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CORRELATION OF HIGH-FREQUENCY OSCILLATIONS WITH THE SLEEP–WAKE CYCLE AND COGNITIVE ACTIVITY IN HUMANS

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Abstract—While several authors have suggested that high-frequency electroencephalogram activity (gamma, >30 Hz) correlates with conscious thought, others have suggested that electroencephalogram activity >30 Hz shows the same relationships to cognitive activity and sleep as activity in the conventional beta frequency band. The existence of coherence of gamma over large distances also remains controversial. We studied quantitatively the relationship of gamma activity to the sleep–wake cycle and cognitive tasks during wakefulness in humans using intracranial electroencephalogram. Gamma activity made up less than 1% of the total power spectrum. A significant relationship was observed between gamma activity and the sleep–wake cycle such that gamma was highest during wakefulness, intermediate during light and rapid eye movement sleep, and lowest during slow-wave sleep. As well, gamma was higher during rapid eye movement sleep with eye movements than during rapid eye movement sleep without eye movements. During a cognitive task experiment, while lower frequencies, including beta, showed a stepwise reduction with increasing task difficulty, gamma was observed to increase during cognitive tasks as compared to the resting state. The relationship between gamma and the sleep–wake cycle and cognitive tasks was independent of brain region and hemisphere. Coherence of gamma activity at distances of 5 mm and greater was not observed.

Our data support previously reported findings that gamma activity has a significant relationship to the sleep–wake cycle. The findings of differences in gamma during REM sleep with and without eye movements suggest that the presence or absence of eye movements may reflect two different states of brain activity. Our findings of differences in the relationships of the beta and gamma bands to both the sleep–wake cycle and cognitive tasks demonstrate that various components of the high-frequency spectrum behave differently in some situations. © 1999 IBRO. Published by Elsevier Science Ltd.

Key words: high-frequency oscillations, gamma, sleep, cognitive activity.

In his first report on human electroencephalography in 1929, Hans Berger raised the question: “Is it possible to demonstrate the influence of intellectual work upon the human electroencephalogram…”.[1] At the time, he reported that: “I am inclined to believe that with strenuous mental work the larger waves of first order (alpha) with an average duration of 90 σ are reduced and that the smaller 35 σ waves of second order (beta) become more numerous”.[1] Since that time, a tremendous amount of research has been done on the relationship of the electroencephalogram (EEG) spectrum to cognitive activity. Berger’s original observation of attenuation of alpha activity with cognitive activity has been substantiated by many reports, while the relationship between beta activity and cognitive activity remains unclear.[17,21,29] In 1938, Jasper and Andrews described the presence of 35–45 Hz EEG activity for which they introduced the term “gamma waves”.[10] In recent years, high frequency rhythms have been observed to be induced by all forms of sensory stimulation (visual, olfactory, auditory, and somatosensory) in both animal and human experiments.[4,7,18,27,35] This activity has also been associated with the initiation of motor tasks, as well as with various other cognitive activities including language, mathematical and visuospatial tasks.[14,18,23,29,35] Recently, animal and human data have shown an association of gamma activity with the sleep-wake cycle and behavior during wakefulness.[2,11,15] In rats, quantitative EEG data has demonstrated increased gamma during active wakefulness and paradoxical sleep and low gamma during slow-wave sleep.[2,15] Llinas and Ribary reported the presence of gamma activity in humans which was highest during wakefulness and rapid eye movement (REM) sleep, as well as reporting coherence of gamma activity across the entire hemisphere.[11] They did not, however, report any quantitative data on the relationship of gamma to sleep, nor did they look at the various stages of non-REM sleep.[11] Based on this information, it has been proposed that gamma activity is an indicator of cognitive activity and that coherent oscillations in this frequency range allow the binding of distant brain regions which is necessary to allow cognitive experience.[11,13] The fact that gamma activity during REM sleep is as high as during wakefulness has been proposed to signify that the two states are associated with similar levels of cognitive activity.[11,13,15]

Several authors have examined high-frequency activity at the intracellular level.[12,22,30,32,34] These studies have demonstrated that high-frequency rhythms are seen at the intracellular level in all clinical states and that this activity is enhanced during brain activation (such as during wakefulness and REM sleep).[2,13,22,30,32,34] Intracellular recordings showed that increased high-frequency activity correlated with increased depolarization of cells.[22,30,32,34] Steriade *et al.* found that coherence of high-frequency activity was observed at distances of one to two millimeters, but fell off rapidly with distances greater than five millimeters.[32] Furthermore, Steriade *et al.* found no consistent peaks in the high-frequency band, but rather a broad band of activity from 10–50 Hz.[30,32,34] Based on these findings, Steriade *et al.* have suggested that high-frequency EEG activity (>20 Hz), like

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Abbreviations: CB, counting backwards; CF, counting forwards; EC, resting with eyes closed; EEG, electroencephalogram; EMG, electromyogram; EOG, electro-oculogram; LS, light sleep; MA, mental arithmetic; REM, rapid eye movement; SWS, slow-wave sleep; W, wakefulness.

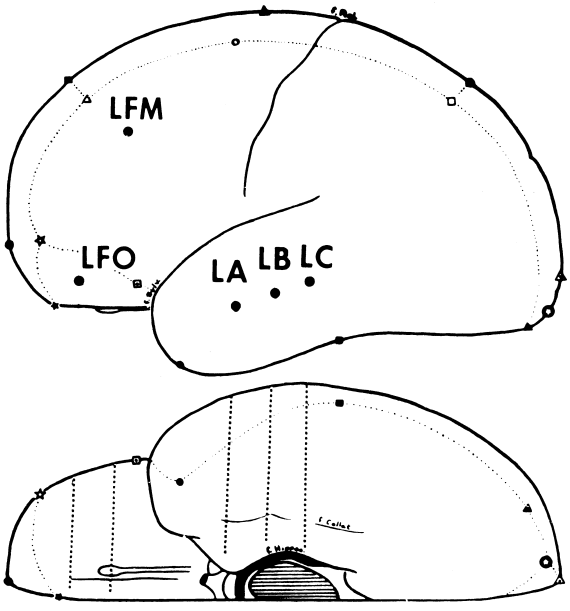

Fig. 1. Example of typical location of depth electrode implantation within the temporal and frontal lobes. Each depth electrode had nine contacts with the contacts being at 5-mm intervals along the length of the electrode. Modified from Gloor *et al*.[6]

lower-frequency EEG phenomena that are observed in association with cell hyperpolarization, (such as spindles in stages II–III sleep and synchronous delta and very low frequency oscillations stages III and IV sleep), are the signature of the degree of depolarization of the cell.[30–34] They have further proposed that there is no rationale for distinguishing between beta and gamma frequency bands.[32]

Thus, at the present time, the existence of gamma activity as a distinct band within the high-frequency range remains controversial, as does the presence of gamma band coherence between distant brain regions. To date, the relationship of gamma activity to sleep has not been studied with intracranial electrodes in humans. The purpose of this investigation was to study the relationship of gamma activity and coherence within the gamma frequency band to the sleep–wake cycle and to cognitive tasks during wakefulness in humans with intracranial EEG. This is the first quantitative study of gamma activity in the human EEG during the different stages of sleep. We studied epileptic patients because of the opportunity afforded by intracranial electrode implantation to study gamma activity close to the generators, as opposed to surface recordings where the generators are distant from the electrodes and the low amplitude gamma activity is attenuated.

EXPERIMENTAL PROCEDURES

Approval was obtained from the Montreal Neurological Institute Research Ethics Committee, as was informed consent from all participants.

Patient selection and recording methods

High-frequency activity was studied in patients undergoing intracranial electrode implantation for the investigation of epilepsy. Patients were implanted with depth electrodes, epidural electrodes, or a combination of the two according to the protocol of Olivier *et al*.[20] Electrode placement was unique to each patient and was based on the individual patient's clinical problem and previous investigations. In all cases depth electrodes were placed orthogonally through a burr hole in the skull. Depth electrodes implanted in the temporal lobe were implanted through the second temporal gyrus with two or three electrodes implanted into one temporal lobe. Anterior, mid and posterior temporal depth electrodes were directed in such a way that the deepest contacts were located within the amygdala, hippocampus and parahippocampal gyrus, respectively (Fig. 1).[6] Depth electrodes implanted in the frontal lobes were implanted orthogonally through the lateral frontal convexity with deepest contacts being located at the mesial frontal cortical surface (Fig. 1).[6] Epidural electrodes were implanted through burr holes in the skull into the epidural space. Patients had between zero and six depth electrodes and zero and 14 epidural electrodes. As with all intracranial recordings done at our institution in the investigation of epilepsy, the reference electrode was an epidural electrode inserted over one parietal lobe. Eye movements were recorded with two EOG (electro-oculogram) electrodes (lateral and above the left eye, and lateral and below the right eye). Muscle activity (electromyogram; EMG) was recorded from two submental surface electrodes.

