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Methohexital-Induced Changes in Spectral Power of Neuromagnetic Signals: Beta Augmentation is Smaller Over the Hemisphere Containing the Epileptogenic Focus

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Summary: Previous research has suggested that methohexital, a short-term barbiturate, alters activity in the primary epileptogenic area. It can be assumed that drug-induced activation of the epileptogenic focus provides a rapid and safe method to obtain a sufficient amount of information relevant for the lateralization and localisation of the primary epileptogenic area. This study shows that methohexital changes spectral power in the beta band derived from magnetoencephalographic (MEG) signals over the hemisphere ipsilateral to the primary epileptogenic area. This effect was demonstrated for 10/13 of the investigated patients suffering from unilateral temporal lobe epilepsy (TLE). The side and location of the primary epileptogenic area of these patients (5 left TLE, 8 right TLE) was determined invasively during presurgical evaluation. During a 1-2 minute interval after intravenous bolus injection of 100 mg methohexital a clear lateralization effect in the beta band was observed, which differed marginally between fronto-central, fronto-temporal and temporo-parietal brain regions. In addition, bilateral spectral power changes were obtained in the theta, alpha and gamma bands that differed between brain regions. Analyses of simultaneously recorded scalp electroencephalographic (EEG) data revealed effects consistent with those of the MEG analysis. The reduced enhancement of beta band spectral power of MEG recordings provides a potential application for the non-invasive lateralization of the primary epileptogenic area.

Key words: MEG; EEG; Methohexital; Beta band activity; Temporal lobe epilepsy; Spectral analysis.

Introduction

Effects of anaesthetics on electroencephalographic (EEG) activity are well known. Barbiturates modify the EEG in frequency and amplitude. These drug-induced changes depend on dose (Brazier and Finesinger 1945; Essig and Fraser 1958; Schwartz et al. 1971) and are more pronounced or even limited to certain scalp regions (Sannita et al. 1990). Some of these effects can be used to localise brain lesions as well as epileptogenic areas (for review see Bauer 1982; Kaplan and Lesser 1990; Modica et al. 1990). Small doses of barbiturates result in an increase of fast activity in the beta band known to be larger over normal brain areas as compared to areas with cerebral lesions (Pampiglione 1952; Kennedy and Hill 1958). In addition, various authors described qualitatively a loss of methohexital-induced beta band activity in the electrocorticogramm (ECoG) over the epileptogenic area (Pampiglione 1952; Lieb et al. 1989; Hufnagel et al. 1992).

Because recordings of neuromagnetic fields have some advantages as compared to recordings of associated electric potentials, we expect the non-invasive magnetoencephalography (MEG) to provide additional information about the origin of methohexital induced changes in its spectral power characteristics. We therefore investigated the value of methohexital induced activity for the presurgical lateralization of the primary epileptogenic area using MEG during a short-time narcosis in patients suffering from temporal lobe epilepsy

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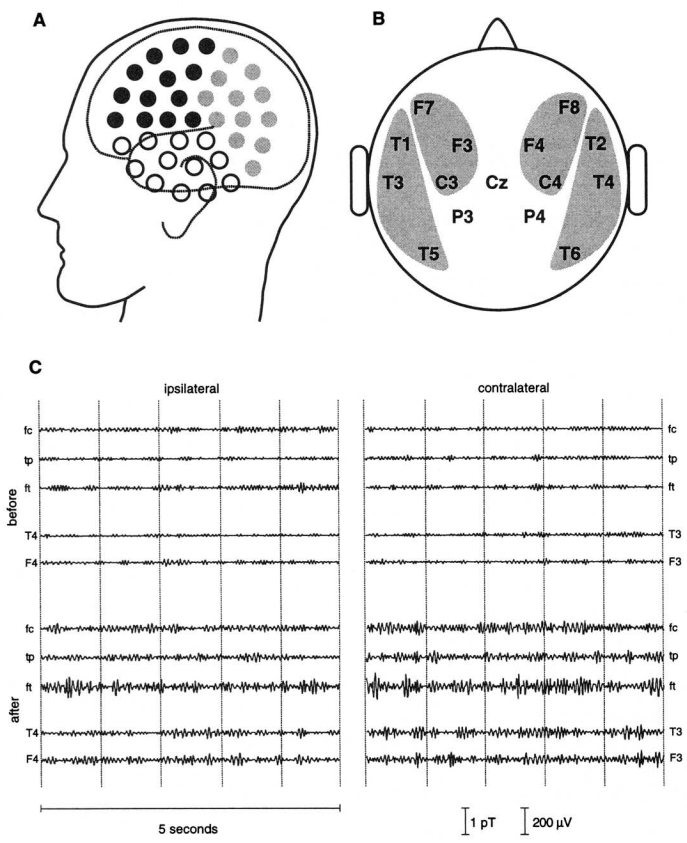

