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The Fingerprint of Rapid Eye Movement: Its Algorithmic Detection in the Sleep Electroencephalogram Using a Single Derivation

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Abstract

The strong associations of rapid eye movement (REM) sleep with dreaming and memory consolidation imply the existence of REM-specific brain electrical activity, notwithstanding the visual similarity of the electroencephalograms (EEGs) in REM and wake states. Our goal was to detect REM sleep by means of algorithmic analysis of the EEG. We postulated that novel depth and fragmentation variables, defined in relation to temporal changes in the signal (recurrences), could be statistically combined to allow disambiguation of REM epochs. The cohorts studied were consecutive patients with obstructive sleep apnea (OSA) recruited from a sleep medicine clinic, and clinically normal participants selected randomly from a national database (N = 20 in each cohort). Individual discriminant analyses were performed, for each subject based on 4 recurrence biomarkers, and used to classify every 30-second epoch in the subject's overnight polysomnogram as REM or NotREM (wake or any non-REM sleep stage), using standard clinical staging as ground truth. The primary outcome variable was the accuracy of algorithmic REM classification. Average accuracies of 90% and 87% (initial and cross-validation analyses) were achieved in the OSA cohort; corresponding results in the normal cohort were 87% and 85%. Analysis of brain recurrence allowed identification of REM sleep, disambiguated from wake and all other stages, using only a single EEG lead, in subjects with or without OSA.

Keywords

brain recurrence analysis, linear discrimination analysis, biomarker function, sleep EEG, REM sleep

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Introduction

Sleep is conventionally classified into 4 stages, REM, and 3 non-REM (NREM) stages, N1, N2, and N3.[1] This staging construct recognizes that REM and NREM sleep differ in fundamentally important ways. Examples include the physiologic response to stressors like hypercarbia or hypoxia,[2] seizure susceptibility,[3] and propensity for abnormal behaviors during sleep such as NREM versus REM parasomnias.

The NREM stages are defined exclusively by features of the EEG, including the morphology, frequency, amplitude, and location of the signal. The REM stage, in contrast, requires measurement of the electro-oculogram and the chin electromyogram to enable scoring because the EEGs in REM and wake are so similar. Even so, brain activity during REM is known to exhibit a unique dynamic interplay between pontine, thalamic, and neocortical networks,[4-6] and REM has strong functional associations with both dreaming and specific types of memory consolidation.[7] Our guiding thought was that REM should be directly detectable in the EEG, but a method for doing so has not been demonstrated.

Analysis of brain recurrence (ABR) is a phase-space-based analytical method designed to detect and quantify temporal patterns in the EEG (nonrandom brain activity) that are not characterized by the conventional EEG features.[8] Using a class of ABR variables that measured what we termed sleep depth, the 3 stages of non-REM sleep were reliably distinguished from one another.[9] However, the values of the depth variables during epochs of REM sleep overlapped those of epochs that were staged wake, N1, or N2, thereby obviating the possibility of detecting clinically staged REM in the EEG using only depth

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Table 1. Characteristics of the Study Groups.

	LSU Cohort	SHHS Cohort
N	20	20
Age in years, mean ± SD	49.1 ± 9.8	62.1 ± 9.2
BMI in kg/m^2, mean ± SD	39.8 ± 7.6	27.6 ± 4.6
Male/female	8/12	7/13
AHI in events per hour, mean ± SD	16.6 ± 8.9	2.0 ± 1.4

Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index; LSU, Louisiana State University; SHHS, Sleep Heart Health Study.

variables. We subsequently defined a *sleep fragmentation* class of variables that measured depth, and presented evidence that in at least one clinical context the fragmentation variables changed in the manner expected as a result of treatment.[10]

Our first aim was to determine whether the variables could be combined to allow detection of REM epochs. Our second aim was to evaluate the generalizability of the detection procedure, by analyzing 2 independent groups of subjects.

Methods

Patients

We reviewed consecutive records of patients, seen in a sleep medicine clinic, who underwent attended overnight polysomnography (PSG) for suspected OSA The study cohort consisted of the first 20 consecutive patients with OSA (apnea-hypopnea index (AHI) ≥5 events per hour) (Louisiana State University [LSU] cohort). Exclusion criteria included <30 minutes of REM sleep (<4% of the PSGs examined), significant medical comorbidities, current use of sleep-altering medications, and prior treatment for OSA.