Intracranial electrodes were manufactured on site. Epidural electrodes consisted of a 60/1000 inch stainless steel pin insulated with shrinkable tubing. Depth electrodes were made from stainless steel wire using a 10/1000 inch central core and 3/1000 inch wire for electrode contacts. To form the contacts, 3/1000 inch wire was wrapped around the core with an interelectrode distance of 5 mm. Each electrode had nine contacts. The depth electrodes were insulated using Teflon coating. During their investigation, patients had at least one overnight EEG/video telemetry recorded digitally with a 32-channel Grass Model 15 amplifier (AstroMed, Providence, RI) and the Harmonie software (Stellate Systems, Montreal, QC) with a sampling rate of 200 Hz with input filter settings of 0.01 and 100 Hz.

Awake electroencephalogram samples

During the recording, each patient had standardized awake samples recorded in the following conditions: resting with eyes closed (EC); eyes closed, counting forwards (CF); eyes closed, counting backwards (CB); and eyes closed, mental arithmetic (counting backward from 100 by sevens) (MA). Due to a static cognitive deficit, one patient was unable to count backward from 100 by sevens. For this patient, counting backwards by twos was used instead. Each patient had two 30-s samples recorded for each clinical state. All artifact free EEG from both trials was used for analysis.

Definition of sleep stages

Sleep was staged using both referential and bipolar montages. Because of the risks of infection in the presence of depth electrodes, scalp electrodes could not be used and, therefore, conventional sleep staging was not possible. In patients who did not require frontal midline electrodes for investigation of their epileptic disorder, it was not always possible to observe sleep spindles, vertex sharp waves or K-complexes. For this reason, the following definitions of sleep stages were used: 'wakefulness (W)'—video demonstrating wakefulness, low-voltage EEG, relatively high EMG amplitude and fast eye movements; 'light sleep (LS)'—presence of sleep spindles or vertex sharp waves, in patients that did not show spindles or vertex sharp waves, light sleep was selected by the combination of a low voltage EEG without delta activity, relatively low voltage EMG, absence of fast eye movements and video evidence of sleep; 'slow-wave sleep (SWS)'—was defined by the presence of greater than 50% delta activity in EEG channels, in combination with relatively low voltage EMG, absence of fast eye movements, and video evidence of sleep; 'REM sleep (REM)'—was selected by the combination of low voltage EEG, low voltage EMG, rapid eye movements and video evidence of sleep (Figs 2, 3).

Fig. 2. EEG recording illustrating episodes from different stages of sleep-waking cycle from a subject with sleep spindles (W, LS, SWS, and REM). Bipolar montage with depth electrodes RS1–3, RS5–7, RO1–3, RO3–5 (50 μV calibration), EOG (30 μV calibration) and chin EMG (20 μV calibration) from subject one (time-scale, 1 s). Depth electrodes were implanted orthogonally with RS directed towards the right supplementary motor area and RO directed towards the posterior cingulate gyrus (for both depth electrodes, contact 1 was most mesial). Sleep spindles are clearly apparent during light sleep.

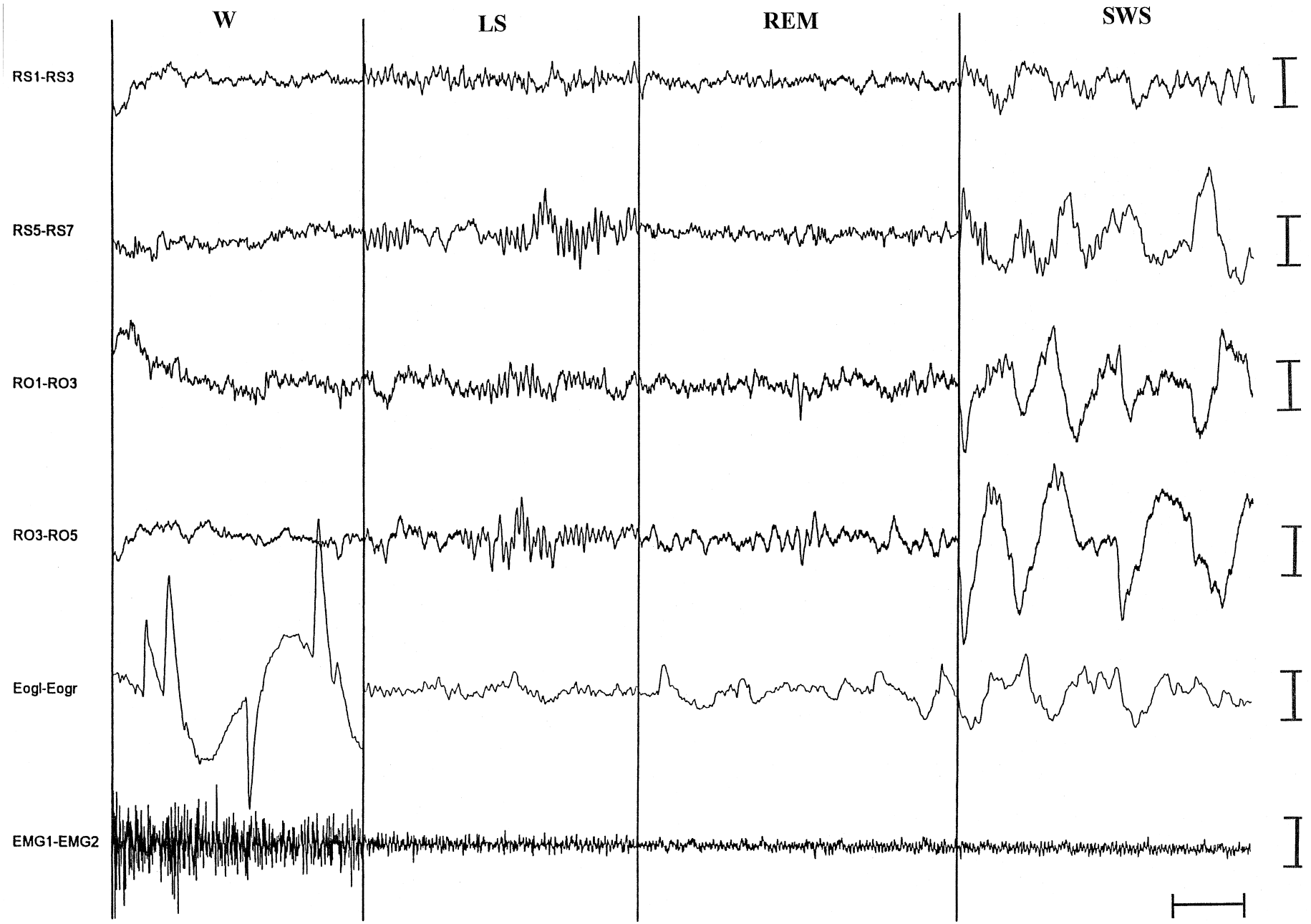

Fig. 2.

Selection of sleep epochs

In order to target potential areas of the record for detailed visual inspection and sleep staging, "trend analysis" (Stellate Systems, Montreal, QC) was done providing a spectral analysis on selected intracranial electrodes and chin EMG for the entire overnight recording with a 60-s time resolution (Fig. 4). Using this data to select broad time slices for visual inspection, the first continuous segment of EEG that met the above described criteria for each stage (W, LS, SWS and REM) was selected and a 1-min artifact-free segment chosen for analysis. Within each REM sleep segment, 20-s segments were also selected with and without eye movements for separate analysis. For patients who had seizures during the recording, segments were not selected if they occurred within 1 h of a seizure. In one record (patient 2) numerous brief subclinical electrographic seizures, lasting 5–10 s, occurred throughout the recording. Segments were selected as far as possible from the electrographic seizures.

