A MEG Study of Sleep

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1. Introduction

No physiological drive is as compelling as that toward sleep. After short deprivation, the need to sleep over- rides all other needs, including hunger and sex and, fi- nally, even that most fundamental of all imperatives, the mandate for self-preservation. This simple fact argues eloquently for the overwhelming importance of the sleep function; yet after six decades of modern research this function is still poorly understood.

By the same token, the field of sleep medicine remains in an early stage of development. While overt sleep prob- lems such as apnea and insomnia are routinely diagnosed and treated, little effort has been devoted to the detection of subtler disorders which are not readily apparent to the sleeper or observer. However, given the overreaching im- portance of sleep argued above, it is not improbable that malfunctions in sleep at night could be at the seat of seri- ous disease in the daytime. This possibility has been lit- tle explored.

Beginning with the development of the EEG in the 1930s much has been learned about the phenomenol- ogy of sleep, particularly in the domains of time and fre- quency. Characteristic rhythms and waveforms have been sorted out and the sleep cycle qualified. However, the topographic properties of the sleep signal, with their potential for localizing activity in the brain, have received much less attention.

In recent years, the advent of new technologies has given rise to a renaissance in sleep research. These ad- vances include PET scans, localized implantation of mi- croelectrodes in animals and magnetoencephalography (MEG). In the current work, we report the results of an initial study designed to set down the basic topography

Abstract

A 64-channel, whole cortex magnetoencephalographic system was employed to obtain sleep data from three healthy subjects. Based upon visual inspection of the signals and the corresponding power spectra, we were able to discern a number of features characterizing the evolution of sleep. These included: (1) the transition from records dominated by the alpha rhythm to records in which alpha is attenuated and slower waves increase; (2) the appearance of sleep spindles, particularly in the parietal channels; and, perhaps most interesting, (3) a slow wave phase whose multichannel spectral signature is a broad rounded maximum in the frequency region around 0.5 Hz. Topographical features of the sleep record were also studied. In two of our subjects, rough lateral symmetry was apparent. As their sleep deepened, the distribution of signal power over the head changed such that the maximum moved in the forward and lateral di-rections, with parietal and temporal signals strengthening relative to the occipital. The records of the third subject showed a tendency toward right dominance, while topographic changes with sleep depth were minimal. Only one of the subjects was able to sustain the deep, slow-wave stage. Here, characteristic multi-detector outbursts appeared, lasting between 150 and 500 ms. During these intervals, widespread topographic patterns were sustained over the head (often with striking dipolar or quadrupolar forms), while crude source modeling yielded two persisting dipoles, laterally paired. Thus, these outbursts seem to represent large-scale, quasi-static configurations of brain activity per- haps related to the K-complexes, which occur earlier in sleep. Finally, we compare our results with those of previous investigators, including work on human electroencephalographic data and research reported by Steriade et al. from animal studies.

Keywords: sleep, magnetoencephalography, MEG, human, topography, source localization
of the magnetic sleep signal and to make a first, crude effort toward localization of sources in the brain. Additional examples of the MEG data discussed here may be found in a brief earlier communication by the authors [13]. Eventually, we hope to codify a magnetic standard for normal sleep and to map out the evolution of brain activity both in time and space as the sleep cycle progresses.

2. Materials and methods

We used a 64-channel, whole-cortex MEG system (CTF Systems, Vancouver), with sensors uniformly distributed on the helmet surface, mean spacing 4.5 cm. The SQUID sensors are 1st-order axial hardware gradiometers with a 2-cm coil diameter and a 5-cm baseline. In addition, there is an array of 32 reference sensors (magnetometers and gradiometers) that can be used for noise cancellation by means of software formation of 2nd- and 3rd order synthetic gradiometers. Recordings were made inside a three-layer magnetically shielded room (Vacuumschmelze).

We obtained sleep data on separate nights from three healthy subjects, two male and one female. The MEG signals were monitored at 250 Hz and filtered on-line with high and low passes at 0.1 and 60 Hz, respectively. The powerline was eliminated with a notch filter. In order to remove breathing artifacts, additional filtering off-line was performed with low pass at 0.35 Hz. However, in recordings where the artifact was not a problem, this filter was suppressed, allowing for the study of very low frequency components. Data were taken for 10-min periods; before and after each of these, the subject’s head position was monitored using localization coils at the nasion and left and right pre-auricular points, a process which typically took 2–3 min. Thus, this interval separated the periods of data acquisition. For the sleep records reported in this study, head movement never exceeded a few millimeters.

