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Statistical analysis of transcallosal propagation of spikes arising from the mesial frontal area

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ABSTRACT – *Objective*. To study the connections between bilateral mesial frontal (MF) regions. *Methods*. We evaluated synchrony of spikes, recorded by subdural electrodes, arising from bilateral MF regions using cross correlation in MF epilepsy. A seven-year-old boy with intractable daily bilateral asymmetric tonic seizures and a normal MRI was investigated. To confirm the lateralization of epileptogenicity, subdural electrodes were implanted bilaterally. Only spikes of an amplitude of 400 μV or more were analyzed. *Results*. Of 92.4% (194/210) of the left MF spikes recorded for 30 minutes, an approximately synchronous spike was also detected in the right MF region. Cross correlation analysis demonstrated that for 88.7% of the bilateral MF spikes (172/194, 88.7%) the left MF spike led the contralateral spikes with relative fixed peak-to-peak intervals (18.9 ± 11.1 ms) and high cross correlation values (0.81 ± 0.10). An estimated conduction velocity of 7.2 ± 9.8 m/sec was calculated (assuming no synaptic delay). After a second period of more extended invasive EEG monitoring, a left partial frontal lobectomy was performed and the patient immediately had a few brief seizures before remaining seizure-free for a follow-up period of 14 months. *Conclusion*. We conclude that the propagation of spikes between bilateral MF regions most likely occurs mainly through myelinated callosal fibres. In addition, this cross correlation method showed that the left MF spikes, most of the time, preceded the right MF spikes suggesting that the epileptogenic zone was localized in the left MF region.

Key words: cross correlation, epilepsy, mesial frontal region, spike

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Electric and magnetic stimulation studies have demonstrated transcallosal connections between homotopic areas of both hemispheres (Shibasaki *et al.*, 1978; Cracco *et al.*, 1989). Furthermore, functional connection, most likely via the corpus callosum, has also been revealed by cortico-cortical evoked potential studies using subdural electrodes (Terada *et al.*, 2008). In these studies, the transit time between hemispheres was 9-11 ms using the jerk-locked averaging technique with somatosensory evoked

potential (Shibasaki *et al.*, 1978), 8.8-12.2 ms by magnetic stimulation (Cracco *et al.*, 1989), and 9.2-23.8 ms by cortico-cortical evoked potential studies (Terada *et al.*, 2008).

Epileptiform discharges arising from one hemisphere often propagate to the contralateral side, most probably passing through the corpus callosum. Lemieux and Blume (1986) studied inter-hemispheric lag times of spikes using computer-generated 3-dimensional field potential maps with scalp electrode. They reported an average inter-hemispheric spike delay of 10.5 ms (ranging from 0 to 25 ms).

Inter-ictal and ictal epileptiform discharges arising from mesial frontal (MF) regions tend to propagate very rapidly to the contralateral homotopic area. However, there are no reports in which inter-hemispheric propagation of epileptiform discharges has been analyzed systematically. In this study, synchrony of inter-ictal epileptiform discharges arising from bilateral MF regions was evaluated using a cross correlation method.

Methods

History

A seven-year-old boy with daily bilateral asymmetric tonic seizures refractory to antiepileptic drugs was admitted for presurgical evaluation. The patient had been suffering from seizures since the age of two years, which were characterized by asymmetric stiffening and stretching of extremities lasting for five seconds to a minute with no loss of consciousness or awareness. Occasionally, clonic seizure in the right leg followed the tonic phase. The MRI was normal. Non-invasive video-EEG monitoring revealed inter-ictal and ictal epileptiform discharges arising from the midline of the fronto-central region. These results suggested that the patient most probably had MF epilepsy although (with the exception of seizure semiology) the results did not clearly lateralize the epileptogenic zone.

