The EEG Fingerprint of REM: Analysis of Brain Recurrence (ABR) Accurately Identifies REM Using a Single EEG Lead

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Introduction

The strong associations of REM sleep with dreaming and memory consolidation imply the existence of REM-specific brain electrical activity. Our goal was to detect REM sleep by means of ABR of the EEG.

Methods

Patients

Patients with OSA recruited from a sleep-medicine clinic, and clinically normal participants selected randomly from the SHHS database were studied (N = 20 in each cohort). All epochs were scored according to standard rules by sleep-medicine physicians. For hypothesis testing, the non-REM sleep epochs were combined.

Characteristics of the study groups

	LSU Cohort	SHHS Cohort
N	20	20
Age (years)	49.1 ± 2.2	62.1 ± 9.2
BMI (kg/m^2)	39.8 ± 1.7	27.6 ± 4.6
Male/Female	8/12	7/13
AHI (events/hr)	16.6 ± 2.0	2.0 ± 1.4

N, number of individuals in the cohort. BMI, body mass index. AHI, apnea-hypopnea index. (Mean ± SE)

EEG Measurements

The EEGs in the LSU cohort were digitized at 500 Hz and exported as CSV files for analysis. The EEGs of the SHHS cohort were obtained as 250-Hz EDF files and interpolated to 500 Hz. All EEGs were digitally filtered to pass 0.5–35 Hz and evaluated using custom codes in a standard numerical computing environment.

Analysis of Brain Recurrence

Analysis of brain recurrence (ABR) is based on complexity conjecture, which assumes that the scalp EEG is a global *delocalized* measure of the instantaneous state of network connectivity.

ABR quantifies patterns (recurrences) inherent in the EEG and demonstrable using the technique of phase-space embedding. ABR effectively measures the change in connectivity (increase in deterministic (non-random) activity) that occurs during sleep.

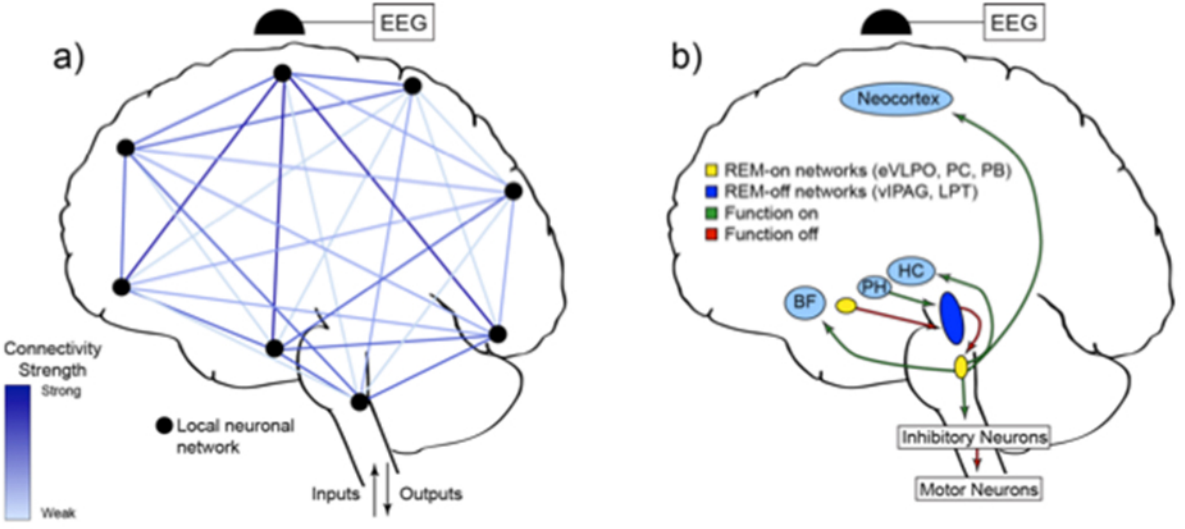
Three-stage Sleep Classification

The four biomarkers for each epoch contained redundant information. The dimension of the data was therefore reduced from four to two using principal components (PC) analysis. For a given patient, the pairs of PCs for all epochs were plotted in two dimensions and an algorithm called a *support vector machine* (SVM) was developed to classify the PC vectors into one of three classes (WASO, REM, or NREM), using clinical staging as ground truth. The lines that best separated the possible class pairs (WASO–REM, WASO–NREM, REM–NREM) were identified on the basis of least errors and maximal margins between the classes. Each epoch was assigned to one of the three classes based on a majority voting system. For each subject, an SVM classifying algorithm was built and epoch-level classification accuracy was calculated using the expert-staged results as ground truth.

