DC MEG Fields During Migraine

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1 Introduction

Recent studies of migraine-with-aura patients involving transmagnetic stimulation and visual stimulation have indicated enhanced excitability of the occipital cortex [1,2]. This hyperexcitability maybe the basis for Spreading Cortical Depression (SCD), which is thought to be the underlying mechanism of migraine-with-aura [3]. SCD and the resulting MEG signals are discussed in reference 4, and 5.

The present study investigates the MEG waveforms arising during spontaneous migraine-with-aura and evoked migraine auras in humans, to ascertain whether similar signals suggestive of SCD occur, and to understand the relations between SCD and migraine [4,5,6].

2 Methods

2.1 Patient studies

Neuromagnetic fields were measured during visual stimulation of the occipital cortex in eight migraine patients: 3 men, 5 women and in six controls: 1 man, 5 women, with no history of migraine headaches. Migraine patients were classified based on the International Headache Society (IHS) criteria [7]. Five ictal migraine patients were studied during spontaneous migraine with aura. All subjects gave written informed consent. These studies were performed utilizing a 148-channel Neuromagnetometer (4D Neuroimaging WH2500).

Migraine patients experiencing a unilateral headache and/or lateralized neurological symptoms at the time of the study were monitored for 15–20 minutes if their symptoms permitted. Migraine subjects not experiencing a headache and controls were monitored for 18 minutes during presentation of a visual stimulus.

The stimulus consisted of a circular checkerboard pattern, with 50-degree radius and 5 degree check size that alternated black and white at 8 Hz. The pattern was projected onto an opaque white projection screen and delivered to the subject using a system of mirrors. Each subject was asked to focus on a black dot in the center of the oscillating image on the screen. All data were digitized at 290.64 samples per second, with a band pass of 0-50 Hz.

2.2 Data Analysis

The Neuromagnetic data collected during the passive viewing of circular checker board pattern stimulus were analyzed for DC MEG shifts that occur when neurons are depolarizing in a propagating manner. The alternating checkerboard stimulus has been used to successfully stimulate migraine auras in previous migraine studies [2]. Data were filtered at 0.001-50 Hz to remove any equipment drift which was coherent in all 148 channels. The data were then decimated from 254 to 11 samples per second to simplify computer manipulations. These two steps did not affect the slowly varying DC shifts, which occur over minutes. Data were normalized to compensate for difference in head sizes of the subjects and the different distances of the head to the sensors. A local sphere was fitted to the back of the digitized head shape, and the distance from the surface of the sphere to pickup coils was calculated for each posterior channel. We assumed that the source of the field was located on the surface of the brain, directly under the detector; this allowed the use a $1/r^2$ fall-off factor to adjust the amplitudes so that all data sets were normalized to a 4 cm distance from scalp to pickup coil. Equivalent current dipole (ECD) source analysis was used to determine location and amplitude of the large

component of the DC shift arising from each subject. Dipole fits were made based on the magnetic field maps. The 57 posterior channels were overlaid; the largest amplitude response was selected; and a dipole fit was made to determine the actual location of the source on the cortex.

3 Results

All M+A subjects experienced migraine with aura and no controls experienced migraine. Slow MEG signal shifts were observed in M+A subjects. Our results show that there are differences between the DC MEG fields of controls (amplitude of shifts <9pT) and M+A subjects (average amplitude of shifts 37 $\pm$ 17 pT). The DC shifts seen in data from M+A subjects had consistently larger amplitudes than those shifts seen in control subjects.

Migraine headaches were induced in 5 (62%) of the 8 migraine subjects and in 0 of 6 of the controls (p=0.031, Fisher's exact test). The migraine and the control groups were similar in age [migraine: mean=44 years, s.d.=9; control: mean=38 years, s.d.=6 (p=0.172, two sample t-test)] and gender distribution [migraine group: 62.5% females; control group: 83.3 % females (p=0.58, Fisher's exact test)]. DC MEG shifts were observed in migraine subjects during evoked migraine-with-aura,as well as in five migraine subjects during spontaneous migraine-with-aura. No DC MEG shifts were seen in control subjects.