Due to the MEG system geometry, the subjects had to sleep in a sitting position. Under these conditions it was not possible to maintain sleep without interruption for longer than about 30 min. One subject (A) was able to reach slow-wave sleep with duration of this order; the other two subjects (B and C) slept more superficially.

Our total recorded data consisted of about forty 10-min periods spread over the three subjects. From these, 10 periods were chosen for analysis: five from subject A (hereafter labeled as A1 through A5); three from subject B (hereafter labeled B1 through B3); and two from subject C (hereafter labeled C1 and C2). These epochs were selected both for the quality of the MEG signals and because they encompassed both shallow and deep sleep. For convenience in data analysis each continuous 10-min period was artificially divided into twenty 30-s segments.

Source models in the form of dipole pairs were constructed to explain the MEG signals at certain special epochs of the data. The method employed was a standard iterative scheme in which the brain is modeled as a spherical conductor. No account was taken of brain anatomy. The models were calculated at instants separated by about 80 ms within periods lasting between 150 and 500 ms. During these interesting periods the topographic distribution of the MEGs signals on the head changed very little. Thus we were led to suspect quasi-static brain states. Indeed, persistent, laterally paired, dipoles were found (see below), but their discovery was frequently not trivial.

Our source-modeling often produced single-dipole solutions which were stable in the sense that they proved largely independent of the initial guess; then, a second dipole could be added to reduce the error. However, the source configurations reached in this manner were frequently nonsymmetric, or else paired front and back instead of bilaterally. Many times, in order to reach the type of solution described above, one had to prejudge a bilateral configuration and guess the location of the first dipole accordingly. Often, only a narrow subset of initial parameters would lead to the sort of solution we sought; this made the process delicate and difficult. However, once an appropriate first dipole was in place, the locating of the second was usually easy.

While at times the intricate procedure detailed above resulted in a drastic improvement in the fit, reducing the error dramatically, at other times the “undesirable” solution was equally good, occasionally even slightly better. However, in no case that we examined did this latter kind of solution persist along the timeline of the quasi-static epoch. The use of such a solution 80 ms later as an initial guess would lead either to a totally new configuration (often bilateral!) or else to a local minimum with unacceptable error. On the other hand, once a bilateral pair was found, and then employed as a starting point for the next instant, the two dipoles would typically change their locations very little during the iteration, and so on to the following instant, and on through the duration of the epoch. Since the scalp patterns within such an epoch have a steady state appearance to the eye, it is logical to seek quasi-static source configurations to explain them. It will be shown below that such configurations do indeed exist and in our experience virtually always take the form of a quadrupole or a bilateral dipolar pair. Thus, in our opinion, an a priori preference for such solutions is justified.

3. Results

3.1. Time and frequency domains

Figure 1a shows the helmet map with sensor positions. In Figure 1b we display as an example of the data the records of a 7-s segment from period A4. This segment corresponds to deep, slow-wave sleep.

Based on visual inspection of the MEG signals and the corresponding power spectra, we were able to distinguish a number of features characteristic of the classic progression of sleep.
(i) The transition from a record dominated by MEG activity within the alpha frequency range to one where alpha breaks down and slower waves increase. This progression from waking to drowsiness and light sleep is illustrated in Figure 2 for subject C. Figure 2a shows MEG records for a 7-s epoch from the waking period C1. Below these records the spectral decomposition for C1 (temporal channel SR45) displays a striking peak in the vicinity of 10 Hz. This may be contrasted with the shallow-sleep period C2, treated in Figure 2b. Here, the peak is no longer visible and the power in the lower frequency bands (below 2 Hz) is relatively larger. The same type of transition was also encountered in the other two subjects.

(ii) Sleep spindles were detected in the MEG signals as sleep deepened. This is shown in Figure 3a from period A1, while Figure 3b gives a spectral decomposition for parietal channel SL16 over the same period. The prominent peak near 12 Hz may be identified with the spindles. The other two subjects also displayed sleep spindles in their records.

(iii) Slow-wave sleep was found in the MEG records of all subjects, but for extended periods only in subject A. Figure 1b presents an example of such data. Spectral decompositions from the slow-wave sleep of subject A are displayed in Figure 4. Each panel shows results for a group of detectors in a given location, as indicated.
Figure 2. MEG records and spectral decompositions for subject C. (a) Top: a 7-s segment from period C1; bottom: spectral decomposition (channel SR45) for the same period. (b) Top: a 7-s segment from period C2; bottom: spectral decomposition (SR45) for the same period.
Perhaps the most interesting feature of the MEG spectral distributions for deep sleep is the broad rounded maximum which can be seen in the region between 0.3 and 0.7 Hz. This feature, most prominent in left temporal channels, is nonetheless seen all over the head. Its ubiquitous presence in the deep-sleep records of subject A marks it as a signature of this individual’s slow-wave sleep.
Figure 4. Spectral decompositions for slow-wave sleep of subject A. Each panel shows a group of detectors from a given region, as indicated.
but neglected the global view. It is to this question of whole-head topography that we now turn. We begin by calculating average signal amplitudes for each of the 10 data periods listed above, namely A1–A5, B1–B3, C1 and C2. The average amplitude in detector $i$ is defined simply by the standard deviation of the signal over the period in question, viz.,