Visual inspection of electroencephalogram

Following the selection of segments for further analysis described above, which was done using unfiltered EEG, EOG and EMG and video data, all selected segments were further inspected visually in detail. EEG channels, selected as described below, were displayed simultaneously using the following digital filters: unfiltered, 15–30 Hz band pass (beta filtered), and 30–58 Hz band pass (gamma filtered). The specific goals of the visual inspection were to study the relationship between gamma activity and beta activity during all states and between high-frequency activity and very low-frequency oscillations (<1 Hz) during slow-wave sleep as described by Steriade *et al*.[32]

Selection of electrodes for analysis

In order to obtain data approximating as close as possible to that of a normal brain, and a relatively stationary EEG record for spectral and coherence analysis, contacts demonstrating interictal epileptic discharges or disturbance of background were excluded. While some patients had a relatively small number of contacts with normal background and no epileptic activity, other patients had a large number of normal appearing contacts. In order to prevent the oversampling of individual patients from biasing our results, a limit to the maximum number of electrode contacts analysed on an individual patient was set at nine.

As cognitive tasks during wakefulness were expected to activate brain regions diffusely, as opposed to activating functional brain regions focally, brain regions were arbitrarily divided as follows: 'mesial temporal', three deepest contacts of depth electrodes in the temporal lobes; 'temporal neocortex', superficial temporal depth electrode contacts as well as epidural contacts over the temporal lobe; 'mesial extratemporal', three deepest contacts of depth electrodes outside the temporal lobes and: 'extratemporal neocortex', superficial depth electrode contacts as well as epidural contacts outside the temporal lobes. Electrode placement was based solely on each patient's epileptic disorder and, therefore, not all patients had electrodes without epileptic activity in all four brain regions. Electrodes were selected in order to sample activity from as many brain regions as was possible in each patient.

Definition of frequency bands

As visual inspection of spectral activity and coherence did not suggest the presence of peaks of spectral activity or coherence in the high frequencies, analysis of spectral activity and coherence was done using broad frequency bands. The following frequency bands were used: delta, 1–4 Hz; theta, 4–8 Hz; alpha, 8–12 Hz; sigma, 12–15 Hz, beta, 15–30 Hz, and gamma, 30–58 Hz. Stopping at 58 Hz rather than 60 Hz avoided possible contamination by the main power source. The sigma band was used specifically to remove spindle activity from the beta band.

Spectral analysis. Frequency spectra were obtained with fast Fourier transformation of each segment with non-overlapping 2.56-s epochs averaged over the 60-s segment, using a referential montage. The total power was calculated for each frequency band and all further analysis performed on total band power. In order to achieve a normal distribution of data for statistical analysis, the log transformation of the power of the spectral bands was used.[5]

Analysis of coherence

Coherence analysis was done using both bipolar and common reference (parietal epidural electrode) montages. Comparison of the level of coherence of the exact same epochs using bipolar and referential montages revealed a much higher coherence for all comparisons in all states with the referential montage. As we felt that the high coherence values with the referential montage represented an artifact of the reference electrode, all statistical analysis of coherence was done using bipolar montages. This is in agreement with recommendations of Nunez *et al*.[19] For depth electrodes, we used bipolar channels with adjacent electrode contacts (5 or 10 mm apart). Coherence analysis was performed on adjacent channels without any common electrodes; for instance, coherence was computed between channels LH1–LH2 and LH3–LH4 of the LH electrode chain in patient five. For epidural electrodes, bipolar channels compared closest neighboring electrodes with coherence analysis performed on adjacent channels (again without common electrodes). The electrode contacts that were used for spectral analysis were also used for coherence analysis, therefore, the number of comparisons that were made for each patient was dependent on the total number of electrodes used for spectral analysis (if four contacts were used, only one pair of channels was available for coherence analysis). Given the limitation of electrode selection and the above methodology, the maximum number of channel pair comparisons that was possible in a single patient was five. Altogether 18 channel pairs were available for analysis. Coherence analysis was performed on 15-s segments, selected from the same intervals as were used for spectral analysis, using 2.56-s non-overlapping epochs. As no consistent peaks of coherence were observed, the mean coherence for the frequency band was used for statistical analysis.

Statistical analysis

All statistical analysis was done using Systat version 7.0.1 software (SPSS). For analysis of frequency band spectra, analysis of variance (ANOVA) was first performed with the state (sleep–wake stage and cognitive tasks) as well as the following independent factors: patient, brain location, hemisphere, and electrode type (intracerebral or epidural). Since no interaction was found between state and patient, location, hemisphere, and electrode type, all of the analysed contacts on all patients were pooled together. For the final analysis, ANOVA (with repeated measures) was performed. For all statistically significant results, post hoc analysis was performed using a C-matrix. For comparison between REM sleep with and without eye movements, a paired *t*-test was used. For analysis of coherence, band coherence was analysed using ANOVA with state as the dependent factor.

RESULTS

Six patients were included in the study (Table 1). One patient (patient 2) had two overnight recordings separated by six days. All other patients had a single overnight recording, therefore a total of seven records were analysed on six patients. Seizures were recorded during four of seven records (Table 1). Details of electrode placement, location of analysed electrodes, interictal and ictal epileptic abnormalities are outlined in the table.

The raw EEG data was inspected visually without filters,

Fig. 3. EEG recording illustrating episodes from different stages of sleep–waking cycle from a subject in which sleep spindles were not observed (W, LS, SWS, REM). Bipolar montage with depth electrodes LH1–3, LH5–7, RH1–3, RH5–7 (30 μV calibration), EOG (20 μV calibration), and chin EMG (2 μV calibration) from subject three (time-scale, 1 s). Depth electrodes were implanted orthogonally with LH directed towards the left hippocampus (LH1 being the most mesial contact and LH7 the most lateral). The RH electrode was implanted symmetrically in the right hemisphere. Light sleep was defined by a low-voltage EEG without delta activity, absence of fast eye movements and relatively low voltage EMG in combination with video evidence of sleep.