Statistics

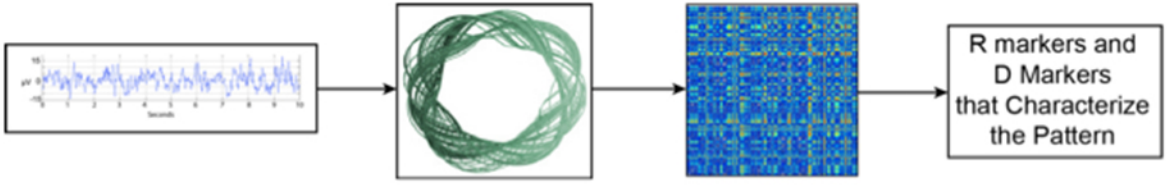
The primary outcome variable was percent REM sleep (%REM), defined as time in REM sleep divided by total sleep time, expressed as a percent. Sleep efficiency (SE) was defined as REM + NREM sleep time divided by total time in bed between lights out and lights on. %REM and SE were computed from the SVM prediction results and accuracy was determined by comparison with the clinical staging results.

Neuronal network interactions governing REM sleep exemplify the complexity conjecture regarding the origin of the human EEG

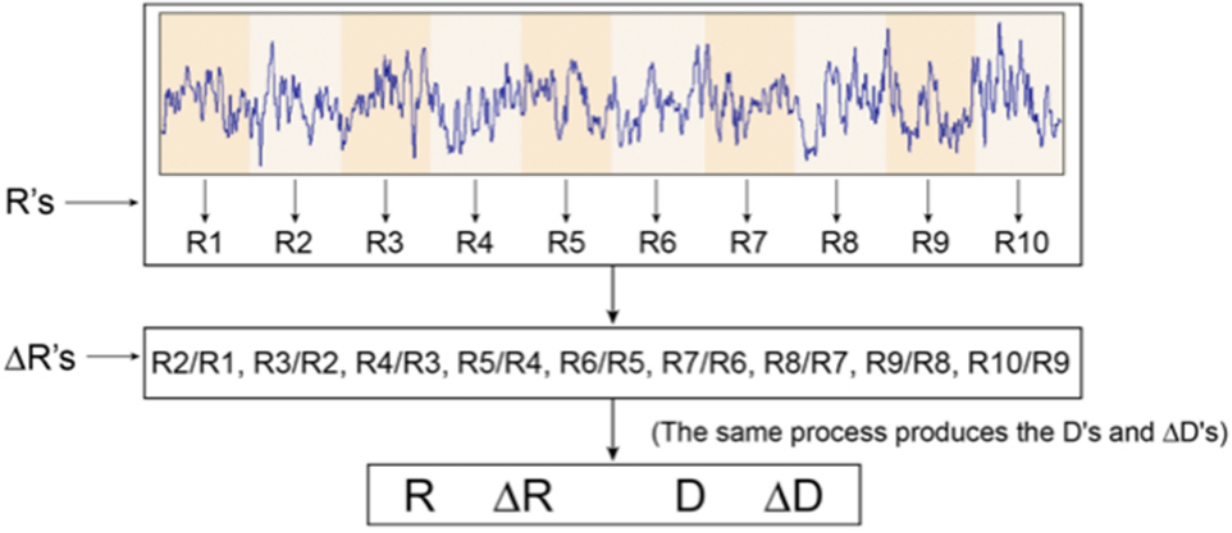


a) The instantaneous strength of the connectivity between local networks is represented by the color intensity of their interconnecting lines. **b)** REM occurs when REM-on neurons in the extended ventrolateral pre-optic area (eVLPO) inhibit REM-off neurons in ventrolateral periaquaductal gray (vlPAG) and the lateral pontine tegmentum (LPT), whose function is to actively inhibit REM-on neurons in the pre-coeruleus (PC) and parabrachial (PB) networks (dorsolateral pons). The PC and PB networks send excitatory projections to the basal forebrain (BF), hippocampus (HC) and neocortex, and to the sublateral dorsal nucleus (not shown) from which neurons project to inhibitory interneurons which produce muscle atonia.

