Cerebral Electromagnetic Activity in the Subdelta Range

Ernst Rodin and Michael Funke

Abstract: The frequency range between 0.1 and 0.9 Hz was investigated with magnetoelectroencephalography-EEG coregistration in 10 adult patients with epilepsy and five children with other neurologic conditions. In all instances, a dominant rhythm between 0.2 and 0.4 Hz could be observed in the waking and sleeping states. It showed a waxing and waning quality and was unrelated to eye opening or closing but increased in amplitude during sleep. The maximum was usually in the occipital areas but occasionally in the frontal regions. The rhythm was more persistent and better seen in the magnetoelectroencephalogram, but subdelta activity was also discernible in the EEG. The magnetoelectroencephalographic rhythmicity and frequency suggested possible respiration artifact. Two normal control subjects were therefore investigated by electroencephalography while respirations were monitored. A clear relation to respiration was established. It persisted during breath-holding, albeit at lower amplitude. Larger amplitude transients occurred before and at the cessation of breath-holding as well as hyperventilation. An observed frequency increase before voluntary hyperventilation suggests a relation to the readiness potential and event-related desynchronization as well as synchronization. Subdelta frequencies, which can be readily recorded without special DC amplifiers, provide additional information for clinical as well as research data. They may also be an interface between autonomic and voluntary functions, especially in regard to respiration.

Key Words: Magnetoelectroencephalography-EEG, Subdelta frequencies, Glia, Respiration.

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Cerebral electrical activity has been traditionally recorded within the frequency range of 1 to 70 Hz. There were two main reasons. One was that analog technology relied on pen and paper recordings, which was limited by pen responses and paper speed. The other was that higher-frequency recordings can be contaminated by muscle activity, even when it does not appear obvious in the raw tracings. Frequencies below 1 Hz were potentially influenced by electrode properties as well as by skin currents, and, because no clinical rationale existed, they have so far not been systematically studied. DC cerebral electrical recordings have been reported as early as 1959 by Caspers and Schultze (1959) in animals and 5 years later by Cohn (1964) in human epilepsy. Although considerable work has been performed in this area since that time, the technique has remained limited to research laboratories and has not yet found wide spread clinical use.

Digital technology now enables us to close the gap between DC and the conventional frequencies. Furthermore, modern data analysis programs allow *post hoc* filtering of the data, which is a major advantage when different frequency bands are investigated for their informational content. The advent of magnetoelectroencephalography (MEG), where recordings can be routinely obtained with a high-pass filter of 0.1 Hz, with EEG coregistration, has provided a unique opportunity to study the subdelta frequency range even in recordings that were obtained earlier for clinical purposes.

This investigation was prompted by reports in the literature about the electrical activity of glia cells, which, in contrast to neurons, propagates over a period of seconds rather than milliseconds (Amzica and Massimi, 2002; Fields, 2004; Tashiro et al., 2002). Since it is known that in rats pentylenetetrazol, when used in subconvulsant doses, produced its first ultrastructural changes in astrocytes rather than neurons (Rodin et al., 1979), it was of interest to see whether or not ultra-slow electromagnetic activity could be observed in resting recordings of patients with epilepsy. The purpose of this presentation is to present some of our results and to draw the attention of clinical neurophysiologists to this neglected frequency band.

MATERIALS AND METHODS

The investigation proceeded in several steps. First, the stored data of 10 adult patients with hippocampal sclerosis, who had been referred to the MEG laboratory as part of a presurgical evaluation, were examined. These patients had been worked up for the conventional frequency range during a study to determine to what extent clinical neurophysiologists can predict on the basis of MEG-EEG coregistration alone the outcome of surgery (Constantino et al., 2004). Since this material was available, the data were then investigated for the subdelta range of 0.1 to 0.9 Hz. Inasmuch as a marked and very regular rhythm could be observed in the MEG of all patients, the question arose to what extent this was related to the patients' seizure disorder. Normal control recordings in the quiet resting and sleeping state were not available, but three children with autism, one child with Down syndrome, and one previously published patient with Landau Kleffner syndrome (Rodin et al., 2004) could be investigated. The data showed that the rhythm was present in these children and therefore unrelated to a specific pathologic entity. The regu-

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larity of the rhythm and its frequency immediately raised the question to what extent, if any, it was related to respiration and represented possible movement artifact. Respiration monitoring was currently not possible in the MEG environment, but we were able to record the MEG *per se* in the resting state, during breath-holding, and hyperventilation in two adult normal control subjects.