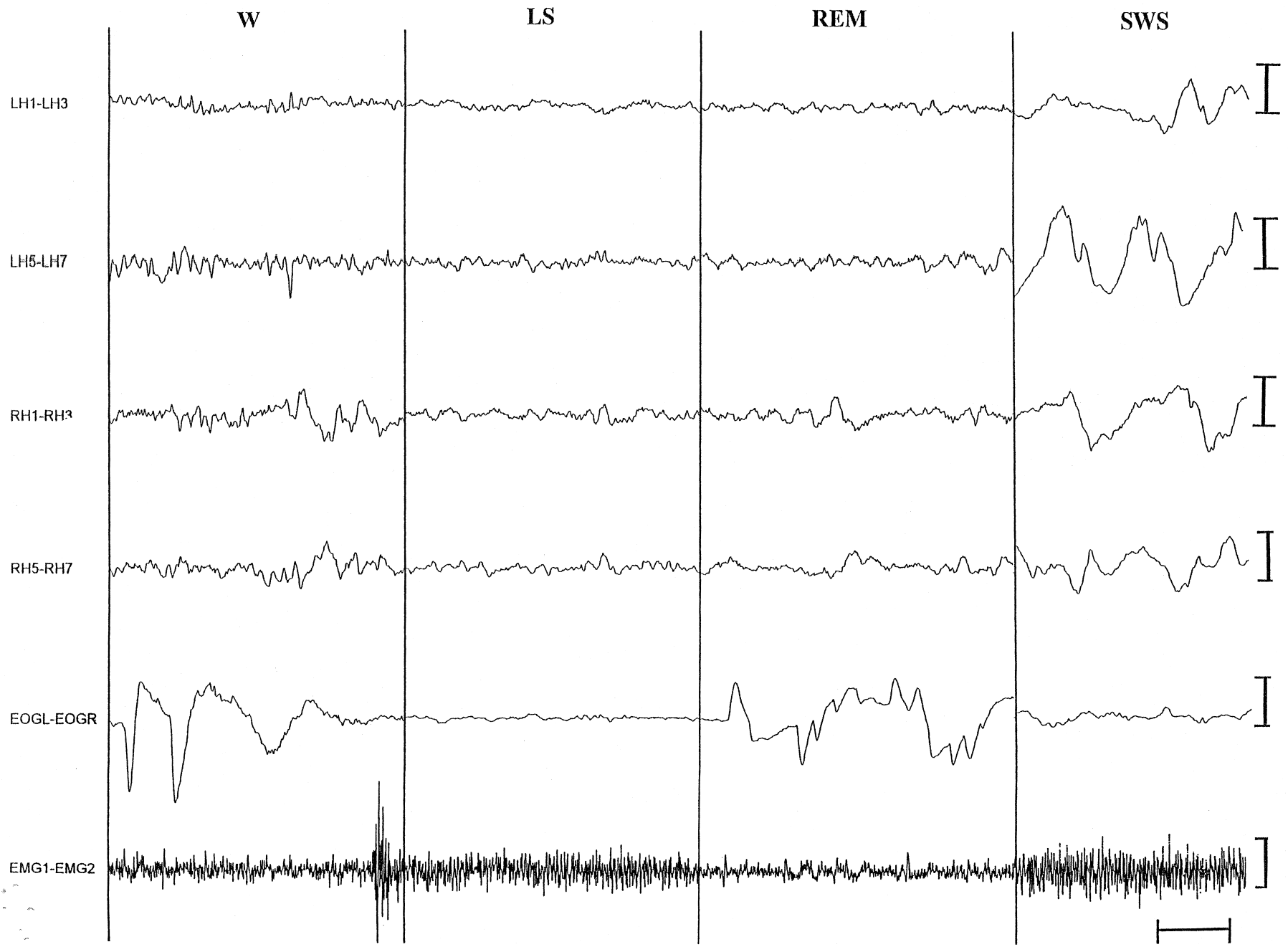

Fig. 3.

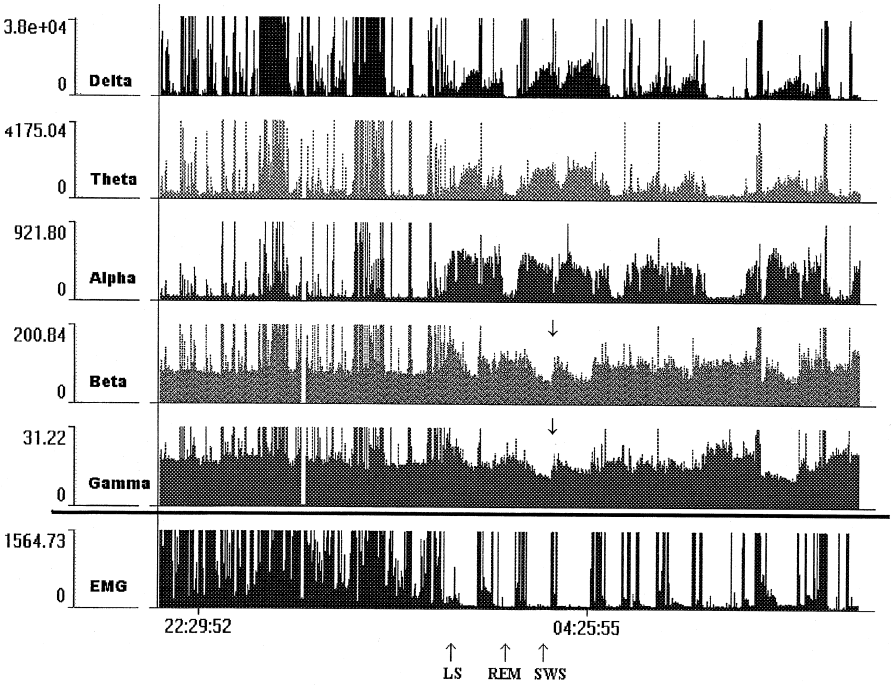

Fig. 4. Trend analysis of EEG frequency band activities during the overnight recording from subject one. The first five rows illustrate the delta, theta, alpha, beta and gamma activities, respectively, for the bipolar channel of the two most mesial contacts of the RS electrode (directed toward the right supplementary motor area) and the final row illustrates chin EMG activity (scales for *y*-axis are in power). During sleep, a clear cyclic pattern of EEG and EMG activities is observed that reflected the various stages of sleep. On some occasions a clear relationship is observed between beta and gamma activity (↓). During the early part of the night, both delta and EMG were observed to be off the scale. During these periods, the patient was awake and actively moving with resultant artifact. In this recording, EEG data were extracted from LS, REM and SWS for spectral and statistical analysis during the different stages of sleep. The segment of wakefulness used in statistical analysis on this subject occurred during the daytime recording of this patient (prior to 22:00:00).

as well as with: 15–30 Hz band pass (beta filtered), and 30–58 Hz band pass (gamma filtered) digital filters. For the most part, activities in the beta and gamma bands were observed to fluctuate independently (Figs 5, 6). During brief periods, in five of seven records, it was possible to see simultaneous increases in activity of the gamma and beta bands (Fig. 5). These peaks of beta and gamma correlated with small epileptic spikes that were visible on the unfiltered EEG (Fig. 5). We had attempted to exclude channels with epileptic activity but small spikes occurring in otherwise normal contacts were sometimes overlooked. As these simultaneous peaks of beta and gamma activity were transient, we did not feel that they detracted from our analysis of background activity.

Very low-frequency oscillations during slow-wave sleep were not clearly observed in all records. In the records where these were clearly observed, the relationship between this activity and the higher frequencies was studied in detail. As illustrated in Fig. 6, no clear correlation between either beta or gamma activity and very low-frequency oscillations during slow-wave sleep was visually apparent.

Spectral analysis

Of a total of 168 intracranial electrode contacts from the seven records, 39 electrode contacts were used for spectral analysis, (four to nine per record). Of these 39 contacts, 15 were from the extratemporal neocortex, six from mesial extratemporal neocortex and nine each from mesial temporal regions and temporal neocortex. Twenty-three electrodes were from the right hemisphere and sixteen from the left hemisphere. As the relationship of frequency band spectra with the sleep–wake cycle and cognitive tasks did not interact with patient, brain region or hemisphere, all electrodes were pooled for statistical analysis.

On visual inspection of the spectra, there was no evidence of consistent peaks of activity within the gamma band. In particular, no peaks of activity were observed at or near 40 Hz. All statistical analysis was therefore done on total frequency band power. The power in the gamma band made up a small proportion of the total spectral power in all electrodes (mean gamma band power of 7.7 compared to mean total power of all bands of 2072). Gamma activity was of highest amplitude in mesial extratemporal contacts during all sleep–wake states and cognitive tasks (results of ANOVA with log power of the gamma band as the variable and brain region as an independent factor were as follows: W, $F = 10.12$, $P < 10^{-3}$, d.f. = 3; LS, $F = 8.34$, $P < 10^{-3}$, d.f. = 3; SWS, $F = 8.53$, $P < 10^{-3}$, d.f. = 3; REM, $F = 12.66$, $P < 10^{-3}$, d.f. = 3; EC, $F = 11.26$, $P < 10^{-3}$,

Fig. 5. Unfiltered (200 μV calibration), beta-filtered (10 μV calibration) and gamma-filtered (2 μV calibration) EEG traces from different stages of sleep (W, LS, SWS, REM) for subject one in referential montage (time-scale, 10 s). Contact RC1 was located in the mesial surface of the right frontal lobe and RS7 in the right lateral frontal convexity. For each channel, identical segments of EEG are presented: unfiltered (top), beta pass-filtered (15–30 Hz, middle) and gamma pass-filtered (30–58 Hz, bottom). Gamma and beta activity fluctuated independently. Visually, gamma appears to be slightly lower during SWS as compared to the other sleep stages. This relationship was confirmed on statistical analysis. During SWS, short bursts of beta and gamma are observed to occur simultaneously with sharp transients visible in the unfiltered EEG.