Each 30-second epoch was classified by 2 sleep medicine physicians using standard rules[1] into N1, N2, N3, REM, or wake after sleep onset (WASO). The experts initially agreed on more than 90% of the epochs, and the remaining epochs were staged by consensus regarding application of the staging rules. For illustrative purposes N1 (<3% of all epochs) and N2 stages were combined. For hypothesis testing, the NREM and WASO epochs were combined, resulting in 2 classes of epochs, REM and NotREM.

To evaluate the possibility that the presence of OSA could affect algorithmic detection of REM, we also studied subjects without OSA, the PSGs of whom were obtained from the Sleep Heart Health Study (SHHS cohort), a multicenter study of the cardiovascular and other consequences of sleep-disordered breathing.[11,12] An SHHS data set, collected in 2001 and 2003 (3295 PSGs), was searched to identify all participants who had an AHI determination based on standard rules; those with heart failure, emphysema, chronic bronchitis, or hypertension were excluded. From that data set (N = 390) we randomly selected 20 participants who had an AHI <5 events per hour (no OSA). Characteristics of the cohorts are listed in Table 1.

All research-related procedures were approved by the institutional review board for human research.

EEG Measurements

The PSGs of the LSU cohort were recorded using commercial equipment (Respironics, Alice 5, Murrysville, PA) and standard EEG derivations (O1, O2, C3, C4, F3, F4, international 10-20 system).[13] The EEGs were digitized at 500 Hz and exported as CSV files for analysis. The EEGs of the SHHS cohort (C3, C4) were obtained as 250-Hz EDF files and interpolated to 500 Hz to permit comparisons of the calculated results with those from the LSU cohort. All EEGs were digitally filtered to pass 0.5 to 35 Hz and evaluated using custom codes in a standard numerical computing environment (Matlab, Mathworks, Natick, MA).

Analysis of Brain Recurrence

Analysis of brain recurrence (ABR) is based on the assumptions that cognition and physiological regulation are mediated by connectivity among spatially distributed neuronal networks (complexity conjecture),[14] and that the scalp EEG is a global delocalized measure of the instantaneous state of network connectivity. ABR quantifies patterns (recurrences) inherent in the EEG that are normally unapparent, but that are demonstrable using the technique of phase-space embedding. ABR differs fundamentally from subjective methods of analyzing the EEG, such as visual pattern recognition, and from objective methods like spectral analysis, which presuppose that the EEG is composed of parts (frequencies). Brain network connectivity is highest in wakefulness, and lower (ie, more deterministic, corresponding to higher values of recurrence) during sleep.[9,15] Thus ABR effectively measures the change in connectivity (increase in deterministic {nonrandom} activity) that occurs during sleep.[9]

The basic signal-processing steps of ABR, and their special applicability to signals having the statistical properties of EEGs, were previously described.[16] Briefly, groupings of 5 points in the EEG (called vectors) were formed that consisted of the EEG amplitude at time t and at 4 earlier times identified by 4 successive lags of 5 points (10 ms because the EEG was sampled at 500 Hz). The particular sequence of all such vectors obtainable from one second of the EEG (480 vectors) was assumed to result from deterministic activity in the EEG. The amount of the activity was quantified using the variables percent recurrence (r), defined as the percent of the 480 vectors in the path that were near other vectors (and hence were recurrent), and percent determinism (d), defined as the percent of the recurrent points that were adjacent to at least one other point. Detailed analysis of these variables provides a theoretical rationale for why they quantify the amount of deterministic activity in the EEG.[16] Applications of the variables in various areas of basic and clinical neuroscience are discussed elsewhere.[8] 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 as well as those for the other parameters used in the calculation were identified empirically and previously found to be useful for analyzing the EEG.

Both variables were computed for each second of the EEG, resulting in approximately 60 seconds × 60 minutes × 8 hours = 28,800 values for a typical 8-hour overnight EEG. Taken in temporal order, the values constituted the time series $r(t)$ and $d(t)$, which were interpreted as independent measures of sleep depth wherein higher values corresponded to deeper sleep.[9,10] Epoch-level biomarkers were created by averaging $r(t)$ and $d(t)$ epoch by epoch, resulting in about 900 pairs of depth markers for each staged epoch.