Since the rhythm had been detectable to some extent in the EEG of the patients and monitoring of respiration was essential, we decided subsequently to study its relation to respiration in the sleep laboratory of the neurology department in the same normal control subjects.

Technique

The MEG was obtained with a Neuromag whole-head system. All patients with hippocampal sclerosis, as well as the children, were recorded with 204 gradiometer as well as 102 magnetometer sensors. The data had been digitized at a sampling rate of 600 Hz and were acquired with a bandpass of 0.1 to 200 Hz. One hour of recording time was available in 10-minute files. An electrode cap was used for EEG recordings, and electrode resistance was kept below 10 kOhm. Sixty-two electrodes had been used in six and 27 electrodes in four of the adult patients. In the children, the EEG recording was unsatisfactory in one; one child was recorded with 62 and the others with 27 electrodes. Fiducial points and electrode positions were digitized with a Polhemus system for subsequent MRI correlations. The records were obtained in the recumbent position, and waking as well as sleep portions were obtained in every patient.

The data had been stored on compact discs and were analyzed with a commercial software program (BESA). After eliminating noisy channels and filtering between 0.1 and 0.9 Hz, the data were displayed separately for MEG and EEG on a 60-second time base, which allowed for easy viewing. Ten-second epochs were then subjected to principal component analysis. Because rhythmic activity was less pronounced in the EEG than the MEG and to compensate for the differences in electrode numbers, the positions were interpolated as well as extrapolated to the 10-to-10 system, as described by Scherg et al. (2002).

The sleep laboratory data contained six EEG channels from the occipital areas referenced to the vertex and three channels for respiration: chest, abdomen, and nasal air pressure. The recordings were obtained in the eyes-closed, recumbent position. The bandpass for the data were from 0.1 to 15 Hz, and electrode resistance was below 10 kOhm.

RESULTS

Adult Patients

Magnetoelectroencephalography

Inasmuch as there were no major differences in the information provided by gradiometers and magnetometers, only gradiometer data will be presented at this time. With filter settings between 0.1 Hz (6 db, forward) and 0.9 Hz (12 db, zero phase) a regular rhythm between 0.2 and 0.4 Hz could be observed in all instances. In eight patients, the frequencies ranged between 0.3 and 0.4 Hz, whereas in two it was approximately 0.2 and 0.3 Hz, respectively. The rhythm was not affected by eyes opening or closing. It was present in the waking as well as the sleeping state. During sleep, the amplitudes ranged from approximately 300 to 1700 fT/cm in different patients, with a mean of approximately 700 fT/cm. When waking and sleep occurred in the same segment, the rhythm increased from approximately 200 to 300 fT/cm in the waking state to 1100 fT/cm during sleep. A waxing and waning quality could also be observed in some patients during sleep, from a low of 600 fT/cm to a high of 1100 fT/cm over a period of 80 seconds. This was followed by an isolated discharge originating in the same sensors with amplitude of more than 4,000 fT/cm. It would disappear thereafter for about 30 seconds to reemerge at a rate of 0.16 Hz and approximately 600 fT/cm before returning to 0.36 Hz and 900 fT/cm. Isolated, even higher discharges to more than 7,500 fT/cm occasionally could be seen to arise from the same region. At times, a relation to EEG arousal from sleep was observed at that time, but it was inconsistent. The data also showed intermittently more diffuse high-amplitude bursting, but, this aspect, as well as the more local high-amplitude discharges, requires further investigation. In nine of the patients, the predominant location was occipital, whereas in one it was prefrontal.