Figure 1. A: Schematic view of MEG recording locations. Spectral power was averaged across data from fronto-central (black circles), fronto-temporal (open circles) and temporo-parietal (light grey circles) sites. B: Schematic view of EEG electrode positions according to the international 10-20 system. Spectral power was averaged across data from fronto-central (F3, F7, C3 / F4, F8, C4) and temporal recording sites (T1, T3, T5 / T2, T4, T6). C: Typical examples of MEG and EEG beta band activity (patient R03) before (upper) and after (lower) i.v. injection of 100 mg methohexital. Data measured over the hemisphere ipsilateral to the primary epileptogenic focus are shown on the left side. During narcosis beta band activity is more enhanced over the hemisphere contralateral to the primary epileptogenic area (right). The selected MEG traces were recorded from fronto-central (fc), temporo-parietal (tp) and fronto-temporal (ft) brain regions, EEG traces (T3, T4, F3, F4) from electrode positions according to the international 10-20 system. Data were digitally bandpass filtered to remove activity from other frequency bands using a 13-24 Hz recursive 8th order Butterworth-filter.

(TLE). The aim of this study was to quantify anaesthesia-induced changes in the spectral power characteristics of simultaneously recorded MEG and EEG signals and to analyse the topographical aspects of these changes with respect to the side of the primary epileptogenic area.

Methods

Patient characteristics

Thirteen patients (age: 34 ± 7 years; range: 23 - 43 years) suffering from pharmacoresistant unilateral temporal lobe epilepsy were investigated. All patients were informed about the procedure before the examination and declared their informed consent. Before performing this study, all patients underwent invasive presurgical evaluation (see Bonn protocol of presurgical evaluation; Engel 1993) using electrocorticographic and intrahippocampal stereo-EEG recordings for the localisation and delineation of the primary epileptogenic area. As confirmed by the post-operative outcome a left temporal seizure origin was found in 5 patients and a right temporal seizure origin in 8 patients. Selective amygdalo-hippocampectomy (AHE) was performed in 8 patients, 2/3 anterior temporal lobe resection and AHE in 4 patients and a resection of a ganglioglioma in one patient. After surgery all but two patients are completely free of seizures for at least 6 month. The present examination was performed while the patients' anticonvulsant medication (Carbamazepine-mono-therapy - 11 patients, Phenytoin-Clobazam-therapy - 1 patient and Carbamazepine-Vigabatrin-Clobazam-therapy - 1 patient) laid within therapeutical range.

Measurement techniques and procedure

Neuromagnetic data were recorded using a 37-channel neuromagnetometer (Magnes™; Biomagnetic Technologies, Inc.; consisting of first-order axial gradiometers with 5 cm baseline and a coil diameter of 2 cm; pick-up coils were arranged in an array of concentric circles with a diameter of 14.4 cm). Measurements were carried out under video control in a magnetically shielded room. The sensor array was positioned first either over the patients' left (4) or right (9) supra-temporal cortex and centered about 1.5 cm superior to T3 or T4 electrode position of the international 10-20 system (figure 1a). The head position relative to sensor pickup coils was measured by a sensor position indicator. EEG data were simultaneously recorded (SYN-AMPS™; Neuro Scan, Inc.) from temporal, frontal, central and parietal electrode positions according to the international 10-20 system with the nose used as reference (figure 1b). To remove a possible influence of the reference electrode the corresponding average reference EEG signal was calculated. Continuous data were recorded in 10 minute blocks using a sampling rate of 297.6 Hz and a passband of 0.03 to 100 Hz.