Implantation of subdural electrodes and EEG recordings

Extracranial EEG study showed spikes with maximum amplitude arising from FCz and Cz, according to the international 10-10 system. Ictal discharges also originated from these two electrodes. Therefore, to lateralize the epileptogenic zone, two burr holes were made at about 1 cm posterior and about 1.5 cm lateral to the bregma, bilaterally and symmetrically. A 1 × 6 subdural electrode strip was manually implanted in the MF region on both sides *(figure 1A)*. Additional three 1 × 6 subdural electrode strips were implanted over the left prefrontal, the left parietal, and the right frontal convexity, respectively *(figure 1A)*. Each subdural electrode consisted of six contacts and individual contacts had a 5 mm diameter. The centre-to-centre inter-electrode distance was 10 mm. In addition, three strips were also placed on the bilateral dorso-lateral frontal regions (one strip on the right and two on the left). On the left side, one more strip was implanted covering the dorso-lateral centro-parietal region *(figure 1A)*. MRI (sagittal view), co-registered with skull X-ray, indicated that MF subdural electrode strips covered the cingulate (MF1 and 2), medial (MF 3, 4, and 5), and superior frontal gyri (MF6) bilaterally *(figure 1C)*. Chronic intracranial EEG monitoring was performed for one night at the Epilepsy Monitoring Unit. EEG data were collected using Neurofax software (EEG-1000 Ver. 05-90, Nihon Kohden Corporation). Recordings were obtained with an EEG sampling rate of 1,000 Hz. This study was analyzed in referential montages using, as reference, a relatively quiet subdural electrode.

Statistical evaluation

Statistical analysis was used to determine the time correlation between spikes arising from bilateral MF regions. For continuous signals the cross correlation function (ccf) was computed as:

$$ccf(\tau) = \lim_{T\to\infty} \frac{1}{T} \int_{-\frac{T}{2}}^{\frac{T}{2}} S_1(t)\, S_2(\tau - t)\, dt$$

for which we approximated the ccf of our discretized signals using

$$ccf[j] = \frac{1}{n} \sum_{i=1}^{i=n} S_1[i]\, S_2[i+j]$$

$$j = 1, .., n$$

The time difference was estimated between a given signal with respect to a reference signal, where s_1 and s_2 are the two signals under study, T is the length of the signal epoch, and τ is the independent time shift that renders the greatest magnitude correlation. We used the greatest (most positive) correlation. Given two signals which are statistically similar but differ by a fixed time shift, the *ccf(τ)* will produce a maximum value at a time corresponding to the time shift difference in the two signals. That is, if $s_1(t)$ is statistically similar to $s_2(t - T)$, then the maximum of *ccf(τ)* occurs at $\tau = T$

This method also helps to determine whether the analyzed signal leads ($\tau > 0$) or lags the reference signal ($\tau < 0$). Additionally, the integral can be also computed efficiently using the Wiener–Khinchin theorem (the exact Matlab code is: ccs1s2 = real[ifft(conj(fft[s1]). *fft[s2])]; ccs1s2 = ccs1s2/std(s1)/std(s2)/length(s1); the (circular) cross correlation is the inverse Fourier transform of the element-by-element complex conjugate product of the Fourier transform of the two signals normalized by the product of the standard deviations and the vector length.