$$b_i = \left\{ \frac{1}{N} \sum_{n=1}^{N} (b_{in} - B_i)^2 \right\}^{1/2}$$

(1)

where $b_{in}$ is the instantaneous reading, and $B_i$ the average reading, in detector $i$ over a period (usually 10 min) consisting of $N$ samples (instants).

In Figure 5 we display the distributions of mean amplitude for six representative periods, two from each subject. Here, the size of an individual dot is proportional to the magnitude of $b_i$, with the same scale employed for all maps. The largest dots in Figure 5 correspond to $b_i$ of 1200 fT, and the smallest to $b_i$ of 100 fT. As one goes from left to right in each of the rows of Figure 5 the progression is from lighter sleep (or perhaps waking) to deeper sleep. It is clear that in this transition the amplitude generally increases.

Closer examination yields some similarities between the data of subject A (top row) and that of subject C (bottom row). In both instances a rough lateral symmetry is discerned. Furthermore, as sleep deepens (left to right) the distribution of signal power over the head changes, such that the maximum moves in the forward and lateral directions, with parietal and temporal signals strengthening relative to the occipital.

The sleep signals of subject B have a somewhat different character, illustrated in the middle row of Figure 5. While the amplitude $b_i$ generally increases with sleep depth, the distribution of power over the head scarcely changes. In addition, the distribution is asymmetric for subject B with the right side dominating, particularly in the temporal and parietal channels.

Figure 5. Values of $b_i$ for six 10-min periods [(N=150,000); see Equation (1)]. Top row: subject A; middle row: subject B; bottom row: subject C. Largest dot: $b_i \approx 1200$ fT; smallest dot: $b_i \approx 100$ fT. In each row, the righthand map corresponds to a period of deeper sleep than the map on the left.

3.2. Topographic description of MEG signal amplitudes

In the previous sections we have mainly treated the magnetic signals at representative individual detectors, but neglected the global view. It is to this question of whole-head topography that we now turn. We begin by calculating average signal amplitudes for each of the 10 data periods listed above, namely A1–A5, B1–B3, C1 and C2. The average amplitude in detector $i$ is defined simply by the standard deviation of the signal over the period in question, viz.,

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Figure 6. Superimposition of all magnetic records over 30-s intervals. Feature marked by arrow for subsequent analysis (see text). (a) From period A1. (b) From period A2. (c) From period A4.
Let us emphasize, at this point, that even the apparent symmetry observed for subjects A and C might not be real. For all we know, the left and right detectors could be “lighting up” at different times; obviously, the averages would be insensitive in this regard. While this matter can only be fully settled by correlation analysis (not yet undertaken), we shall nonetheless present below evidence pointing at an important role for hemispheric symmetry.

Figure 7. Analysis of plume marked in Figure 6c; left: instantaneous magnetic scalp maps, made at intervals of ~80 ms; center: two-dipole source models corresponding to maps at left; far left: goodness of fit.
3.3. "Plumes"

In order to determine whether consistent patterns occur in a relatively large number of MEG channels, we superimposed the records of all MEG channels over a given epoch. Figure 6 shows three such representations, each of 30-s duration and progressing in order of increasing sleep depth. The central dark band, with width of ~1 pT, portrays a zone of average behavior for all the sensors, normalized to zero mean in each. Stretching above and be-

Figure 8. Analysis of plume from period A2; top: a 30-s record, channels superimposed, plume indicated by arrow; below: setup as in Figure 7.
low this band are features which represent outbursts of amplitude in individual sensors or in groups. In Figure 6a, drawn from period A1, these features take the form of rather thin peaks of relatively low amplitude, reflecting the presence of bursts of activity with somewhat larger than normal variance. As sleep deepens (Figure 6b, period A2), the amplitude of the peaks grows and they tend to coalesce in broader outbursts, until in deeper sleep (Figure 6c, period A4) striking “plumes” of large amplitude rise or fall from the mean record, attaining values of thousands of femtotesla.