Patients were lying on their side with their head and body fixed by a vacuum cushion. They were instructed to avoid eye blinks and head movements. After a 2 min baseline recording a dose of 100 mg methohexital was

applied intravenously (i.v.) in a bolus injection according to the conditions used during the invasive presurgical evaluation (Hufnagel et al. 1992). After a break of 41 min mean (range: 22 - 89 min) exactly the same procedure was repeated on the opposite hemisphere. This break is sufficient for the recovery of the patient with respect to consciousness and recovery of MEG and EEG back to the baseline due to methohexital's short half-life time of approximately 2 min. Anaesthetic monitoring and standby was provided, and precautions were taken to counteract anaesthetic complications. During the measurements an anaesthetist was within the magnetically shielded room.

Data Analysis

Off-line the data were digitally bandpass filtered using a 4-48 Hz recursive Butterworth-filter (2nd order) to remove low-frequency artefacts (like patient movements due to hiccup etc.) as well as frequency components above the gamma-band especially the 50 Hz noise. The spectral power was estimated for each magnetic and electric channel. Data sets of 300 seconds length starting 20 seconds before injection of methohexital were analysed using an overlapping segmentation technique. The length of the Parzen-windowed segments was 512 points which corresponds to 1.720 s. According to Press et al. (1988) the segments were overlapped by one half of their length to obtain the smallest spectral variance per data point. Power spectra of these segments were averaged within 19.785 seconds time windows. Thus, one mean spectrum across a 19.785 seconds window before and 14 windows after the administration of methohexital were calculated (the 19.785 seconds premedication baseline proved representative for the whole baseline in all cases). Due to different distances between MEG sensors and the patient's head, spectra were normalised by dividing each mean spectrum by the mean spectrum of the time before the injection of methohexital separately for each channel.

The spectral power in the theta, alpha, beta and gamma band represents the integrated power within the border frequencies (theta: 4.07-7.55 Hz, alpha: 8.13-12.79 Hz, beta: 13.37-23.83 Hz and gamma: 24.41-47.66 Hz). To further reduce the data, spectral band power was averaged across neighbouring channels separately for each hemisphere. MEG channels were collapsed over fronto-central, temporo-parietal and fronto-temporal brain regions (figure 1a), EEG-channels over fronto-central and temporal recording sites (figure 1b).

The resulting normalised (i.e., with respect to the baseline) spectral power values (termed NSP) of each frequency band were statistically tested for differences between hemispheres and brain regions as dependent variables. For MEG data we used two-way univariate analyses of variance (ANOVA) for a 3 brain-region (fronto-central vs. fronto-temporal vs. temporo-parietal) x 2 side-of-focus (ipsilateral vs. contralateral side) design. For the statistical analyses of EEG data the factor brain-regions had only two steps (fronto-central vs. temporal). Wherever appropriate, a Greenhouse-Geisser correction of the degrees of freedom was applied.

Results

General observations

No adverse effects during or after anaesthesia were noticed by either the patients or the investigators. Patients recovered quickly and had no clinical excitatory effects or signs like vomiting and nausea. No seizure was elicited. MEG and EEG raw data of one representative patient for time segments before and during the methohexital activation recorded over the ipsilateral and contralateral hemisphere are shown in figure 1c. In contrast to the baseline recording, a high amplitude beta band activity was obtained after administration of methohexital.

Spatial aspects of methohexital-induced changes in MEG/EEG spectral band power

In order to exclude a possible influence of repeated anaesthesia, spectral band power values of the baseline were statistically tested for differences. Wilcoxon matched pairs test and Student's t-test yielded no significant differences between baselines recordings.

The dynamics of changes in the theta, alpha, beta and gamma band NSP over hemispheres in the course of the methohexital activation are illustrated in figure 2. A well pronounced difference of both MEG and EEG beta band spectral power between the hemispheres ipsi- and contralateral to the epileptogenic focus was observed two minutes after the injection of methohexital for a period of 1-2 minutes. While these changes included activity in the alpha band of the EEG recordings, they were especially obvious in the gamma band activity of the MEG recordings.

In order to evaluate the influence of the factors brain-region and side-of-focus statistical analyses were based on changes of each band NSP obtained during the third minute after methohexital injection. In contrast to EEG recordings ANOVA showed the factor brain-region to significantly affect NSP in the theta, alpha and gamma band of the MEG recordings (theta: $F(2/24)=4.55$, $p<0.03$; alpha: $F(2/24)=14.60$, $p<0.0001$); gamma: $F(2/24)=6.22$, $p<0.008$). The influence of the side of the primary epileptogenic area, however, was not evident in these frequency bands of both MEG and EEG recordings.