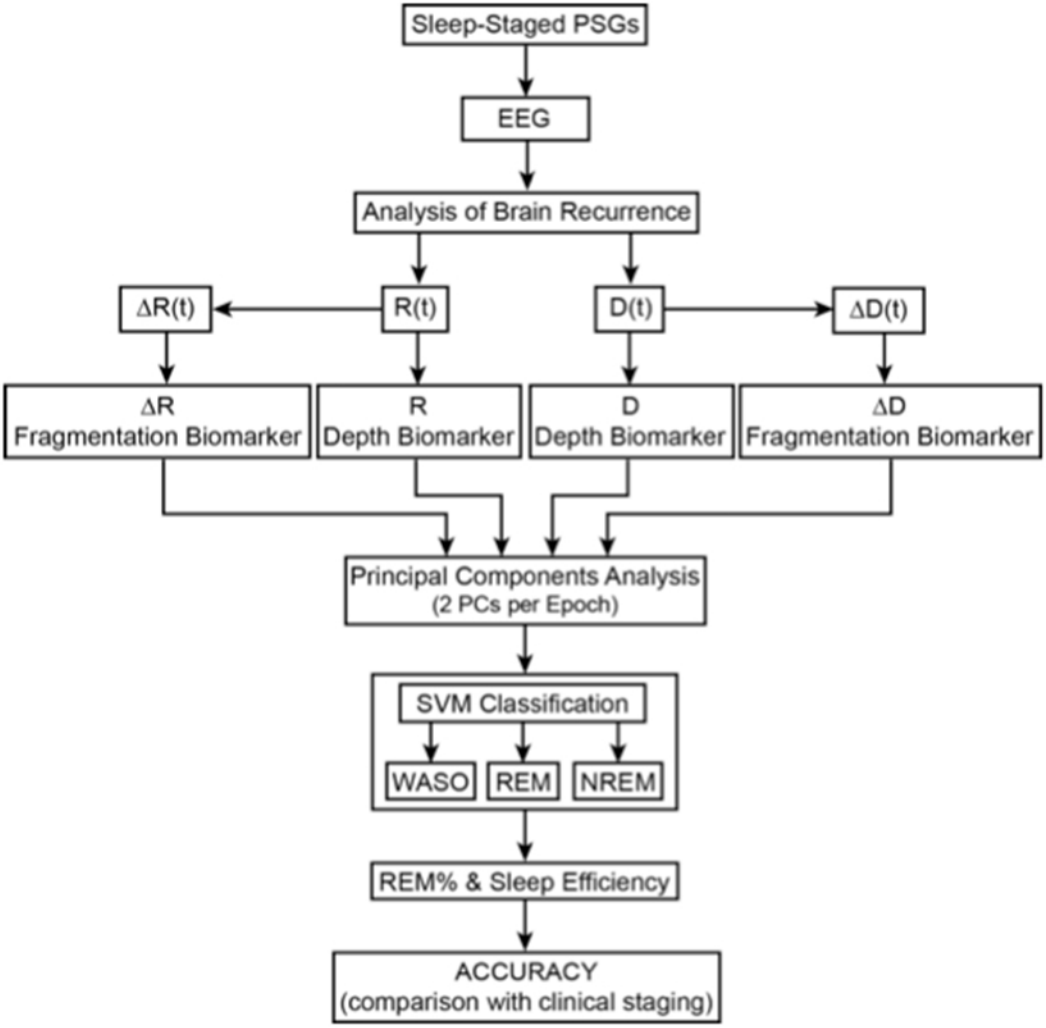
Analysis of brain recurrence (ABR)