Principal component analysis (PCA) for 10-second segments showed values ranging from 91% to 47% for the first component, which represented the slow wave rhythm, and 36% to 4% for the second. One patient had only a single component, which accounted for 99.5% of the variance. The patients with the lowest percentage for the first PCA component had also the slowest rhythm.

Electroencephalography

The EEG data were more polymorphic, at times influenced by eye movements, and the dominant EEG frequencies tended to be slower than in the MEG. The best overall similarity to MEG data was observed with a virtual 10-to-10 electrode montage on average reference. However, even when only 27 actual electrodes were available, activity at varying frequencies between 0.1 and 0.9 Hz could be seen with amplitude between 2 and 80 μV in different channels and different records. The records also showed intermittent, higher-voltage, more isolated discharges lasting approximately 2 seconds and an amplitude of 70 to 200 μV. These tended to coincide with vertex and midfrontal transients of sleep on conventional filter settings.

The complexity of the records is perhaps best represented in the PCA investigation. The first component accounted for between 67% and 32% of the variance, whereas the second ranged between 30% and 3%. Table 1 presents a comparison of MEG and EEG for the same time epoch. The percent variance, which accounted for the first three components, is listed. Although the average percentage for the first MEG component was 72%, it was only 50% for the EEG.

Figure 1 represents an example of raw data for MEG and the EEG over a 60-second segment. Amplifications are 15 fT/cm for magnetic data and 5 μV for electrical data. Figure 2 is a collage for averaged data from two patients and allows for comparison between EEG and MEG data in a "top

TABLE 1. Principal Component Analysis for 10 Patients with Epilepsy

Patient No.	MEG (Gradiometer Data)			EEG		
1	99	0	0	50	24	12
2	78	9	4	43	23	13
3	61	23	5	58	30	2
4	91	3	2	32	30	17
5	86	4	4	66	25	4
6	77	8	6	47	27	12
7	67	22	3	51	18	13
8	47	36	4	34	22	11
9	47	19	10	51	30	11
10	73	14	7	67	17	8

Percentage of variance accounted for by the first three components of the same 10-second data epoch for MEG and EEG. The usually greater complexity of the EEG is apparent.

view" representation. The pattern recognition module of the BESA program was used for two consecutive MEG waves, and the average consisted of 100 samples for the patient shown in the left column (same one as in Fig. 1) and 56 samples for the patient in the right column. The time base is 7 seconds.

Pediatric Patients

The findings from the five children (ages 7 to 9 years) differed in the MEG only insofar as the dominant frequency was slower than in the adults, ranging mainly between 0.15 and 0.20 Hz, with amplitudes between 300 and 2,000 fT/cm. The EEG findings were comparable to the adult patients.

Respiration Data

Magnetoelectroencephalography

As mentioned, the dominant MEG frequency of approximately 0.3 Hz and its rhythmicity raised the question to what extent one might be dealing with respiration artifact. This could have resulted from imperceptible head movements within the helmet. Although MEG coregistration with respiration monitors was not possible, gradiometer and magnetometer data could be obtained in two normal control subjects. During those recordings, the subjects were asked to hold their breath for 10 seconds and after recovery to hyperventilate for 10 seconds. Subject 1's excellent 0.3-Hz rhythm at 2,300 fT/cm diminished markedly during breath-holding and was replaced by activity from 40 to 200 fT/cm in different channels. Hyperventilation (HV) increased the recorded frequencies from 0.3 Hz (1903 fT/cm) to 0.7 Hz (2576 fT/cm). Similar findings were obtained from subject 2. In both subjects, a high-amplitude transient was seen before and after breath-holding as well as hyperventilation.

Although these observations clearly established a relation between respiration and the dominant MEG rhythm, it could not address itself to the possible head movement artifact problem.