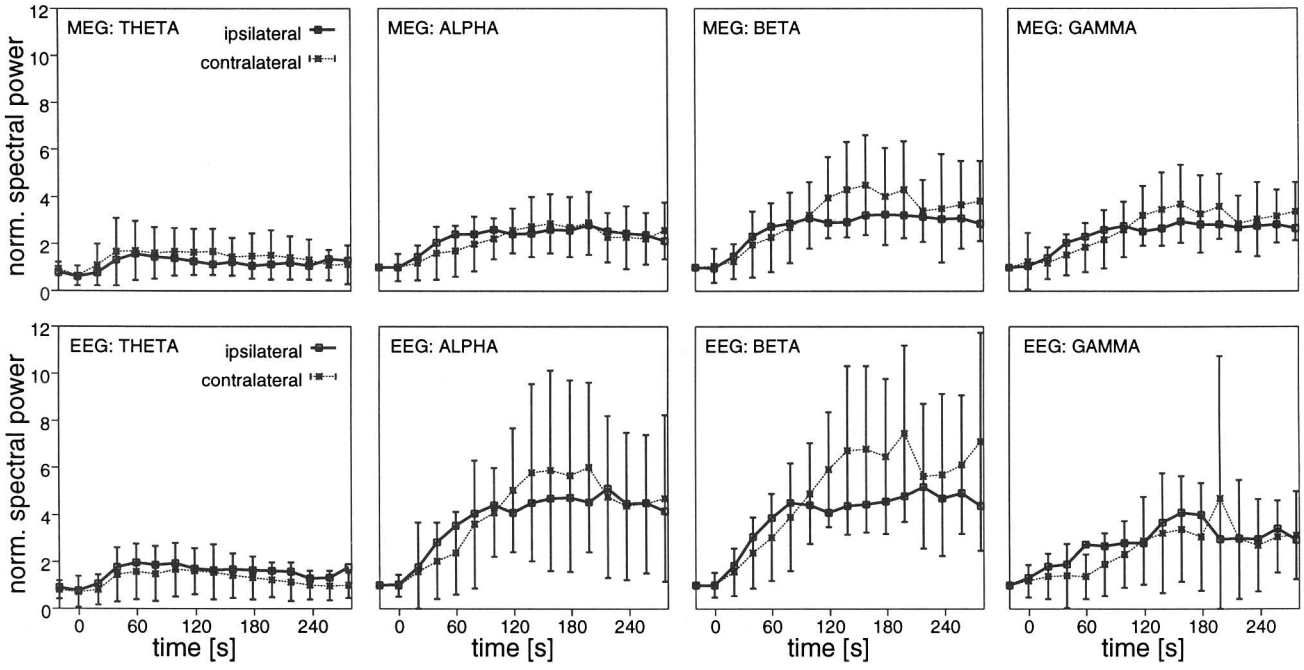

Figure 2. Changes of theta, alpha, beta and gamma band spectral power in the course of the methohexital activation for MEG (upper) and EEG (lower) recordings, averaged across all subjects. The standard deviation is shown for the contralateral side (dotted lines) only. Note that the standard deviations of EEG spectral power in the alpha, beta and gamma band are much larger than for the corresponding MEG spectral band power.

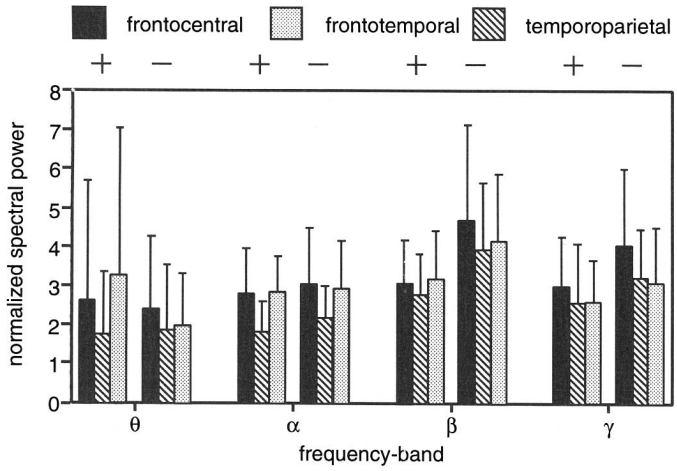

Figure 3. Means and standard deviation of normalised MEG spectral power in the theta, alpha, beta and gamma band over different brain regions. The hemisphere ipsilateral to the side of the primary epileptogenic area is marked with a (+), the contralateral side with a (-).