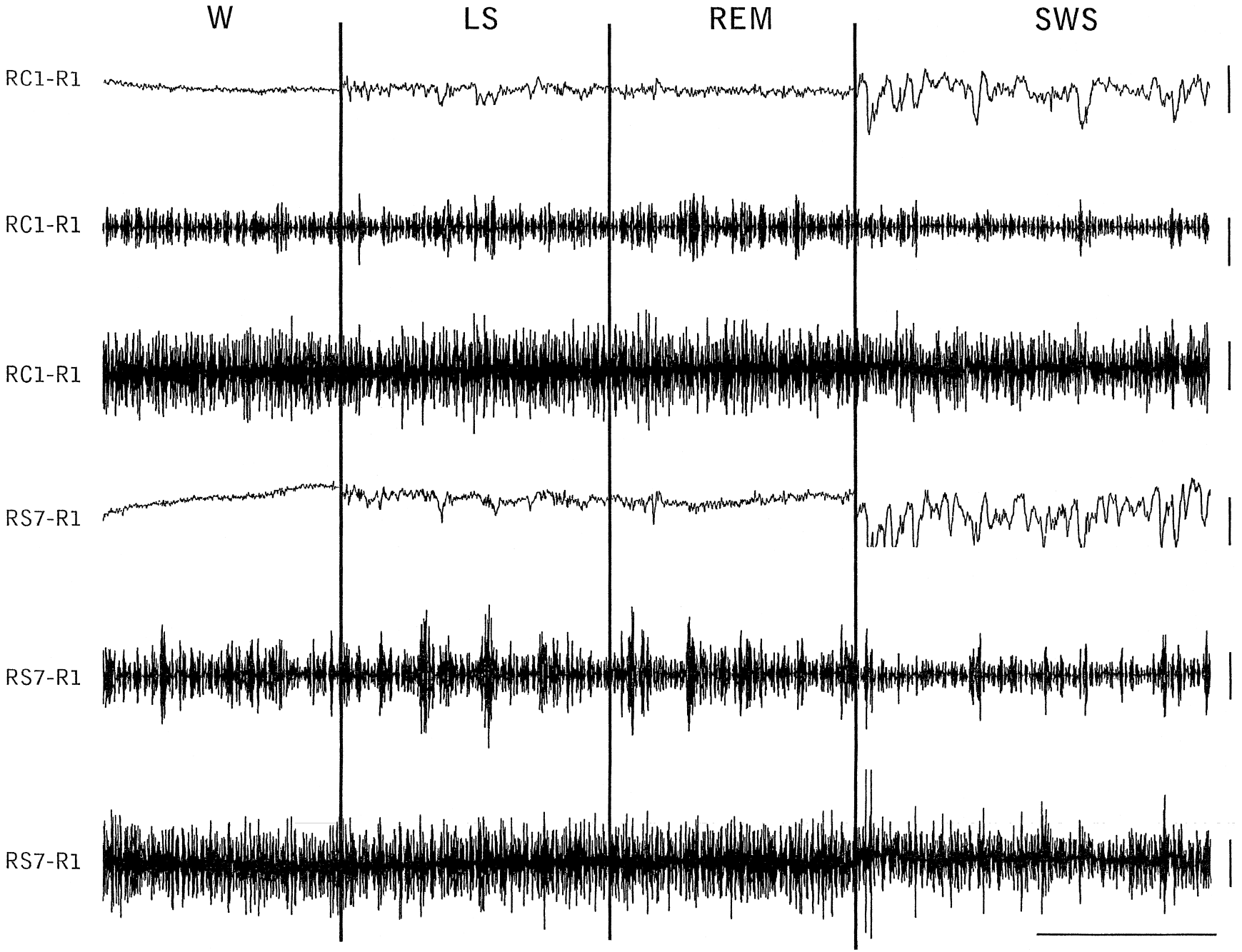

Fig. 5.

Table 1. Details on electrode implantation, epileptic foci, and electrode contacts used for analysis in individual patients

Patient	Age	Location of implanted electrodes	Location of interictal epileptic abnormalities	Location of seizure onset	Location of analysed electrodes
1	18	unilateral right epidural—C depth—SMA, Ci	right inferior central/ precentral	right inferior central/ precentral—10	extratemporal mesial—4 neocortical—5
2	48	unilateral right epidural—FCTP	diffuse right FCTP, max inferior FC	no clear localization, max inferior FCTP	extratemporal neocortical—4
3	28	depth bitemporal symmetrical	bitemporal, clear right predominance	RT—37 LT—3	temporal mesial—3 neocortical—3
4	33	unilateral left depth—T, OF, Ci epidural—T1	left temporal neocortex	LT—5	extratemporal mesial—2 neocortical—2
5	28	depth bitemporal symmetrical	bitemporal with clear right predominance	RT—24 (23 clinical, 1 electrographic)LT—1 electrographic	temporal mesial—3 neocortical—3
6	23	depth bitemporal symmetrical	bitemporal with clear left predominance	LT—12 (11 clinical, 1 electrographic)RT—1 electrographic	temporal mesial—3 neocortical—3

C, central; Ci, cingulate; SMA, supplementary motor area; FC, fronto-central; FCTP, fronto-central-temporal-parietal; LT, left temporal; OF, orbitofrontal; RT, right temporal; T, temporal; T1, first temporal gyrus.

d.f. = 3; CF, $F = 12.69$, $P < 10^{-3}$, d.f. = 3; CB, $F = 9.93$, $P < 10^{-3}$, d.f. = 3; MA, $F = 10.37$, $P < 10^{-3}$, d.f. = 3.

ANOVA with repeated measures demonstrated a significant relationship between gamma activity and the sleep-wake cycle ($F = 30.3$, $P < 10^{-3}$, d.f. = 3) (Fig. 7). Post hoc pairwise comparisons demonstrated the following stages to be significantly different: W–LS ($F = 14.5$, $P < 10^{-3}$, d.f. = 1), W–SWS ($F = 71.1$, $P < 10^{-3}$, d.f. = 1), W–REM ($F = 16.1$, $P < 10^{-3}$, d.f. = 1), LS–SWS ($F = 61.9$, $P < 10^{-3}$, d.f. = 1) and SWS–REM ($F = 24.1$, $P < 10^{-3}$, d.f. = 1). As well, a significant difference was found within REM sleep, where gamma activity was higher during REM sleep with eye movements than during REM sleep without eye movements ($t = 3.2$, $P = 0.003$, d.f. = 38) (Fig. 7).

Although beta band activity also showed a significant relationship to the sleep–wake cycle ($F = 31$, $P < 10^{-3}$, d.f. = 3), the pattern of this relationship was somewhat different, with beta highest during wakefulness and light sleep, lowest during slow-wave sleep, intermediate during REM sleep (Fig. 7). Post hoc pairwise comparisons demonstrated the following stages to be significantly different: W–SWS ($F = 64.1$, $P < 10^{-3}$, d.f. = 1), W–REM ($F = 7.5$, $P = 0.009$, d.f. = 1), LS − SWS ($F = 142.2$, $P < 10^{-3}$, d.f. = 1), LS–REM ($F = 18.9$, $P < 10^{-3}$, d.f. = 1), and SWS–REM ($F = 23.7$, $P < 10^{-3}$, d.f. = 1). No significant difference was observed in beta activity between REM sleep with and without eye movements.

For the cognitive task experiment, repeated measures ANOVA demonstrated a significant relationship between gamma activity and the cognitive tasks, gamma being higher during all tasks as compared to resting with eyes closed ($F = 14.1$, $P < 10^{-3}$, d.f. = 3) (Fig. 8). Post hoc pairwise comparisons demonstrated the following pairs to be significantly different: EC–CF ($F = 20.5$, $P < 10^{-3}$, d.f. = 1), EC–CB ($F = 22.3$, $P < 10^{-3}$, d.f. = 1), EC–MA ($F = 18.3$, $P < 10^{-3}$, d.f. = 1) and CB–MA ($F = 11.0$, $P = 0.002$, d.f. = 1).

In contrast to gamma activity, alpha activity was observed to decrease during cognitive tasks as compared to resting ($F = 28.6$, $P < 10^{-3}$, d.f. = 3). Post hoc pairwise comparisons demonstrated a stepwise reduction in alpha activity from resting, counting to mental arithmetic (EC–CF: $F = 23.4$, $P < 10^{-3}$, d.f. = 1; EC–CB: $F = 28.6$, $P < 10^{-3}$, d.f. = 1; EC–MA: $F = 54.5$, $P < 10^{-3}$, d.f. = 1; CB–MA: $F = 26.3$, $P < 10^{-3}$, d.f. = 1; CB–MA: $F = 15.6$, $P < 10^{-3}$, d.f. = 1) (Fig. 8).