While these plumes are related to the well-known slow-wave content of deep sleep, it is perhaps more productive to think of them as “outbursts of activity” as mentioned above. Most interesting of all are those “bipolar” outbursts in which the plumes simultaneously extend both above and below the mean band. We shall argue below that these episodes represent steady state brain source configurations that endure for hundreds of milliseconds.

In Figure 7, we return to the record of Figure 6c, focusing on the large plume (denoted by arrow) with the center near 22.5 s. At the left, scalp maps show the magnetic field configuration at seven instants separated by intervals of approximately 80 ms and spanning the 450-ms plume width. The detailed scalp pattern changes gradually while large-scale features persist. The eyeball impression of a quasi-steady state is reinforced by solutions to the inverse problem in the form of twin dipoles. These are represented on the right of Figure 7. In Figure 9, we display records of a plume episode plus surrounding data. The plume corresponds to a transient deflection that is apparent not only in the temporal channels but also in parietal and occipital detectors, and even in the frontal channels SL31 and 32. Thus the plume appears to represent a deep lying generator, or perhaps a generalized activity, detectable over most of the head.

The scalp maps we encountered corresponding to bipolar plumes often had striking dipolar or quadrupolar configurations, easily recognizable to the eye; at other times their character was less readily discerned. However, in general, what most distinguished the maps within plumes from those without was their quasi-static nature, i.e., the persistence of large-scale features over the duration of the plume, ranging from 150–500 ms. As a final example, Figure 10 shows a plume-like outburst from

Figure 9. (a) A 7-s record from period A2; the interval containing the plume of Figure 8 is enclosed by vertical lines.
another subject (period B3, light to deepening sleep). Below the time record are three instantaneous scalp maps formed at ~80 ms intervals, each with a corresponding source configuration to its right. The large-scale structure of the scalp pattern persists for around 150 ms. At the first snapshot the source is a deep, centrally located quadrupole very near the midline. This quadrupole splits very slightly at instant 2, finally separating into a bilateral dipole pair at the end of the plume. In some sense, all three source configurations consist of two opposite, bilateral paired dipoles, “equivalent” to a single quadrupole located between them. Finally, we note that these source models are paired between the hemispheres. This turned out to be the case for most of the handful of plume-like structures we examined from the sleep of subject B.

4. Discussion

The study we report here had a number of shortcomings, all mentioned above. First, the MEG apparatus required a sitting position. Second, data was taken from just three individuals, only one of whom slept deeply. And, finally, the source-modeling we employed was extremely crude. Each of these imposes its own limitations on the conclusions we may draw from our results, and all must be improved in future work.

The topographic similarities for subjects A and C (bilateral symmetry, forward and lateral progression with sleep depth) were somewhat contradicted by data from subject B. The latter slept with less erect posture, head slipping downward and leaning on the front side of the helmet, orientated somewhat to the left. It is unknown to what extent posture will affect topography, but this problem should be greatly ameliorated with the next generation of MEG detectors which will allow subjects to lie down.

The deep-sleep records of subject A were characterized by two striking properties: the rounded spectral maximum between 0.3 and 0.7 Hz and the presence of “plumes.” While it is tempting to think of these as general features of slow-wave sleep (indeed, we shall assert this tentatively below), clearly more subjects must
be examined before such a conclusion could be drawn with any certainty. This must be a goal of further study. The finding of a spectral maximum in the MEG recordings between 0.3 and 0.7 Hz is akin to the low-frequency component with a mean peak value around 0.7 Hz (range 0.55 to 0.95 Hz) identified in the EEG power spectrum of human non-REM sleep [1]. Both the MEG and EEG variations likely correspond to the very slow oscillation described first in neocortical neurons intracellu-
larly by Steriade et al. [14] in anesthetized animals and also during natural slow-wave sleep, and discussed fur-
ther below in relation with the phenomena of “plumes” and K-complexes.

We have identified the bipolar plumes in the sleep of subject A with steady-state brain configurations consisting of laterally paired dipoles, or quadrupoles. These configurations emerged from the crude source modeling described above. Although we have argued that the ob-
served quasi-static nature of plumes justifies a priori pref-
erence for such dipoles, it is clear that much more sophis-
ticated source models will be required if we are to nail down these conclusions and proceed beyond them to an understanding of what is actually occurring in the brain during slow-wave sleep.