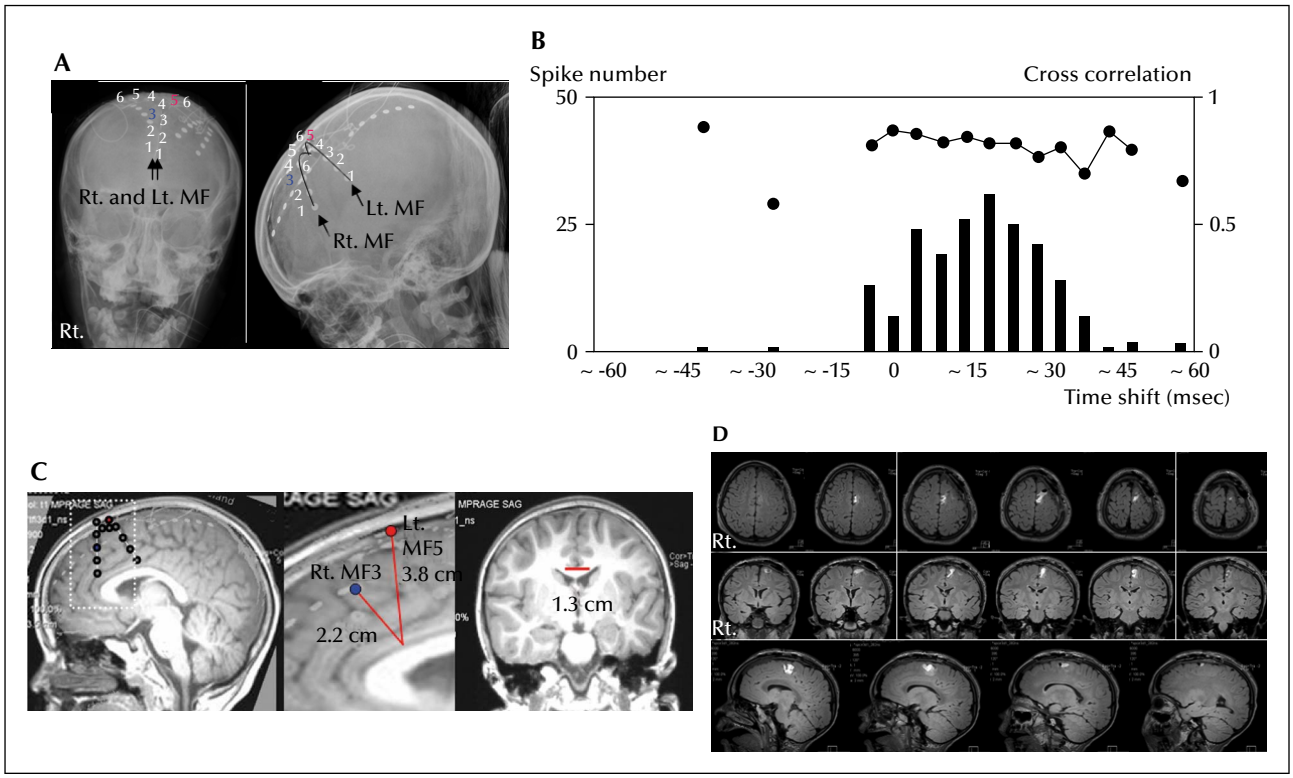

Figure 1. A) X-ray images (left: anterior-posterior view; right: lateral view) show the location of subdural electrodes bilaterally. Note the location of the two contacts from which spikes were analyzed in this study (blue: Right MF3; red: Left MF5). MF: mesial frontal; Rt: right; Lt: left.
B) The histogram shows the relationship between the number of MF spikes and the peak-to-peak time difference between right MF3 and left MF5 spikes. The line graph shows averaged cross correlation values. High cross correlation values are shown.
C) MRI sagittal view co-registered with skull X-ray left subdural electrodes (left). The distance between the right MF3 subdural electrode and the callosal sulcus was 2.2 cm and the distance between the left MF5 subdural electrode and the callosal sulcus was 3.8 cm (middle). Blue circle: right MF3 subdural electrode; red circle: left MF5 subdural electrode. Coronal MRI image (right). The distance between the bilateral fundus of cingulated sulcus was 1.3 cm. The total distance between the left MF5 subdural electrode and right MF3 subdural electrode was estimated as 7.3 cm.
D) Postsurgical FLAIR MRI shows the limited mesial frontal resection.
Upper: axial images; middle: coronal images; lower: sagittal images.

This also permits interpolation of the estimated time shift by zero padding the vector in the frequency domain. We could have interpolated to give a greater accuracy to the time differences, however this was not done since the results were sufficiently accurate for our purposes. The theory of frequency domain interpolation was as follows: after transforming a block of signal data into the frequency domain, we added a block of zeros representing zero energy at frequency components above the Nyquist frequency. We then inverse transformed the data back into the time domain with the results, such that additional (interpolated) sample points existed.

In this study two different contacts, which showed no epileptiform discharge in inter-ictal phase, were used as reference (the most anterior two neighbouring contacts of the subdural electrode strip covering the right prefrontal convexity). Frequencies between 3 and 300 Hz were included for evaluation of cross correlations. Each inter-ictal spike was analyzed with a 500 ms window.

Results

Spikes occurred almost synchronously on the left MF 2, 3, 4, 5, and 6 subdural electrodes. On the contrary, only two electrodes showed spikes on the right side (right MF3 and MF4). Spikes arising from the left MF5 subdural electrode and the right MF3 subdural electrode were analyzed because these two contacts were the most active contacts in the left and right MF regions, respectively *(figure 1A)*. In other words, on both sides, these were the most frequent spikes with the greatest negativity in reference montage. Only spikes of an amplitude of 400 μV or more were analyzed for 30 minutes of recording. Spikes with amplitude of more than 400 μV occurred from only three electrodes, namely the left MF5 and the right MF3 electrodes, and less frequently from the left MF5 electrode. Repetitive spikes or rhythmic spikes were recorded only very infrequently. However, to exclude an ictal phase in the final analysis, the ictal EEG and a 30-minute

post-ictal period was not included in this study. All epileptiform discharges analyzed in the study were clearly defined isolated spike-and-waves. A total of 213 spikes exceeding 400 μV were seen from these two contacts (spikes occurring almost synchronously on both electrodes were counted only once): 92.4% (194/210) of the left MF spikes were almost synchronous with spikes from the right MF region (there were 16 independent left MF spikes). Only three spikes (1.4%) occurred independently of the right MF.

