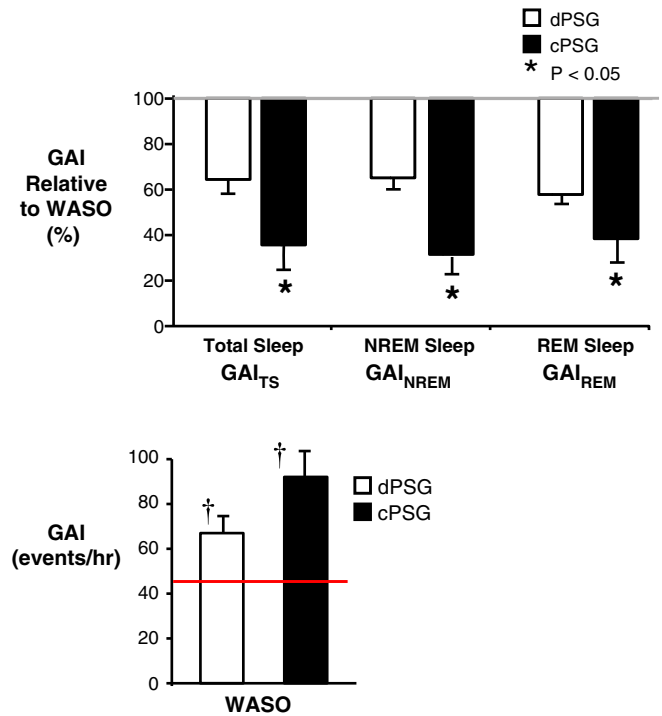
The group-level results (Figs. 3 and 4) were reflected at the level of individual patients to the extent that 15 of 20 patients exhibited an increase in the depth marker and 14 of 20 patients exhibited a decrease in the fragmentation marker (Fig. 5).

#### 4. Discussion

Sleep depth and sleep fragmentation are continuous, deterministic (non-random) features of the instantaneous state of brain electrical activity (brain states), but suitable methods for quantifying the features have not been developed. Recurrence analysis is well suited to the task, at least to the extent that the features are reflected in the EEG, which is a temporal output signal of the brain. Our aim was to show that improvements in sleep depth and sleep fragmentation that were established by clinical observation could be objectively quantified by recurrence markers and statistically verified. Specifically, we asked whether mean normalized recurrence (recurrence-based sleep depth) in patients who exhibited REM rebound during cPSGs was significantly increased, regardless of sleep stage, compared with the mean value in the corresponding diagnostic dPSGs. Further, because correcting sleep fragmentation caused by arousal events is the accepted physiological basis for the therapeutic improvement



**Fig. 3.** Increase in sleep depth as a consequence of CPAP treatment (N = 20 patients). Recurrence in the EEG from C3 was calculated second-by-second for the diagnostic and CPAP-titration studies and normalized using the patient's average recurrence value for WASO (gray line). D, D<sub>NREM</sub>, D<sub>REM</sub>, normalized sleep depth for total, NREM, and REM sleep, respectively. Lower panel, mean recurrence during WASO. Red line indicates  $\bar{r}$  ( $11.6 \pm 1.3\%$ ) in N = 20 vigilant subjects. †p < 0.05 compared with vigilant EEG (unpaired t test).



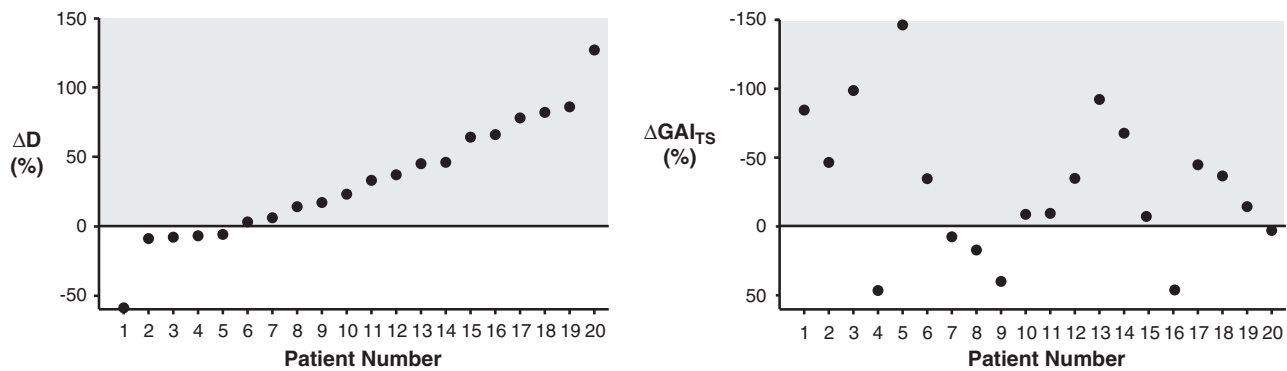
**Fig. 4.** Decrease in the sleep generalized arousal index (GAI) as a consequence of CPAP treatment (N = 20 patients). GAI was calculated from  $r(t)$  and normalized using the patient's GAI for WASO. GAI<sub>TS</sub>, GAI<sub>NREM</sub>, GAI<sub>REM</sub>, normalized GAI for total, NREM, and REM sleep respectively. Lower panel, mean GAI during WASO. Red line indicates GAI ( $45.1 \pm 5.7$  events/hr) in N = 20 vigilant subjects. †p < 0.05 compared with vigilant EEG (unpaired t test).

produced by CPAP, we expected that the GAI (a recurrence-based marker for sleep fragmentation) would be decreased in the same patients during the cPSG compared with the dPSG.