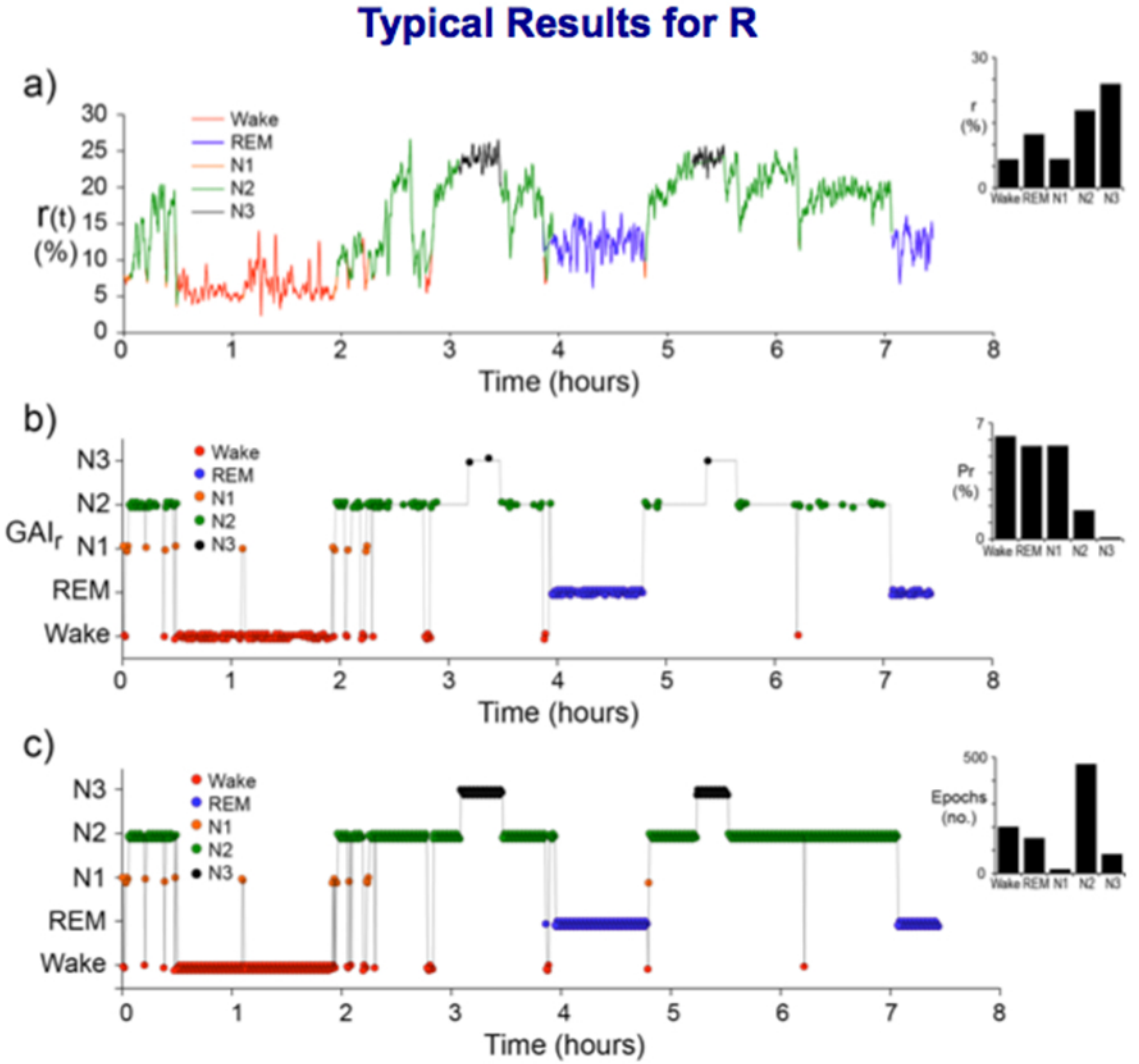
Biomarkers can be constructed from the pattern *and* from the way it changes



Experimental Design



Each of the time series R(t), D(t), and their associated general arousal series (ΔR, ΔD) were computed from the EEG, resulting in four biomarkers for each epoch. The data was reduced to two dimensions using principal components analysis. A 3-stage SVM classifier was formed and its accuracy was determined by comparison with the results of clinical staging.