REM sleep comprises phasic and tonic activity, a feature that suggested to us the possibility that the accuracy of computer-based identification of REM sleep could be improved by adding a biomarker for deterministic variability. Such markers were created by generalizing the conventional definition of EEG arousals.[1] For $r(t)$ and for $d(t)$, the ratio of the mean for 3 seconds (1 value per second) to the mean of the preceding 10 seconds (10 values) was determined, and the process was repeated using successive steps of 3 seconds, resulting in a time series of approximately 9000 ratios for an overnight EEG. Whenever the ratio increased by more than 100% for $r(t)$ or 50% for $d(t)$ (levels determined empirically during preliminary studies), the change was counted as a generalized arousal (GA). The term denotes an identifiable shift in generalized connectivity during the brain state being studied. GA indices for each depth marker were computed for each staged epoch by counting the number of arousals in the epoch (expressed as number of events per hour). Thus, 2 depth and 2 arousal biomarkers were determined for each staged epoch. The epochs were divided into REM and NotREM classes for discriminant analysis (Figure 1).

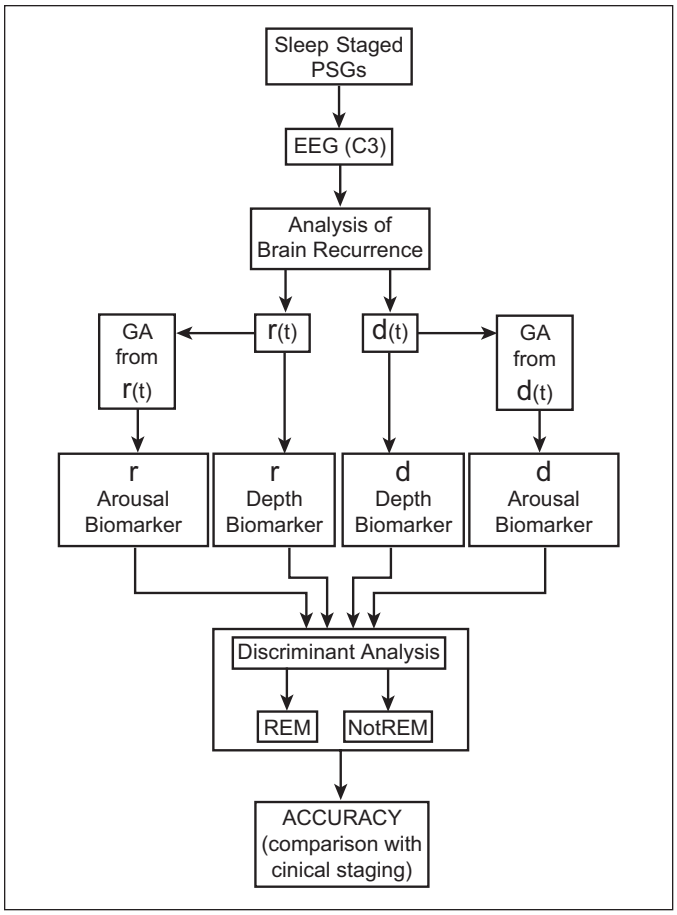

Figure 1. Experimental design. Each of the time series, ($r(t)$, $d(t)$), and their associated general arousal (GA) series were computed from the EEG, resulting in 4 markers for each epoch. Epochs were divided into rapid eye movement (REM) and NotREM classes, which were used to train a biomarker function that could classify the individual epochs into 1 of the 2 groups.

Statistics

For each subject, Fisher's linear discriminant analysis was used to determine the coefficients of a linear biomarker function that combined the four sleep biomarkers in the way that best separated REM and NotREM epochs for that subject.[17] The reliability of the biomarker function (the extent to which it correctly classified epochs that were not part of the data set used to create the function) was assessed by means of 10-fold cross validation. To implement that process, the biomarker function was determined using 90% of the subjects in the cohort, and the resulting function was used to classify the remaining 10%. The procedure was repeated ten times with differing choices for the composition of the training and evaluation sets, and the results of the 10 subanalyses were averaged. Classification accuracy was calculated as the ratio of true positive and true negative classifications to the total number of epochs, expressed as a percent.

For clarity of presentation of the overnight $r(t)$ and $d(t)$, the curves were smoothed using a cubic 119-point Savitzky-Golay filter (Sgolayfilt, Matlab).

Results

Percent recurrence ($r(t)$) and percent determinism ($d(t)$) computed from the EEGs of OSA patients exhibited ultradian rhythms consisting of 2 to 5 cycles, as expected[9,10]; a typical result for $r(t)$ is shown in Figure 2A. The values were lowest during wake and N1 and progressively higher during deeper sleep. The REM values were commonly located between N1 and N2, as noted in prior work. Generalized arousals occurred most often during WASO and REM, and were essentially absent during N3 (Figure 2B).