Analyzing the spatial fine structure of these induced changes in MEG recordings (see figure 3) post-hoc Scheffé comparisons revealed significant differences in the theta band NSP between fronto-temporal and temporo-parietal regions ($p<0.04$). In the former NSP exceeded the corresponding baseline level by a factor of 2.6 while in the latter the enhancement (E) amounted to 1.8 only. NSP in the alpha-band was remarkably lower over temporo-parietal brain regions (E=2.0) than over both the fronto-temporal (E=2.9; $p<0.0005$) and the fronto-central areas (E=2.9; $p<0.0005$). The brain-regions effect in the gamma band was mainly originated by the marked NSP enhancement over the fronto-central regions (E=3.5) as compared to the temporo-parietal (E=2.9; $p<0.03$) or to the fronto-temporal brain area (E=2.8; $p<0.02$).

Only in the beta band, the factor side-of-focus significantly influenced the normalised spectral power of both MEG ($F(1/12)=10.56$, $p<0.007$) and EEG ($F(1/12)=5.45$; $p<0.04$) recordings. This effect was evident over all brain regions with a slight predominance over fronto-central regions, without preferring one of them. The mean enhancement (i.e., averaged over all brain regions) in beta band NSP ipsilateral/contralateral to the primary epileptogenic area amounted to 3.0/4.3 for the MEG recordings and 5.3/7.6 for the EEG recordings.

Lateralization of the primary epileptogenic area

Based on interhemispheric differences in beta band NSP of MEG recordings a correct lateralization the primary epileptogenic area was possible in 77% (10) of the

Table I. Lateralization of the primary epileptogenic focus using the reduced enhancement of the normalised beta band spectral power as a measure in comparison to the result of the presurgical evaluation. Abbreviations: RIC = ratio of the beta band power ipsi- to contralateral.

Pat.	MEG Lateralization	EEG Lateralization	RIC MEG	RIC EEG
R01	correct	correct	0.71	0.51
R03	correct	correct	0.56	0.69
R04	correct	correct	0.53	0.56
R05	false positive	false positive	1.08	1.36
L06	correct	false positive	0.76	1.35
R07	correct	correct	0.79	0.63
L08	correct	correct	0.64	0.76
R09	false positive	correct	1.22	0.57
L12	correct	correct	0.63	0.25
L13	correct	false positive	0.63	1.21
L14	correct	correct	0.64	0.32
R16	false positive	false positive	1.69	2.21
R17	correct	correct	0.44	0.35

investiagted patients (see table I), while false positive decisions would have been made in 23% (3). EEG recordings yielded a correct lateralization in 69% (9) and false positive decisions in 31% (4) of the cases.

Discussion

The aim of the presurgical evaluation of patients with pharmacoresistant epilepsies is the correct localisation and exact delineation of the primary epileptogenic area. In order to avoid the invasive and time-consuming procedure of recording seizures via intracranial electrodes reliable non-invasive recording techniques are required. However, ictal symptoms render non-invasive recording techniques as the MEG non-feasible in the majority of the cases. To overcome these problems, the evaluation of drug-induced activities provides an alternative method for the rapid and safe localisation of the primary epileptogenic area. Up to now, research has focussed on drug-induced activities using EEG and ECoG recordings (Fuster et al. 1948, Pampiglione 1952; Kennedy and Hill 1958; Brazier 1969; Wilder 1969, 1971; Harris and Paul 1969; Celesia 1972; Wyler et al. 1987; Aasly et al. 1989; Hufnagel et al. 1992). Thus, the aim of the present study was to evaluate possible advantages of MEG compared to EEG/ECoG recordings. We analyzed drug-induced activities because of the follwing advantages compared to interictal or ictal activities: due to specific interactions of the short-acting barbiturate methohexital with the epileptogenic focus it can be expected that a sufficient amount of relevant data can be obtained within short acquisition times. Furthermore, movement artefacts that represent a major source of error in MEG recordings are minimised or even suppressed during the short-time narcosis.