Electroencephalography

Inasmuch as the dominant MEG rhythm was usually in the occipital areas and the electrode cap that was used in the coregistration did not have low occipital and inion electrodes, we used those channels in the sleep laboratory where respiration could be measured in conjunction with the EEG. MF's background activity with filters set between 0.1 and 0.9 Hz was of very low amplitude (1.5 μV). There was no dominant rhythm, although events lasting for 2 to 3 seconds were observable, as well as at times brief rhythmic activity around 0.8 Hz. During breath-holding, MF's recording was essentially unchanged, except for a higher-amplitude transient (4 μV) immediately before and after holding the breath. Hyperventilation at a rate of 0.8 Hz was preceded by a 5-μV transient and followed by one of 6 μV. During HV, the 0.8-Hz EEG rhythm became more prominent, especially when the data were filtered between 0.5 and 0.9 Hz to remove the slower components.

ER's background activity likewise consisted of a mixture of frequencies without a sustained dominant background rhythm when the data were filtered between 0.1 and 0.9 Hz. Amplitudes were between 1 and 2 μV. Although MF had been requested to hold his breath on command, ER did so on his own volition and also hyperventilated at a time of his choosing. Breath-holding was preceded as well as followed by higher-amplitude transients similar to MF and what had been observed in the MEG on a previous occasion. Although amplitudes increased after breath-holding in the channels that monitored respiration, the EEG did not reflect this fact after the initial transient. The top half of Fig. 3 shows the breath-holding data, whereas the bottom half demonstrates HV observations. Approximately 7 seconds before HV, while the decision was being made, the EEG changed to a 0.5-Hz, 6-μV rhythm. Initially, the respiratory rate that had been at 0.16 Hz also increased to 0.5 Hz, and as respirations speeded up to about 1 Hz, the EEG frequency increased to 0.7 Hz. This was again better seen with filter settings between 0.5 to 0.9 Hz.

DISCUSSION

These observations show that reliable recordings can be obtained from MEG and EEG in the subdelta frequency range in normal individuals as well as patients with epilepsy and children with other neurologic disorders. The dominant rhythm between 0.15 and 0.5 Hz was seen in the waking and sleeping states. Its amplitude and persistence increased during sleep, but the rhythm itself was not dependent on sleep. It was also independent of the amplitude and abundance of the alpha rhythm. It was more persistent in the MEG but present to some extent in the EEG also. This difference reflected itself in the PCA, where the EEG showed greater complexity.

In assessing the significance of the prominent MEG slow wave rhythm, one needed to be mindful of several potential artifacts, especially in the MEG environment. The fact that the rhythm was less pronounced in the EEG might have lent credence to the artifactual nature of the data. This was especially worrisome because the MEG recordings frequently showed a marked cardiac contribution in the posterior head regions when the rhythm was dominant in the back of the head and in the frontal areas when the rhythm was maximal in front. On the other hand, when a low-pass filter at