The difference between migraine and control groups in the percent of subjects with DC shifts greater than 9 pTesla was significant (migraine, 100% with DC shift; control, 0% with DC shift; p=0.003, Fisher's exact test). Figure 1 displays the DC shifts from a visually evoked migraine-with-aura subject. Note the arrows denoting the start and end of the DC MEG shift of interest, 800-840 Seconds. This time interval was used to calculate an equivalent current dipole source. The results of ECD were poor, with correlations of less then 0.60. The data were then imported to Matlab where a multi source technique (2DII) was applied: see paper in this conference [8].

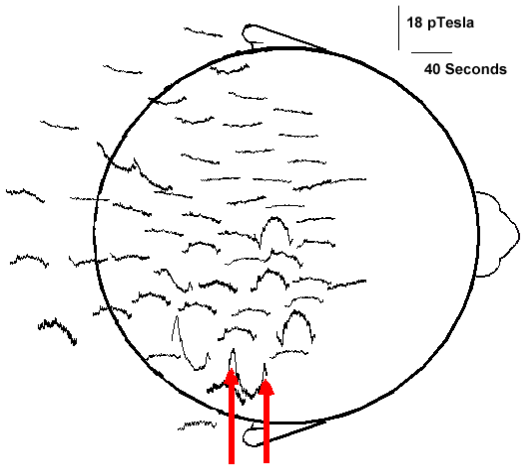

Figure 1*) DC MEG shifts during visual stimulation in a migraine patient.*

Figure 2 displays the occipital MEG channels collected during 300 seconds of visual stimulation of a normal control subject. Data were collected for 18 minutes and normalized as described earlier and no DC-MEG shifts were seen in the data. Small spikes seen in the data are from patient movement.

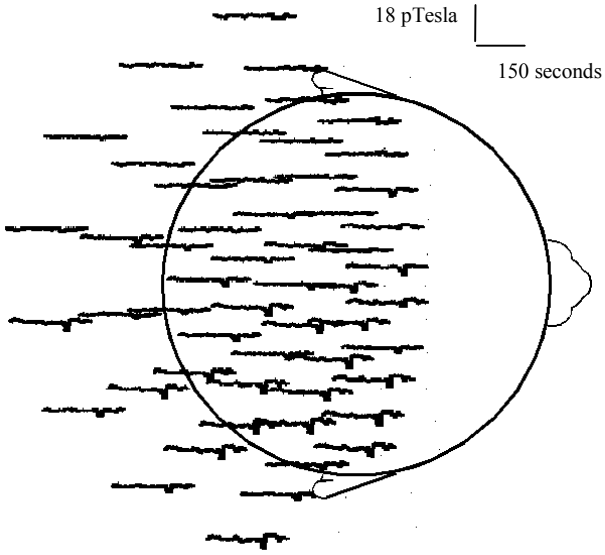

Figure 2) *MEG data from a control subject during visual stimulation. Small spike is from movement artifact.*

Figure 3 displays the MEG normalized data during a spontaneous aura. Data collection was started approximately three minutes after

the aura had started. This subject was a member of the laboratory staff, and therefore it was only a short time from onset of aura to data collection. Large amplitude DC MEG signals were seen arising from the right hemisphere. The large downward deflection seen in three channels represents the magnetic field going into the subject's head, and an upward deflection representing the magnetic field coming out of the subjects head, is seen in the channels over the midline, indicating that there

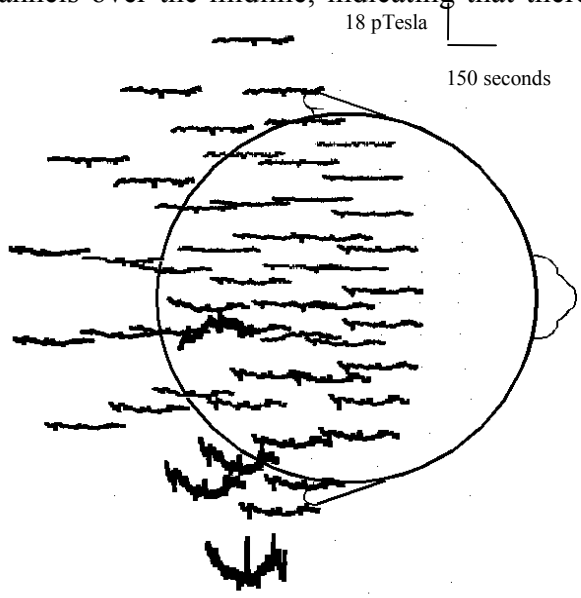

Figure 3*) DC MEG shifts during spontaneous visual aura in a migraine patient.*

is neuroelectric activity occurring under these channels. The pattern of shifting DC MEG signals seen in association with spontaneous migraine are similar to those seen with induced migraine. Of the five subjects studied during spontaneous auras, one subject produced too much artifact noise to be able to discern the actual MEG signal, and was excluded from the study.