Using the 4 ABR biomarkers, the results of independent discriminant analyses for the individual patients in the LSU cohort showed that algorithmic determination of REM epochs matched ground truth with accuracies of 70% to 99% (90% on average); comparable results were obtained during cross-validation (79% to 96%, 87% on average; Table 2).

To evaluate the possibility that the ability to reliably identify REM epochs using ABR biomarkers was restricted to OSA patients, we performed a parallel analysis on 20 clinically

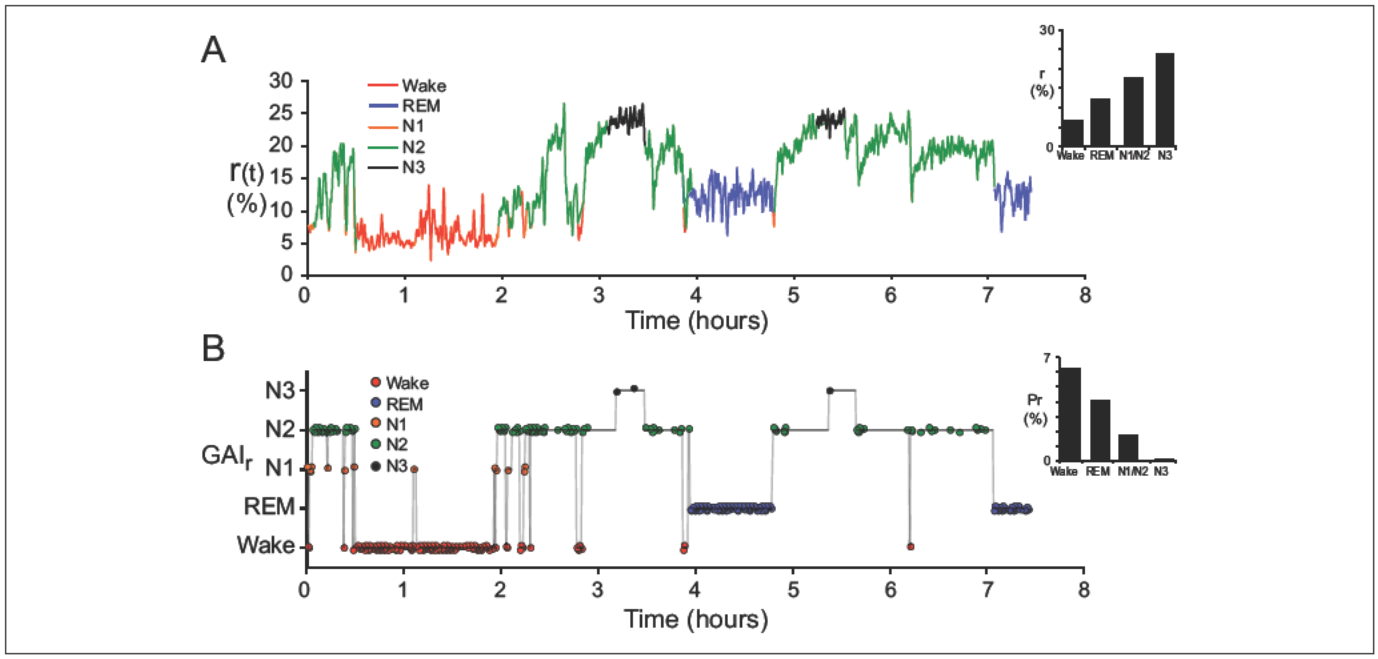

Figure 2. Typical results for percentage recurrence ($r(t)$) (A) and general arousal index (GAI) (B) computed from $r(t)$ (GAI_r) for an obstructive sleep apnea (OSA) patient (LSU cohort). Percentage recurrence was calculated every second from the C3 derivation, averaged epoch-by-epoch and color-coded by sleep stage. The arousals observed in $r(t)$ were color-coded to indicate the stage in which they occurred. Stage-averaged values are given in the inserts. P_r, post hoc probability of an arousal (patient 1 in Table 2).

Table 2. Algorithmic Determination of REM Sleep in OSA Patients (LSU Cohort).