Mean sleep depth for total sleep (all sleep stages) (D) was 12% above WASO during the dPSGs, but 64% above WASO in the cPSG, resulting in an increase in sleep depth of 52% (Fig. 3). The effect on depth was reflected in both NREM and REM sleep, during which the respective increases were 44% and 19%. The validity of recurrence markers computed from the EEG as surrogates for the sleep features was further supported by the finding that fragmentation in sleep depth (evidenced by the changes in GAI) was significantly reduced during total sleep and during the NREM and REM stages ( $P < 0.05$ ) (Fig. 4). On average, therefore, analysis of the sleep EEG permitted objective characterization of recurrence markers for the clinical concepts of sleep depth and sleep fragmentation, as hypothesized. Although computing sleep depth and fragmentation does not directly yield specific mechanistic insights into sleep physiology or result in clinical improvements, the capability to objectively characterize those features of sleep may permit mechanistic and translational studies that would otherwise be difficult to perform.

At the level of the individual patient, the hypothesized changes occurred in 75% and 70% of the patients for depth and fragmentation, respectively (Fig. 5). At least one of the effects occurred in 19 of the 20 patients. But the manner in which the two measures of dynamical change in the EEG during sleep might be combined to produce an overall objective measure of sleep quality is unclear. When the results for change in sleep depth were ordered by increasing effect, the corresponding changes in fragmentation exhibited no correlation with patient number (Fig. 5), suggesting that a simple linear combination of changes in the recurrence markers probably would not correlate with subjective sleep quality [2].

The relative contributions to sleep quality due to changes that occurred during NREM sleep compared with REM sleep also remain to be assessed. Even though the study group was chosen because it exhibited an increased amount of REM sleep (the clinical indication taken to indicate improved sleep quality), improvements in recurrence-based depth



**Fig. 5.** Changes in depth of total sleep ( $\Delta D$ ) and normalized general arousal index for total sleep ( $\Delta GAI_{TS}$ ) for individual patients. The differences in the markers were computed for each of the 20 patients by subtracting the values in the diagnostic PSG from those in the corresponding CPAP PSG. The patients were numbered in ascending order of  $\Delta D$ . Stippled region indicates the quadrant where the change in recurrence marker for the patient was hypothesized to occur.

and fragmentation were greater during NREM sleep. One possibility is that the distinction between NREM and REM may not be critical with regard to the problem of combining recurrence markers for the purpose of computing an overall measure of sleep quality. Alternatively, sleep quality may depend on differently weighted contributions from NREM and REM sleep, depending on the nature and severity of the underlying sleep disorder. The issues could be addressed empirically, for example by employing principle components analysis.

During REM sleep the EEG resembles that of wakefulness, and there is typically a subjective sensation of global relaxation, an increased likelihood of complex dream imagery, and a strong subjective sense of deep sleep. The tendency to awaken during REM may depend on whether an external stimulus is incorporated into the dream, suggesting that dreaming and/or dream content may determine the depth of REM at any given moment [6]. Despite the complexity and variability of REM, at any particular moment it must correspond to a specific brain state reflected in the EEG, similar to all other moments of sleep. Recurrence analysis continuously characterizes all moments of sleep without the need to incorporate special adjustments to accommodate the unique clinical character of REM sleep.

Our overall results regarding recurrence characterization of brain states during sleep (Figs. 2–5) were unaltered when the EEGs from derivations other than C3 were analyzed. This outcome was consistent with the basic assumption of cognitive neural science that brain-wide nonlinear laws mediate cognitive function [21–23]. But even though the EEG signal reflects an integrated confluence of global brain activity, the observed redundancy of results from different derivations was not evidence that recurrence analysis of EEG signals reflected *only* nonlocalized information about brain activity. The possibility exists that other parametric choices in the analysis (vector dimension, number of lag points, as examples) might be useful for detecting determinism that occurs at other temporal and/or spatial locations. Moreover recurrence analysis involves more variables than  $r(t)$  [17]. We expect that useful information regarding sleep states may be obtained by exploring the spatial extension of brain activity using other recurrence variables and parametric values.

In summary, recurrence analysis provides a potentially useful framework for integrating and interpreting sleep depth and stability across all stages of sleep on a continuous, real-time numeric scale.

### Conflict of interest statement

The authors have no conflicts of interest to report.

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