While direct, straight-forward comparisons between the results of previous work and the current investiga-
tion are difficult, there are nonetheless a few places where common ground seems to emerge. One of these regards the finding that sleep EEG/MEG activity is not a homo-
geneous global phenomenon but displays regional differ-
ences that depend on cortical area and sleep stage. Such differences, long documented in EEG sleep spectra 1, 4, 6, 8, 15 and 16, albeit with many fewer derivations, are il-
ustrated in the MEG data by topographic changes which occur as sleep deepens (see Figure 5). However, the EEG and MEG results also show some possible discrepancies, notably in the temporal dominance we found for the very slow MEG activity (peak near 0.5 Hz), compared with the emphasis on slow components recorded from fronto-ce-
tral derivations in the EEG investigation by Werth et al. [15]. These apparent discordances can only be resolved by future studies using whole-head EEG and MEG sleep data, simultaneously recorded.

A second commonality between the present investiga-
tion and past work involves the relationship between delta activity and K-complexes. Recent literature on the latter has been summarized by Numminen et al. [12]. Originally identified and studied in the EEG record, the K-complexes also possess a magnetic trace, albeit one with less stability and coherence. Bilateral dipole pairs have been proposed as a source model by various authors 9 and 11, including Numminen et al. [12], who neverthe-
less emphasized that this model frequently failed.

In the context of the present study, the two-dipole source model links together plumes and K-complexes, two phenomena which already share an outburst char-
acter. If this linkage is correct, it suggests a picture in which the K-complexes represent early, sometimes local-
ized, manifestations of the large-scale, bilateral outbursts that will show themselves as plumes once sleep deepens. Indeed, some uni-hemispheric deep sleep records [11] show multidetector eruptions which might well resemble plumes if complementary data were available for the neglected side. With respect to our own records, while the lack of an EEG component makes the discernment of K-
complexes rather uncertain, there do appear in the deep-
ening sleep records of subject B a few outbursts with plume-like character, which might be associated with the K-complex phenomenon.

The role of K-complexes in slow-wave sleep is also dis-
cussed by Amzica and Steriade [2] who find the cellular substrate of this phenomenon in a hyperpolarizing–depo-
larizing sequence which also causes a “slow rhythmicity” observed in anesthetized and naturally sleeping animals [14]. Interestingly enough, the spectral power corre-
sponding to the K-complexes was found to peak in the region between 0.5 and 0.7 Hz [2], i.e., just in the vicinity of the rounded maximum that the current study has associ-
ated with the slow-wave phase.

The idea of K-complexes as forerunners of slow-wave phenomena is an old one [10]. More recently, the hypo-
thesis that K-complexes and slow EEG sleep activity are re-
lated was tested in a neural network model of sleep EEG activities [5]. The simulations showed that K-complexes can be considered as responses of the simulated neu-
ral networks to random impulses on condition that the system’s mode of activity is within the delta frequency range.

While Numminen et al. [12] dispute the link between K-complexes and slow waves on the basis of some differ-
ces observed in their respective distributions, a more detailed investigation of the question is perhaps war-
ranted, particularly in view of strong temporal readings for both K-complexes and delta waves in previous work [12], and for plumes in the current investigation. If the plumes are, as suggested here, a characteristic phenom-
emon, they should be readily discernable in any whole-
head magnetic record of deep sleep.

A third area for comparison involves PET scans made on sleeping subjects 3 and 7. These studies determined correlations between regional cerebral blood flow (rCBF) and sleep depth, finding particular areas of the brain where covariances with slow wave sleep, whether posi-
tive or negative, were significant. Andersson et al. [3] re-
ported a highly significant decrease in rCBF in the frontal and parietal association cortices during sleep. By analogy we may assume that the strength of the MEG signal that we found to be most prominent in the temporal channels but also in frontal and occipital detectors would corre-
spond to relatively low values of cortical rCBF.

However, according to Hofle et al. [7] the foremost among the cortical regions where rCBF covaried posi-
tively with slow wave sleep were the visual and auditory cortices in both hemispheres, whereas the cortical regions
where negative covariance was found were the anterior cingulate and the orbitofrontal cortices; the latter areas are most probably less reflected in the MEG signals due to their location deep in the brain. These results of PET studies do not yet give a clear picture of the relationship between sleep depth as measured by EEG or MEG, on the one hand, and rCBF on the other. We think that a more precise analysis of such correlations should take into account two of our present findings, namely, (1) that slow wave sleep activity, detected with whole-head MEG recordings, is not distributed homogeneously and in a static way over the scalp, and (2) that there is a forward and lateral progression of the MEG signal strength as slow wave sleep is established.

Whereas normalization by subtraction (or, in this case, correlation) is a common practice during evoked response experiments, the highly choreographed nature of sleep and, indeed, the current MEG results, further suggest that raw values of radioactivity counts may well be meaningful in PET sleep studies. Publication of such results could help open the way to detailed comparisons between the two techniques.

References