	Ground Truth		ABR Calculated				ABR Result		GT-ABR Agreement	
Subject	REM	NotREM	TP	FN	TN	FP	REM	NotREM	Initial (%)	CV (%)
1	124	787	115	9	641	146	261	650	83	80
2	153	776	128	24	609	168	296	633	79	80
3	87	724	86	1	620	104	190	621	87	86
4	150	844	142	8	694	150	292	702	84	83
5	216	806	213	3	742	64	277	745	93	91
6	165	672	161	4	629	43	204	633	94	92
7	92	594	95	0	474	117	212	474	83	79
8	127	763	127	0	702	61	188	702	93	92
9	158	765	150	7	621	145	295	628	84	81
10	152	691	152	0	679	12	164	679	99	96
11	104	840	102	2	744	96	198	746	90	88
12	113	800	111	2	719	81	192	721	91	87
13	110	757	110	0	661	96	206	661	89	86
14	113	743	109	4	631	112	221	635	86	84
15	173	671	173	0	630	41	214	630	95	94
16	100	828	96	4	746	82	178	750	91	87
17	113	712	109	3	617	96	205	620	88	86
18	180	832	168	12	725	107	275	737	88	82
19	136	648	136	0	637	11	147	637	99	95
20	127	820	126	0	764	57	183	764	94	93
Mean ± SD									90 ± 5	87 ± 5

Abbreviations: REM, rapid eye movement; OSA, obstructive sleep apnea; LSU, Louisiana State University; GT, ground truth; CV, cross validation; ABR, analysis of brain recurrence; TP, true positive; FP, false positive; TN, true negative; FN, false negative.

Table 3. Algorithmic Determination of REM Sleep in Normal Subjects (SHHS Cohort).

	Ground Truth		ABR Calculated				ABR Result		GT-ABR Agreement	
Subject	REM	Not REM	TP	FN	TN	FP	REM	Not REM	Initial (%)	CV (%)
1	224	590	186	38	492	98	284	530	83	87
2	191	851	137	53	563	289	426	616	67	71
3	158	734	155	3	680	54	209	683	94	90
4	133	913	133	0	746	167	300	746	84	89
5	90	812	87	3	736	76	163	739	91	87
6	132	876	124	8	752	124	248	760	87	80
7	190	657	178	12	577	80	258	589	89	90
8	201	767	169	32	585	182	351	617	78	83
9	185	655	152	32	515	141	293	547	79	84
10	189	641	185	4	620	21	206	624	97	96
11	199	592	188	11	512	80	268	523	88	94
12	188	625	174	14	558	67	241	572	90	81
13	188	565	170	18	494	71	241	512	88	93
14	237	564	199	37	469	96	295	506	83	81
15	249	744	233	15	659	86	319	674	90	92
16	88	750	87	1	682	68	155	683	92	84
17	214	532	178	36	434	98	276	470	82	84
18	191	897	191	0	740	157	348	740	86	85
19	217	950	182	35	746	204	386	781	80	70
20	116	620	107	8	579	42	149	587	93	81
M ± SD									86 ± 7	85 ± 7

Abbreviations: REM, rapid eye movement; SHHS, Sleep Heart Health Study; GT, ground truth; CV, cross validation; ABR, analysis of brain recurrence; TP, true positive; FP, false positive; TN, true negative; FN, false negative.

normal participants (SHHS cohort). When biomarker function was trained on the ABR biomarkers for the REM and NotREM epochs, the accuracies of the determinations of REM matched that obtained in the LSU cohort (Table 3).

For both cohorts, the overall results when using the other derivations were similar to the results found using C3 (data not presented).

Discussion

REM sleep is a prime example of the connectivity model of cognition because REM is mediated by a dynamic array of interconnected neuronal networks (Figure 3). ABR is a method for quantifying brain connectivity that is particularly useful for studying sleep. We previously found that ABR depth variables were correlated with NREM stages, but were unable to distinguish REM from WASO.[9] To overcome this problem, we defined an index of variability in sleep depth, and tested the hypothesis that REM could be identified using a statistical combination of ABR markers. In both cohorts studied, we found that the ABR results matched ground truth as determined by expert staging (Tables 2 and 3), with accuracies of 86% to 90% in the initial statistical evaluations, and 85% to 87% in the cross-validation studies. Thus, as hypothesized, REM sleep could be reliably identified using a single EEG channel, irrespective of the presence or absence of OSA.

The demonstration of the ability to find REM in the EEG depended on knowledge of ground truth (expert staging), which is necessary for creation of a biomarker function.[19] The accuracy achieved in doing so (Tables 2 and 3) is evidence that REM had an objectively discernable fingerprint in the EEG—the showing of which was the study objective. Even so, success in training a classifier to recognize REM is no guarantee or indicator that any specific classifier will recognize REM in subjects on which the classifier has not been trained. We partially addressed this question by showing that the cross-validation results were essentially identical to those found in the initial analysis.