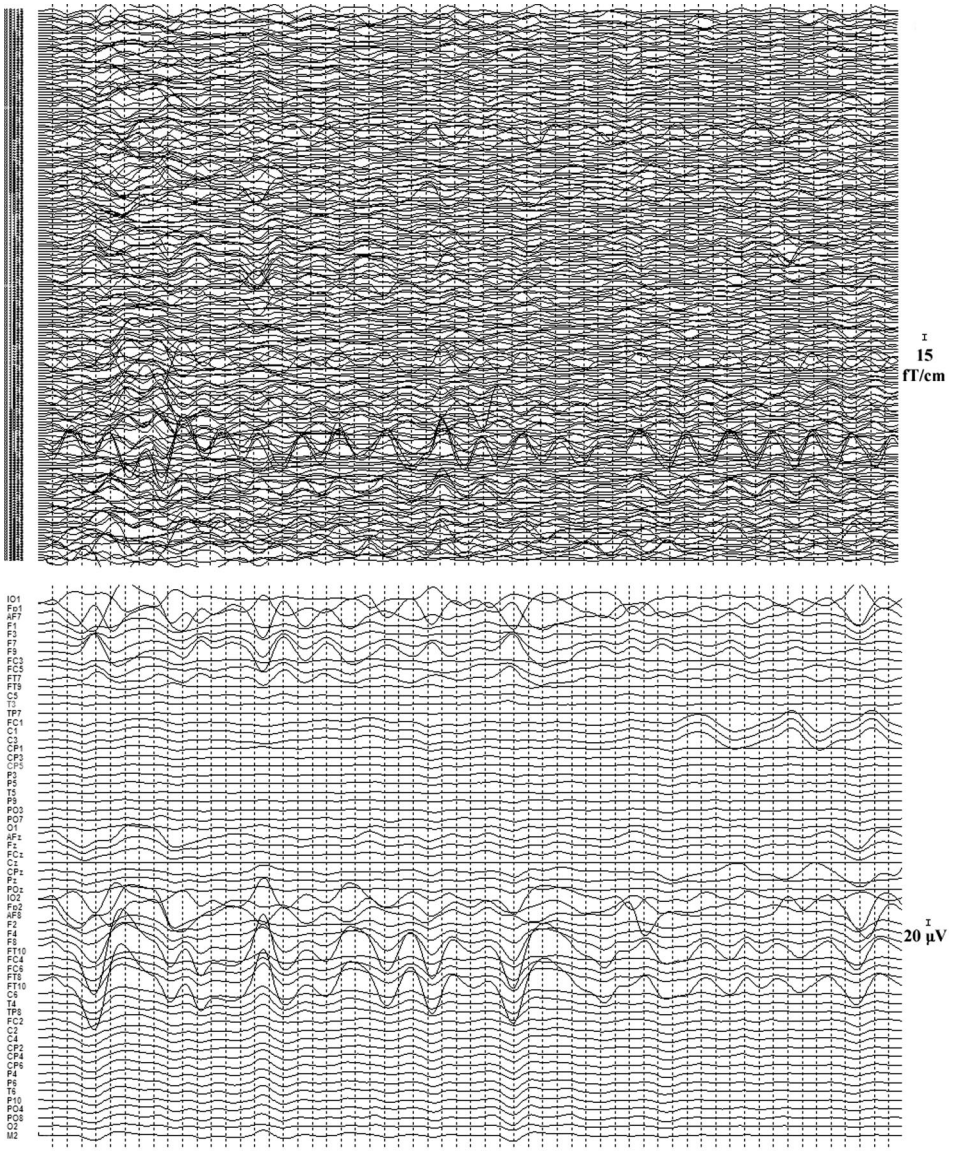

FIGURE 1. Top half shows MEG; bottom half, EEG of an adult patient with partial complex seizures and left mesial temporal sclerosis. Eyes-closed waking record. EEG data are more polymorphic and in part influenced by eye movements. Nevertheless, there is evidence of cerebral subdelta frequency activity. Amplifications, 15 fT/cm for MEG and 20 μV for EEG. Filters, 0.1 to 0.5 Hz. Display time, 60 seconds.

0.9 Hz is used, the cardiac components are diminished and are as such not likely to cause this rhythm. Another source of artifact might be filter properties. That this was not the case could be demonstrated when the high-pass filter was inactivated. Under those circumstances, even slower activity could be seen in MEG and EEG; amplitudes increased slightly, but the frequency of the dominant rhythm remained unchanged.

This left the most obvious cause of artifact, namely, respiration, as a major possibility. However, the waxing and waning nature in the MEG, with its intermittent buildup over tens of seconds and abrupt termination for 10 or more seconds, made it unlikely that the rhythm was related to a mechanical artifact. Nevertheless, it was imperative that respiratory rate be monitored to prove or disprove the artifact hypothesis. While the manuscript was in the review process, a respiration monitor, which was compatible with the MEG environment, was obtained. We found that the magnetic observations of before and after breath-holding as well as decrease in activity during breath-holding and the increase in frequencies during hyperventilation did in fact coincide with respiratory changes. The most intriguing aspect, however, was that rhythmic activity increased in frequency and amplitude several seconds before voluntary initiation of hyperventilation.