Percent recurrence was calculated every second from the C3 derivation, averaged epoch-by-epoch and color-coded by sleep stage. b) Each arousal is color-coded to indicate the stage in which it occurred. c) The conventional hypnogram (one point per epoch). Stage-averaged values are given in the inserts. P_r, post hoc probability of an arousal (Patient 1 in Table 2).

Overall Classification Results

LSU Cohort

Subject	Sleep Efficiency (%)		%REM	
	Expert Scorer	Individual SVMs	Expert Scorer	Individual SVMs
1	84	91	16	23
2	78	82	21	21
3	85	89	13	16
4	86	95	18	21
5	94	94	23	23
6	95	95	21	21
7	84	89	17	21
8	94	95	15	15
9	85	90	20	17
10	99	99	18	18
11	86	87	13	11
12	90	93	14	16
13	91	93	14	12
14	86	90	15	18
15	96	96	21	21
16	91	95	12	14
17	89	92	15	10
18	85	90	21	14
19	99	99	18	18
20	94	94	14	14
Mean ± SD	89 ± 5	92 ± 4	17 ± 3	17 ± 4

SHHS Cohort

Subject	Sleep Efficiency (%)		%REM	
	Expert Scorer	Individual SVMs	Expert Scorer	Individual SVMs
1	94	94	29	29
2	78	84	23	25
3	84	89	21	18
4	65	74	20	17
5	68	69	15	14
6	84	86	16	16
7	96	96	23	23
8	87	89	24	25
9	96	96	23	23
10	97	97	24	24
11	84	85	30	29
12	95	95	24	24
13	92	92	27	27
14	90	90	33	33
15	93	93	27	27
16	82	82	13	14
17	94	94	31	31
18	86	87	20	20
19	81	94	23	33
20	86	90	18	19
Mean ± SD	87 ± 9	89 ± 7	23 ± 5	24 ± 6

Algorithm determinism of percent REM sleep and sleep efficiency in OSA patients (LSU cohort) based on recurrence analysis of the EEG (C3). Expert, ground truth (clinical staging results). SVM, algorithmic results from patient-based SVMs.

SVM Validation

LSU COHORT					SHHS COHORT				
	Sleep Efficiency (%)		%REM			Sleep Efficiency (%)		%REM	
N	Expert Scorer	Average SVM	Expert Scorer	Average SVM	N	Expert Scorer	Average SVM	Expert Scorer	Average SVM
20	89 ± 5	91 ± 4	17 ± 3	18 ± 4	20	87 ± 9	90 ± 6	23 ± 5	25 ± 2

For each cohort the 20 individual SVMs were averaged, and the average SVM was used to classify all 900 epochs per PSG x 20 PSGs = ~18,000 epochs. The results for each subject were then determined and compared with the gold standard (expert scorer). The grand average for sleep efficiency and %REM in each of the two cohorts are shown.

Discussion

We previously found that ABR depth variables were correlated with NREM stages but were unable to disambiguate REM from N1 and N2 sleep. To overcome this problem we defined an index of variability in sleep depth that captured short-term temporal changes occurring within the depth variables, and tested the hypothesis that REM could be disambiguated using a statistically determined combination of ABR biomarkers for sleep depth and variability.

When the principal components of the ABR biomarkers were computed and used in 3-class SVMs, the results matched ground truth (expert staging) using a single EEG signal for subjects with or without OSA.

Thus, within the limitations of a computational approach, we conclude that REM sleep can be disambiguated from the other stages of sleep by means of ABR.

ABR is consistent with the idea that REM can be conceptualized as a generalized brain state, similar to the way the progressively deeper stages of non-REM sleep are conceptualized.

ABR of sleep EEGs could potentiate the identification of heretofore unrecognized fingerprints of disorders such as depression, narcolepsy, and alcoholism during acute withdrawal and abstinence, perhaps allowing more robust classification compared with sleep-related markers recognized by conventional means.

References

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Abbreviations

ABR	Analysis of brain recurrence	%REM	100 x REM/(REM+ NREM)
EEG	Electroencephalogram	SHHS	Sleep Heart Health Study
NREM	Non-rapid eye movement	SVM	Support vector machine
OSA	Obstructive sleep apnea	WASO	Wake after sleep onset
REM	Rapid eye movement		