Beta activity was also observed to decrease with cognitive activity ($F = 14.3$, $P < 10^{-3}$, d.f. = 3) (Fig. 8). Post hoc pairwise comparisons demonstrated the following pairs to be significantly different: EC–CF ($F = 7.7$, $P = 0.009$, d.f. = 1), EC–CB ($F = 22.4$, $P < 10^{-3}$, d.f. = 1), EC–MA ($F = 23.9$, $P = 0.03$, d.f. = 1), CF–CB ($F = 4.9$, $P = 0.03$, d.f. = 1), CF–MA ($F = 9.4$, $P = 0.004$, d.f. = 1).

Visual analysis of data suggested that gamma activity was

Fig. 6. Unfiltered (50 μV calibration), beta-filtered (3 μV calibration) and gamma-filtered (1.5 μV calibration) EEG during slow-wave sleep from subject five in referential montage (time-scale, 2 s). LS1 and LS3 are both left mesial temporal electrodes with LS1 being most mesial and LS3 10 mm lateral to LS1. For each channel, identical segments of EEG are presented: unfiltered (top), beta pass-filtered (15–30 Hz, middle) and gamma pass-filtered (30–58 Hz, bottom). In the unfiltered data, low-frequency oscillations (<1 Hz) are evident. No relationship is apparent between the low-frequency oscillations and activity in the beta or gamma band. Activity in the beta and gamma bands is observed to fluctuate independently.

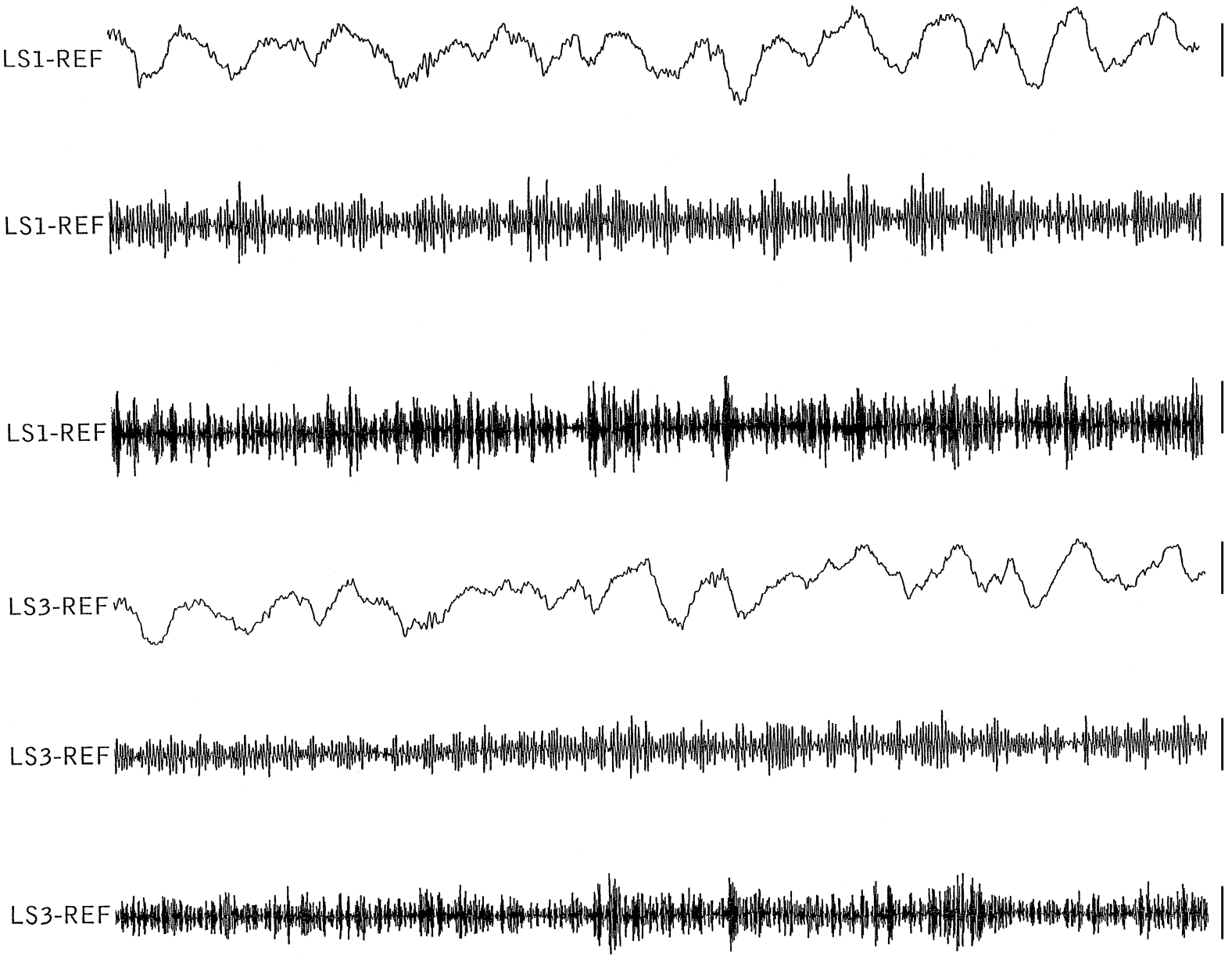

Fig. 6.

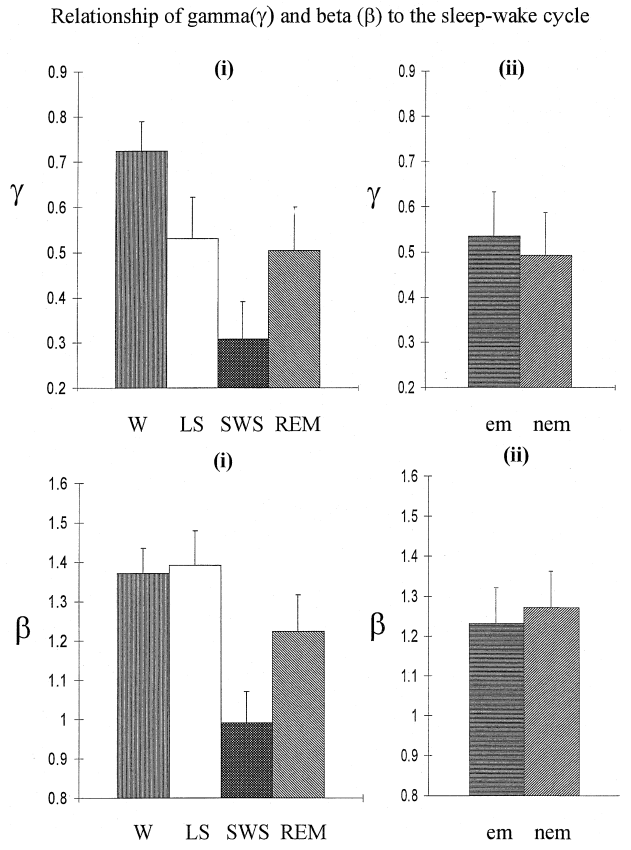

Fig. 7. (i) Relationship of gamma and beta activities to sleep–wake stages (W, LS, SWS, REM). (ii) Relationship of gamma and beta activities to REM sleep with (em) and without (nem) eye movements. Data are presented as mean (and S.E.M.) log power for the respective frequency bands. Gamma activity varied significantly as a function of stage ($F = 30.3$, $P < 10^{-3}$, d.f. = 3). On post hoc analysis, all paired comparisons except LS–REM were found to be different at a significance level of $P < 0.05$. Gamma activity during REM sleep varied significantly as a function of the presence or absence of eye movements, being higher during em ($t = 3.2$, $P = 0.003$, d.f. = 38). Beta activity also varied significantly as a function of stage ($F = 31.0$, $P < 10^{-3}$, d.f. = 3). On post hoc analysis all paired comparisons except W–LS were found to be different at a significance level of $P < 0.05$. No significant relationship was observed between beta activity during REM sleep with and without eye movements ($t = 2.0$, $P = 0.16$, d.f. = 38).

considerably higher during wakefulness from the sleep-wake study (W) as compared to the cognitive task experiment. Repeated measures ANOVA confirmed a significant difference ($F = 10.6$, $P < 10^{-3}$, d.f. = 4) with post hoc pairwise comparisons demonstrating gamma to be significantly higher during wakefulness from the sleep–wake study as compared to all tasks except counting backwards (W–EC: $F = 17.1$, $P < 10^{-3}$, d.f. = 1; W–CF: $F = 6.7$, $P = 0.01$, d.f. = 1; W–MA: $F = 9.7$, $P = 0.004$, d.f. = 1).