These observations raise the question to what extent the phenomenon might be related to the Bereitschaftspotential (readiness potential), which has been observed under a wide variety of circumstances in EEG and MEG (Deecke, 1990;

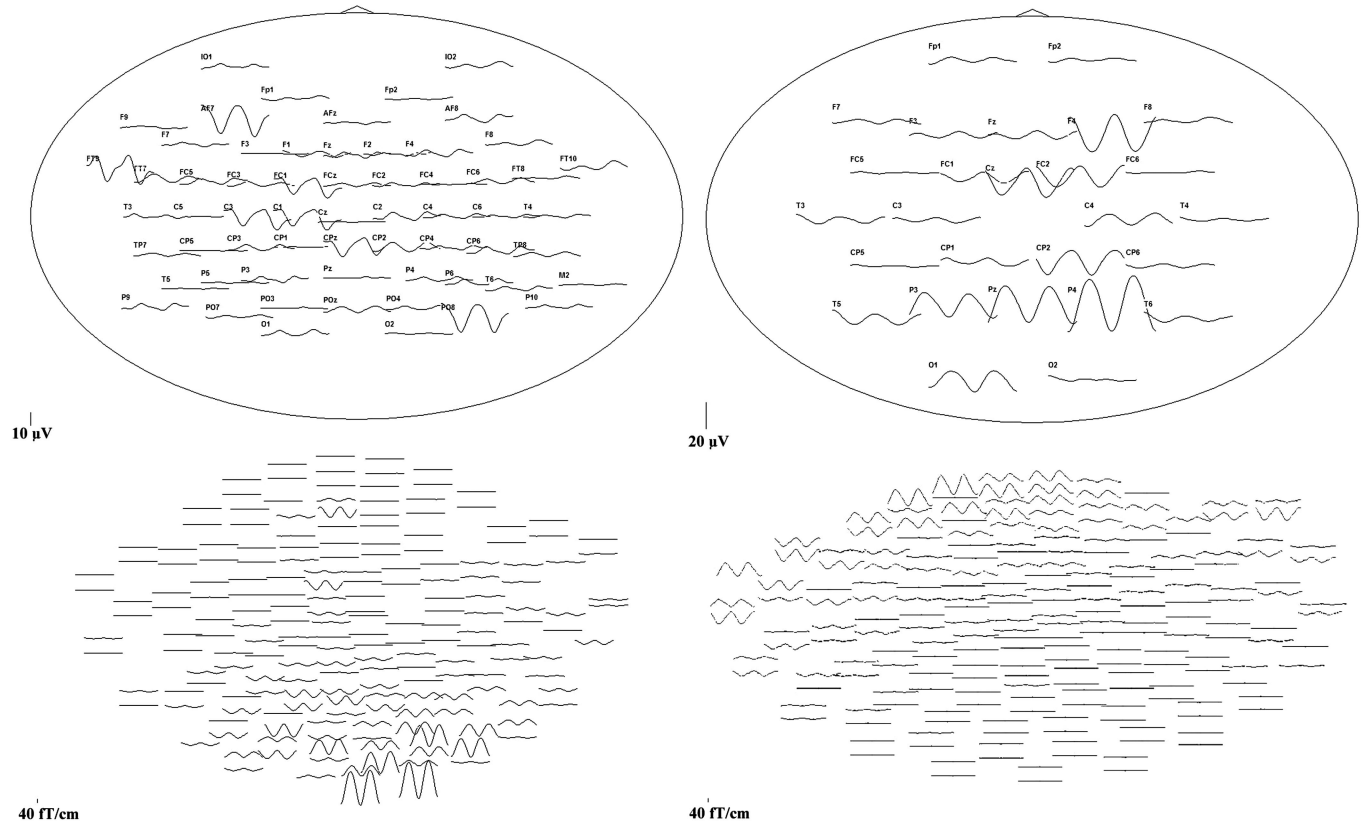

FIGURE 2. Top view of two patients represents the averages of two consecutive slow waves obtained by pattern search from gradiometer data. EEG is on top; MEG data on the bottom. Left side of the figure is from the same patient as in Fig. 1. Right side, same data from another patient with intractable partial complex seizures. BESA program allows top view of EEG for only a preprogrammed average reference montage, which accounts for fewer channels than in Fig. 1. MEG displays raw data. EEG also contains slow frequencies but in different distribution. MEG maximum in the posterior head regions is typical; frontal maximum, less common; amplifications, 40 ft/cm. EEG amplifications, 10 and 20 μV, respectively. Filters, 0.1 to 0.5 Hz. Display time, 7 seconds.