Tables 1 (evoked) and 2 (spontaneous) list results for subjects studied with MEG. Of the 8 migraine subjects visually stimulated, 5 had headaches induced. The difference in magnitude of the DC shifts between migraine subjects who experienced headache and those who did not was not significant (with HA mean=34.8$\pm$18.6; without HA mean=26.0$\pm$24.3; p=0.553, Wilcoxon two sample test).

Table 1 Evoked subjects studied with MEG. Type of subject (control[C] or migraine-with-aura[M+a]), presence of any DC shifts in the data (yes[Y], no[N]), maximum amplitude of these DC shifts in picoTesla (pT), and whether or not a headache (HA) was induced (yes[Y], no[N]).

	Age	**Sex**	**Type**	**DC Shift**	**Max** (pT)	**H A**
1	54	F	M+a	Y	54	Y
2	34	F	M+a	Y	27	Y
3	40	F	C	N	Shifts<9	N
4	43	F	C	N	Shifts<9	N
5	40	M	M+a	Y	11	N
6	37	F	C	N	Shifts<9	N
7	38	M	M+a	Y	12	Y
8	32	F	M+a	Y	54	Y
9	47	F	M+a	Y	27	Y
10	52	M	M+a	Y	13	N
11	43	F	C	N	Shifts<9	N
12	26	M	C	N	Shifts<9	N
13	36	F	C	N	Shifts<9	N
14	52	F	M+a	Y	54pT	N

Table 2 Spontaneous subjects

	Age	**Sx**	**Type**	**DC Shift**	**Max (pT)**	**Ha Now/ Later**
15	49	F	Ictal M+a	Y	11p T	N/Y
16	64	M	Ictal M+a	Y	22p T	N/Y
17	42	F	Ictal M+a	Y	10p T	N/Y
18	38	M	Ictal M+a	Y	20p T	N/Y

4 Discussion

Our results support the hypothesis that migraine subjects have more excitable cortices than normal controls. This hyperexcitability leads to the cascade of depolarizing neurons, known as spreading cortical depression, which is detected by MEG as multiphasic DC shifts. Migraine aura subjects displayed more DC shifts in their MEG data, due to an underlying cortical neuronal depolarization.

We can reliably evoke migraine aura in human subjects and have shown in this study that spontaneous and evoked migraine give rise to similar large amplitude DC MEG signals. The MEG signals arising from SCD crossing a sulcus, in animal model [4,5], are very similar to those measured with our whole head neuromagnetometer during spontaneous or visually stimulated human migraine aura. We believe this constitutes the first direct measurement of neuronal activity in human migraine suggestive of an SCD-like event.

MEG waveforms provide a characteristic signature of SCD-like events occurring in the human brain. These signals agree with the theoretical predictions based on the convolutions of the cortical surface [5,9]. There are measurable differences in MEG recordings between migraine and non-migraine subjects. Further studies that include subjects who experience migraine-without-aura will help to determine if MEG can detect differences between migraine-with-aura and migraine-without-aura.

Neuromagnetic signals from migraine aura subjects were multiphasic and intricate. Therefore simple ECD did not work since the MEG signals arose from an extended propagating source rather than a local static source on the cortex. Propagation of a wave of hyperexcitation across a convoluted cortex will give rise to complex field patterns due to the propagation in different directions across multiple sulci. Further analysis and modeling may determine more precisely the locations on the cortex giving rise to DC MEG shifts.

These experiments suggest the possibility of utilizing MEG to gain deeper understanding of the neurological disturbances linked to SCD-like events. Combining MEG with other functional imaging modalities such as EEG, fMRI, PET, and SPECT, each co-registered with the subject's MRI, will help produce a more detailed picture of the underlying biophysics occurring in the human brain.

Acknowledgements

This research was supported by NIH/NINDS Grants RO1- NS30914, and P50-NS32399

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