Coherence analysis

Coherence analysis was performed on 18 channel pairs (one to five channel pairs per patient using bipolar montage comparing nearest neighboring electrode contacts) as explained in the Experimental Procedures section. In one patient (patient 1) a clear peak of coherence was observed at 12 Hz during light sleep; it was not present during any other stage and correlated with the frequency of sleep spindles visually apparent in the light sleep segment. No peaks of coherence were observed within the gamma band. The mean coherence for the gamma band was low (less than 20%) for all sleep stages in all patients and in all brain regions. Regarding the relationship of coherence to the sleep–wake cycle, no consistent pattern was observed. For example, in one patient two consecutive channel pairs were observed to have completely different relationships with gamma coherence being highest during wakefulness for one and gamma coherence being lowest during wakefulness for the other channel pair. Similar inconsistencies for channel pairs in other patients and in comparisons of channel pairs across patients were observed both in the sleep–wake and cognitive task experiment. Statistical analysis showed no evidence for a relationship between gamma band coherence and the sleep–wake cycle or the cognitive task experiment (at distances of 5 mm and greater).

DISCUSSION

With gamma band activity being such a small component of the total spectrum, the first question that arises is whether the gamma activity that we recorded originated in the brain or could represent noise generated extracerebrally. Our findings of a statistically significant correlation of gamma activity with the sleep–wake cycle, along with a significant correlation with the cognitive tasks, demonstrates that the gamma activity was not random and suggests that it originated from the brain. In order to clearly differentiate between high-frequency brain activity and artifact, it is necessary to address the question of whether it is possible that the high-frequency activity represents EMG activity, which also fluctuates with behavior. It is clear that this is much more a problem during scalp recordings. It is still possible; however, that EMG activity generated at the scalp is conducted through the skull and appears on intracerebral electrodes. This is sometimes visible in clinical intracranial investigations. One could argue that the increased gamma activity observed during wakefulness as compared to all sleep stages could relate to an increase in muscle activity during wakefulness. However, the finding of gamma being higher in REM sleep than during slow-wave sleep cannot be explained by muscle artifact as muscle activity during REM sleep is at least as low as during slow-wave sleep. Another argument against the observed gamma activity being of EMG origin is that if gamma activity was conducted from the scalp, it would be expected that the maximum amount of activity would be observed in the most superficial electrodes, whereas it was highest in mesial extratemporal electrodes.

All patients were being treated with anticonvulsant medications. Although some anticonvulsant medications can affect the overall amount of high-frequency activity,[3] there is no reason to believe that this effect should be different on different stages of the sleep–wake cycle. Since the focus of this study was on the relationships of high-frequency activity to the sleep–wake cycle and cognitive tasks and not the overall power, we do not believe that medications would have an important effect on our results.

Previous authors have studied the relationship of gamma band activity to the sleep–wake cycle.[2,11,15] Maloney *et al*. demonstrated that, in the rat, gamma activity was lowest during quiet wakefulness and slow-wave sleep and highest during active wakefulness and paradoxical sleep.[15] Bragin *et al*. have also demonstrated increased gamma activity

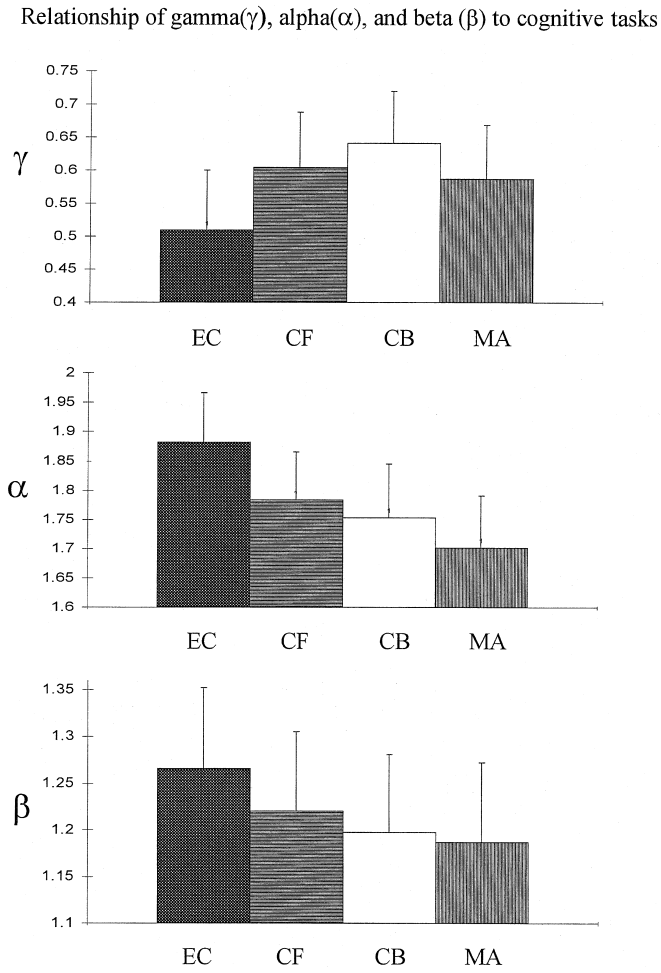

Fig. 8. Relationship of gamma, alpha and beta activity to cognitive tasks (EC, CF, CB and MA). Data are presented as mean (and S.E.M.) log power for the respective frequency bands. A significant relationship was observed between gamma activity and cognitive tasks ($F = 14.1$, $P < 10^{-3}$, d.f. $= 3$). A difference between pairs at a significance level of $P < 0.05$ was found for all tasks as compared to wakefulness, as well as between CB–MA. A significant relationship between alpha activity and cognitive tasks was observed such that with increasing difficulty of tasks, alpha activity progressively dropped ($F = 28.6$, $P < 10^{-3}$, d.f. $= 3$). On post hoc analysis, all pairs except CF–CB were found to be different at a significance level of $P < 0.05$. A significant relationship between beta activity and cognitive activity was also observed such that with increasing difficulty of tasks, beta activity progressively dropped ($F = 14.3$, $P < 10^{-3}$, d.f. $= 3$). On post hoc analysis, all pairs except CB–MA were found to be different at a significance level of $P < 0.05$.

during active wakefulness and paradoxical sleep in the hippocampus in rats.[2] Llinas *et al.*'s magnetoencephalography study in humans demonstrated that a peak of activity at 40 Hz was observed during wakefulness and REM sleep, with lower values during slow-wave sleep.[11]

At the intracellular level, fast brain oscillations have been shown to occur with depolarization of cells.[2,12,22,30,32,34] Steriade *et al.* have stated that fast brain oscillations occur as a result of a given cell's intrinsic properties, in combination with the summation of synaptic activities.[30,32,34] During wakefulness and REM sleep, cortical neurons become relatively depolarized (primarily as a result of activation of ascending cholinergic pathways).[30,32,33] With depolarization, cells show a burst firing pattern with an intraburst frequency of 200–400 Hz and a recurrence rate of 30–40 Hz.[30,32]

As in these studies, we found a significant relationship between gamma activity and the sleep–wake cycle with gamma being lowest during slow-wave sleep. Our results are different from those of Maloney *et al.* in that we found gamma to be higher during wakefulness than REM sleep whereas Maloney *et al.* found the opposite.[15] We do not have an explanation for this discrepancy; however; the finding suggests the possibility that the degree of cellular depolarization is not the same during REM sleep in rats and humans. The fact that we did not find a peak of activity at 40 Hz could possibly be explained by a difference in methodology between our study and that of Llinas *et al.* in that we did not use a narrow filter (35–45 Hz) prior to our analysis.[11] We observed that, during REM sleep, gamma activity was higher during periods with rapid eye movements as compared to periods without eye movements. Several authors have demonstrated differences in hippocampal theta activity during paradoxical sleep with and without eye movements in cats and rats.[25,26,36] Hong *et al.* demonstrated that the number of eye movements during REM sleep positively correlated with visual imagery in dream recall.[9] They also observed that the number of eye movements during REM sleep correlated with increased ^{18}fluoro-deoxy-glucose uptake in brain regions associated with control of saccadic eye movements as well as attention.[8] Our findings, in conjunction with these studies, suggest that REM sleep in humans and paradoxical sleep in rats and cats are not uniform cognitive states and that REM sleep with eye movements may be associated with increased cellular depolarization as compared to REM sleep without eye movements.