Apart from an induction of epileptiform activity like spikes and spike-burst-suppression patterns (see Brockhaus et al. 1997 for a MEG based localization of these patterns), a loss of barbiturate-induced beta activity over the side of the primary epileptogenic area has been described qualitatively and quantitatively in a number of studies based on EEG or electrocorticographic (ECoG) recordings (Lieb et al. 1974; Duffy et al. 1984; Lieb et al. 1986; Hufnagel et al. 1992; Dasheiff and Kofke 1993; Brockhaus et al. 1995). Our results, based on a spectral analysis of simultaneous MEG and EEG recordings confirm these findings. A less pronounced induction of beta-band activity ipsilateral to the primary epileptogenic area was clearly expressed during a 1-2 minute interval starting approximately two minutes after the administration of methohexital and could be established in 10 (MEG-based lateralization) or 9 (EEG-based lateralization) of the 13 investigated patients.

The loss of methohexital-induced beta activity over the side of the primary epileptogenic area has also been reported by Hufnagel et al. (1992), who described the phenomenon qualitatively in ECoG recordings, measured under comparable experimental conditions. Although they concluded that a reduction of drug-induced fast activity over the epileptogenic area may be an addi-

tional aid in the localisation of cerebral lesions and functional epileptogenic foci, a beta reduction could only be observed in 48% of the investigated patients. The most likely reason might probably be due to the fact that frontal electrode strips were implanted only when indicated by previous investigations. However, a drug-induced enhancement of fast beta activity is more pronounced at frontal, fronto-lateral and temporo-lateral aspects of the brain but is rarely recordable using temporo-basal strip electrodes.

Regardless of the better signal-to-noise ratio of ECoG recordings compared to EEG recordings, both methods seem to have common disadvantages for the registration of the spatio-temporal dynamics of barbiturate interactions with the epileptogenic focus. Obviously, MEG shows some advantages for the description of drug-induced focal activities. Besides the independence of a reference electrode, MEG has the advantage of the body being transparent to low frequency magnetic fields up to the kHz range. Thus, the MEG is not attenuated by surrounding tissue as holds true for the EEG. Furthermore, it can be expected that a blurring of the recorded magnetic activity due to secondary sources produced by concentric inhomogeneities of the conductivity of the body is much less pronounced as for the electric potential. This is consistent with our finding of an additional barbiturate-induced gamma-band activity in the MEG compared to a more pronounced alpha-band activity in EEG recordings. These effects may reflect differential sensitivities of the recording techniques to brain activity in different frequency bands.

The mechanism of drug-induced beta reduction over the epileptogenic area is still unclear. However, our results indicate that the loss of methohexital-induced enhancement of beta band spectral power in MEG and EEG might contribute to the non-invasive lateralization of the primary epileptogenic area in patients suffering from pharmacoresistant temporal lobe epilepsy. This holds true particularly in those cases not exhibiting an increase of drug-induced spike activity or spike-burst-suppression (SBS) patterns in the MEG or EEG recordings, the latter pattern being of high significance for the lateralization and localisation of epileptogenicity to the ictogenic temporal lobe based on invasive ECoG recordings via subdural strip electrodes (Hufnagel et al. 1992).

Although the number of patients investigated so far is still too small in order to determine the value of the presented method for non-invasive presurgical evaluation, we would have correctly lateralized the primary epileptogenic area in 77% of the cases applying the calculated threshold of MEG beta band power only. This illustrates the potential significance of this method for presurgical lateralization of the primary epileptogenic area based on non-invasive MEG recordings.

In conclusion, our findings of a reduced enhancement of beta band spectral power in MEG recordings ipsilateral to the side of the primary epileptogenic area confirm previous studies using EEG recordings. In order to determine the value of this method for the non-invasive presurgical evaluation, additional investigations on a larger number of cases, especially with single or multiple epileptogenic foci in brain regions other than temporal lobes are required. Future investigations should also make use of the now available whole head MEG systems, which will allow simultaneous measurements from both hemispheres.

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