Erdler et al., 2000; Huckabee et al., 2003; Kornhuber and Deecke, 1965; Libet et al., 1983). The major discrepancy between our observations and the readiness potential is that the latter has been reported to precede voluntary movements by 1 second or less, whereas in our case, EEG changes began to occur approximately 7 seconds before breath-holding as well as hyperventilation. The study by Nagamine et al. (1996) may, however, be relevant in this respect. These authors observed that while studying the readiness potential for motor movements, spontaneous background activity at approximately 10 Hz "started to dampen 2 to 3 seconds before the movement onset in the somatomotor areas of both hemispheres with contralateral predominance." They reported, furthermore, a higher frequency rebound in the same areas approximately 1 second after termination of the movement. Pfurtscheller (1998) also reported a time period of about 3 seconds for event-related desynchronization and a postevent increase in synchronization. It is therefore possible that we are dealing in the subdelta frequency range with analogous findings.

During the preparation of this manuscript, the literature was reviewed to determine whether or not others had previously described the subdelta rhythms. PubMed listed three reports (Girton et al., 1973; Simon et al., 2003; Simon et al., 2000). The first investigation by Simon et al. described an MEG spectral event of approximately 0.5 Hz in three normal volunteers during sleep. The second report deals with the same three patients and an expanded mathematical analysis of the data. The authors reported that the rhythm was present at drowsiness and onset of sleep and increased in amplitude with depth of sleep thereafter. This agrees with our findings, but the suggestion that this frequency component is likely to correspond to slow oscillations of neocortical neurons during anesthesia or sleep, or to the K complexes of normal sleep, is not supported by our data because it does also occur in the waking state. Since Simon et al. did not have waking records, they believed that the phenomenon was unique to sleep, which is not the case. It seems more likely that the increase in amplitude during sleep may be tied to increased regularity and depth of respiration.

The paper by Girton et al. (1973), of which Simon et al. seemed to have been unaware, is of even greater interest because it describes "very slow oscillations" (5 to 8 c/min, 50 to 75 μV) in the EEG of 16 normal, awake control subjects.