Since Berger's original report, the question of whether it is possible to demonstrate the influence of intellectual work upon the human EEG has been considered. At the time, Berger's impression was that waves of first order (alpha activity) were reduced while waves of second order (beta) became more numerous during strenuous mental activity.[1] Since that time, many researchers have examined this question. The finding of attenuation of alpha activity with cognitive activity has been well documented by many authors.[17,21,24,29] The findings regarding beta activity have been less consistent. Papanicolaou *et al.* found augmentation of beta activity with cognitive processing.[21] Mundy-Castle found attenuation of beta activity in some subjects and augmentation in others.[17] Spydell and Sheer found a reduction of beta activity with problem solving tasks.[29] As the association of beta activity with cognitive activity has been inconsistent, attention has now been directed towards the association of gamma oscillations with cognitive activity. A positive correlation has been demonstrated between gamma activity and cognitive activity, which is maximal over the hemisphere assumed to be engaged in the task.[14,28,29] With regards to mathematical problems, Spydell *et al.* did not find any lateralization of 40 Hz activity.[28] They concluded that this was probably related to the task not being lateralized but rather requiring bilateral activation.[28]

Based on the hypothesis that increased levels of cognitive activity will increase gamma activity, we devised an experiment in which the level of cognitive activity progressively increased with each successive task. The tasks that were used were designed to activate brain regions diffusely as opposed to focal activation. We therefore did not expect to see focal activation of specific functional brain regions. Our finding of a stepwise reduction of alpha activity supports the premise that the tasks did require progressively increasing cognitive activity. Our finding of a stepwise reduction of

beta activity supports the findings of Spydell and Sheer that increased cognitive activity is associated with a reduction in beta activity.[29] Our finding of attenuation of alpha activity and augmentation of gamma activity during cognitive tasks, is consistent with the findings of Pfurtscheller and Neuper who reported similar results locally over sensorimotor cortex during voluntary movements in humans.[24]

Although we did find gamma activity to be increased for all tasks as compared to the resting state, suggesting that cognitive tasks were associated with increased depolarization of cells, a stepwise increase in gamma was not observed. This finding leads us to conclude that our cognitive tasks were not the only factors influencing the state of cell depolarization. Although we attempted to limit confounding variables, further analysis of our experiment reveals that at least one potential confounding variable was present: the frequency of vocalization. With counting forward and backwards, the subjects were asked to count slowly aloud at a constant rate. With mental arithmetic, the subjects made the first calculation, stated the answer, and then paused to make the next calculation before stating the next answer. Subjects therefore, spoke less often during the mental arithmetic task than during the two counting tasks.

If a comparison is made between gamma activity during the cognitive activity experiment and the sleep–wake experiment, gamma during the awake state of the sleep–wake experiment was significantly higher than during the eyes closed condition of the cognitive task experiment. The difference between wakefulness during the two experiments was that during the cognitive activity phase of the experiment, the subjects were observed in a controlled situation (eyes closed, not moving), whereas during the sleep–wake experiment, epochs were selected retrospectively based on video, EEG, EMG and EOG evidence of wakefulness. In order to be confident that epochs of wakefulness were selected for the sleep–wake experiment, all patients had their eyes open as confirmed by video and EOG. Therefore, one major difference between the two awake states was that subjects had their eyes open during the uncontrolled state and closed during the controlled state. Previous studies have demonstrated that visual stimulation (along with auditory, somatosensory, and olfactory stimulation) can induce gamma rhythms.[4,7,18,35] We hypothesize that increased gamma during uncontrolled wakefulness as compare to resting with eyes closed, was due to the higher level of sensory stimulation of subjects during uncontrolled wakefulness.

Llinas and Ribary illustrated coherence of 40 Hz activity over the entire hemisphere with a phase shift from frontal to occipital regions in humans with magnetoencephalography.[11] Maloney *et al*. observed peaks of coherence within the gamma band which were higher during wakefulness and paradoxical sleep.[15] Bragin *et al*. demonstrated coherence of high-frequency activity along the length of the hippocampus.[2] We did not have multiple contacts along the length of the hippocampus, and, therefore, we were unable to assess whether Bragin *et al*'s. finding of coherence along the length of the hippocampus was also observed in humans.[2] We were, however, unable to demonstrate any evidence of coherence at distances of 5 mm or greater.

The most likely explanation for the discrepancy between our results and those of Llinas is the difference in methodology. A single neuron generates a potential that is not measurable at the scalp. If, however, a population of neurons are firing synchronously, the summation of the potentials generated by these neurons will lead to a signal that can be recorded from the scalp. Although synchronously firing neurons may represent a small fraction of the total number of neurons in a region, a small number of synchronously firing neurons may be sufficient to generate measurable electromagnetic signal at the scalp along with statistically significant coherence. With intracranial recordings, however, electrodes are implanted close to the generators such that local activity can be recorded from a relatively small number of neighboring neurons. As surface recordings are biased towards the recording of large populations of synchronously firing neurons while intracranial recordings record field potentials that are much more local, the difference in observed coherence between extracranial and intracranial studies is not surprising.

Our findings are consistent with those of Menon *et al*. who were also unable to demonstrate gamma band coherence at short distances (greater than 14 mm) during intracranial recordings in humans,[16] and Steriade *et al*. who found that coherence in the gamma frequency range fell off rapidly with distances greater than 5 mm in cats.[30,32] These findings suggest that, at least locally, coherence of gamma activity is low and does not appear to be related to the sleep–wake cycle or cognitive activity.[16,30,32] Our findings do not, however, exclude the possibility that coherence of gamma activity could be present over large distances as measured extracranially.

Steriade *et al*. have proposed that there is no reason to split fast rhythms into separate beta and gamma bands.[32] The reasoning behind this statement was as follows. First, although some neurons can be observed to oscillate within a narrow frequency range (35–50 Hz), the majority of cells demonstrate a broad range of activity (from 10–40 Hz).[32] Second, Steriade *et al*. observed that the frequency of oscillation of a given neuron could change dramatically over brief periods (less than 5 s) without any obvious change in the global state of the animal.[32] We agree that there is no precise cut-off between the beta and gamma bands and our results confirm a broad band of activity across the entire beta and frequency ranges. As well, when looking at trends over continuous overnight recordings, it is apparent that the activity in the beta and gamma bands can fluctuate simultaneously (Fig. 4). However, in several circumstances, we found differences between the activities in the beta and gamma bands. Beta activity was the same during wakefulness and light sleep while gamma during light sleep was lower than during wakefulness. A significant difference in gamma was observed during REM sleep with and without eye movements but not in beta. Beta dropped with task difficulty while gamma increased with all tasks as compared to the resting state. Some of our findings and experimental results[32] lead us to conclude that activities in the beta and gamma bands probably demonstrate a continuum, representing the depolarization state of the cells. Nevertheless, it is still important to examine various narrower bands within the high-frequency spectrum separately as these narrower bands behave differently under certain situations.

Llinas *et al*. proposed that cognitive activity during REM sleep and wakefulness is higher than during slow-wave sleep based on their finding of higher gamma activity during wakefulness and REM sleep as compared to slow-wave sleep.[11,13] They have suggested that 40 Hz activity is the "correlate of consciousness" and that coherence of gamma activity over

distant brain regions allows for binding of distant regions during conscious thought.[11,13] We have found further evidence to support Llinas *et al*.'s findings of a relationship between gamma activity and sleep, and cognitive activity during wakefulness. We were, however, unable to demonstrate evidence of coherence within the gamma band at distances of 5 mm and greater. Furthermore, our findings suggest that augmentation of gamma activity is a less sensitive indicator of cognitive activity during wakefulness than attenuation of alpha and beta. From our observations during wakefulness it is clear that the mechanisms involved in the generation of high-frequency oscillations are complex. The discrepancy between our findings and those of Llinas *et al*. indicates that we still do not completely understand what the relationship of gamma activity to the sleep–wake cycle implies. Although we have come a long way in our understanding of the electrophysiology of the CNS, we are still unable to fully answer Berger's question, "Is it possible to demonstrate the influence of intellectual work upon the human electroencephalogram…".[1]

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