REM sleep is a prime example of the connectivity model of cognition because REM is mediated by a dynamic array of interconnected neuronal networks (Figure 3). ABR is a method for quantifying brain connectivity and is therefore suited for studying REM. ABR is consistent with the idea that REM can be conceptualized as a generalized brain state,[7] similar to the way the progressively deeper stages of non-REM sleep are conceptualized. Our observation that the overall accuracy of algorithmic identification of REM in the EEG did not depend on the derivation of the signal supports this notion. The ability to identify REM directly from the EEG could facilitate studies of the nature and purpose of REM sleep. For example, it is recognized that REM may be identifiably altered by various disorders, including depression,[19] narcolepsy,[20] and alcoholism.[21] ABR could help identify unrecognized REM fingerprints of these conditions in the sleep EEG. Furthermore, in principle,

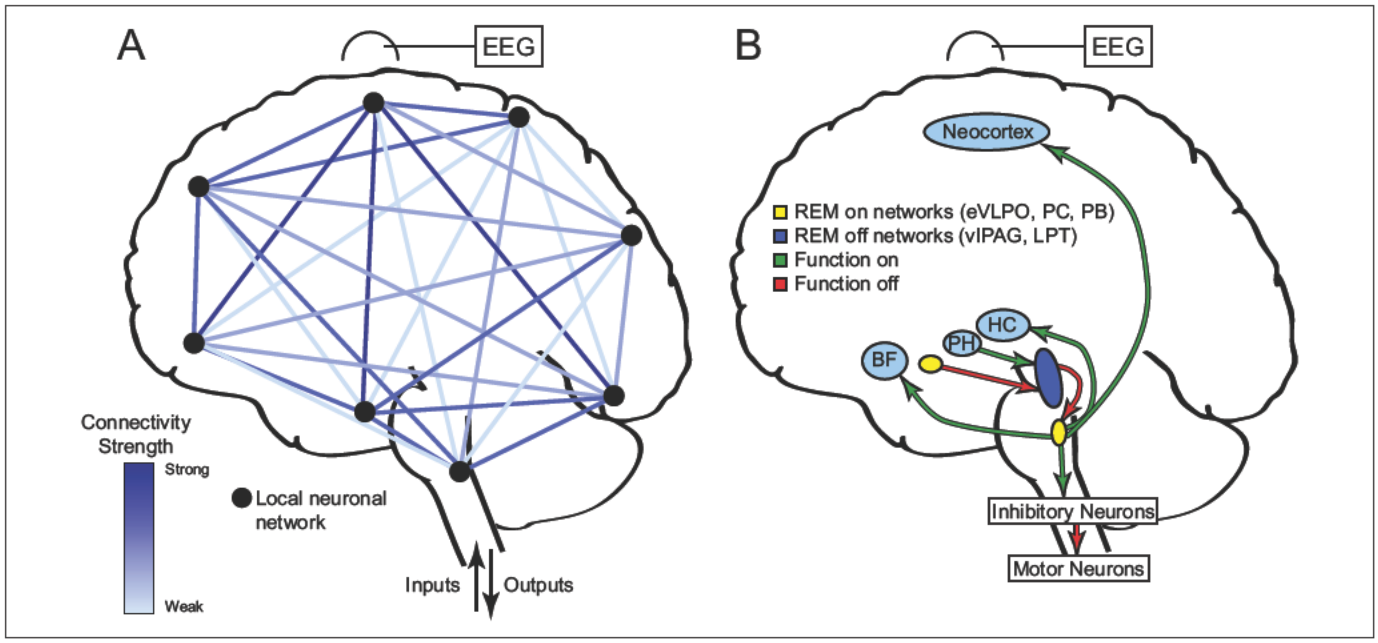

Figure 3. Neuronal network interactions governing rapid eye movement (REM) sleep exemplify the complexity conjecture (A) regarding the origin of the human EEG. A) The instantaneous strength of the connectivity between local networks is represented by the color intensity of their interconnecting lines. (B) REM occurs when REM-on neurons in the extended ventrolateral preoptic 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 precoeruleus (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.

ABR could increase the temporal resolution of sleep, leading to a finer-grain understanding of REM.

In conclusion, ABR analysis allowed reliable identification of REM epochs in subjects with or without OSA, using the EEG from a single derivation.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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