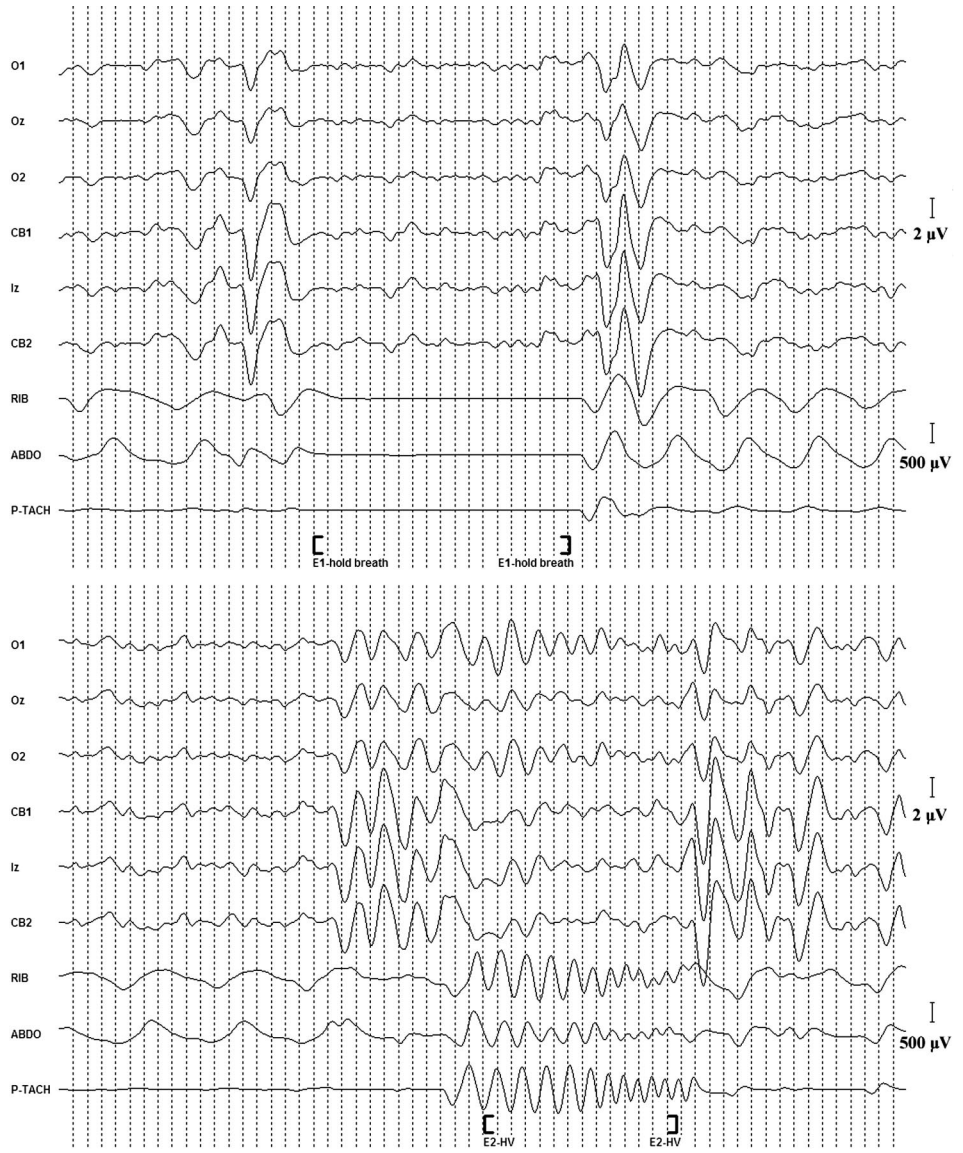

FIGURE 3. EEG relations to respiration in a normal control subject. An episode of voluntary breath-holding is in the top half and hyperventilation in the bottom half. Six occipital EEG and three channels for respiration (chest, abdomen, and nasal airflow) are shown. Top half: Increased EEG amplitude before voluntary breath-holding is not associated with increased depth of respiration. Bottom half: EEG increases in amplitude and frequencies when the decision to hyperventilate is made. During HV, the frequencies, especially at O1 and O2, are similar to respiration rate; also higher voltage activity at cessation of HV, especially in Cb channels. Filters, 0.1 to 0.9 Hz. Display time, 60 seconds.

The same waxing and waning effect, as reported by us in the MEG, was observed, and no relation to eyes closed, eyes open, or a variety of mental stimuli could be discerned. Just as in our investigation, these rhythms were at times phase-locked to respiration but not at others and persisted during breath-holding, which indicated that it was not respiration artifact. There is no mention of hyperventilation effects in that study. The authors speculated that the rhythm might be related to other spontaneous slow oscillations, as have been reported to occur in regard to oxygen availability and blood pressure.

To what extent subdelta activity bears any relation to glial currents cannot be answered on clinical grounds, but the paper by Amzica and Massimini (2002) on the interaction of neuronal and glial activity in the neocortex may be of considerable relevance. Coregistration of neuron-glia pairs showed that neuronal discharges were accompanied by glial events lasting between 1 and 1.5 seconds. Slower glia rhythms with a repetition rate of 10 to 20 seconds have also been observed (Amzica, personal communication, 2004).

From the data presented here, it is apparent that the subdelta frequency band deserves considerable further study.

The relation to known EEG-MEG phenomena in health and disease needs to be elucidated, and, as the respiration data showed, these frequencies may also represent an interface between autonomic and voluntary activity. They are therefore likely to become important not only to clinicians but also to investigations in the areas of psychophysiology.

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