Cross correlation analysis demonstrated that 88.7% of the left MF spikes (172/194) led the contralateral spikes with a relative fixed peak-to-peak interval (18.9 ± 11.1 ms) and high cross correlation values (0.81 ± 0.10) *(figure 1B)*. Of the spikes from bilateral MF regions, 3.6% (7/194) occurred simultaneously and 7.7% of the spikes (15/194) from the left MF5 subdural electrode were preceded by spikes from the right MF3 subdural electrode by 5.9 ± 10.4 msec. Of the 15 spikes in which a left MF spike was preceded by a contralateral spike, two spikes had extremely large time shifts *(figure 1B)*. The difference in number between the two types of spikes most probably resulted in the different conduction velocity. The averaged cross correlation value obtained from all spikes was 0.81 ± 0.01 and there was no relationship between cross correlation value and the difference of time-shift *(figure 1B)*.

Using co-registration of the presurgical MRI and post-surgical CT scan, and assuming that the epileptiform discharges travel through callosal connections, the absolute distance between the left MF5 subdural electrode and the right RF3 subdural electrode was estimated at 7.3 cm *(figure 1C)*. Although this method was just an approximate summation of visually obtained data from MRI, the distance we calculated was similar to the distance estimated by Demeter *et al*. (1990) (ranging from 10 to 13 cm) which considered a convoluted fibre path (Aboitiz *et al*., 1992). This calculation leads to an estimated conduction velocity of 7.2 ± 9.8 m/sec if we assume no synaptic delays.

Visual analysis of the ictal and inter-ictal subdural recordings obtained with this preliminary limited invasive study clearly lateralized the epileptogenic zone to the left MF region. The fact that the majority of left MF spikes lead right MF spikes by a significant delay also supports this conclusion.

A left frontal craniotomy was performed one day after the first implantation of subdural electrode strips and more additional subdural electrodes covering the left MF region, including the supplementary sensory motor area (with 1 × 4, 1 × 6, and 2 × 6 subdural electrode strips), the left prefrontal convexity (with 1 × 6 and 2 × 8), and the upper primary motor area (with 1 × 4, 1 × 6, and 2 × 4) were placed. In this second evaluation, the EEG seizure onset zone was localized to the left MF region (the EEG seizure originated from nine contacts of the left MF electrode strips). After chronic EEG monitoring for one week, a very limited left mesial frontal resection was performed. The patient continued having seizures after the surgical resection and returned for complementary invasive studies 15 months later. This led to additional resection of brain tissue immediately adjacent to the first surgical resection. The patient has been seizure-free for more than six months since the second surgery *(figure 1D)*.

Discussion

This study shows that spikes arising from the MF region propagate to the contralateral side with a relatively fixed time-shift and high cross correlation values. The averaged time-shift in the study was 18.9 ± 11.1 msec for spikes originating from the left frontal region. This inter-hemispheric time lag was similar to data obtained from other studies such as peripheral nerve stimulation (8-9 msec) (Shibasaki *et al*., 1978), transcranial magnetic stimulation (8.8-12.2 msec) (Cracco *et al*., 1989), and cortico-cortical evoked potentials (9.2-23.8 msec) (Terada *et al*., 2008). The data were also comparable with the results obtained from scalp recorded spikes (average: 10.5 msec, ranging from 0 to 25 msec) by Lemieux and Blume (1986).

Anatomical studies indicate that the inter-hemispheric propagation between MF regions occurs *via* the corpus callosum. Musgrave and Gloor (1980) reported the role of corpus callosum in bilateral spike synchrony in penicillin epilepsy. They demonstrated that bilateral spike synchrony disappeared after complete section of the corpus callosum and the anterior commissure. Our study revealed very high cross correlation values (0.81 ± 0.01) between spikes arising from bilateral MF regions, most likely due to transcallosal spread. Aboitiz *et al*. (1992) estimated the relationship between axonal diameter, conduction velocity, and inter-hemispheric transfer in humans. They reported that myelinated callosal fibres have conduction velocities of 5.2 to 67 m/s with an inter-hemispheric conduction time of 1.5 to 24.9 msec (10-13 cm). For unmyelinated fibres which have a diameter of 0.6 to 1.5 μm, they calculated a conduction velocity of 0.3 to 3.2 m/s with an inter-hemispheric conduction time of 50 to 433 msec. Pandya and Seltzer (1986) and Lamantia and Rakic (1990) described the cytological and quantitative features of the corpus callosum in monkey brains. They reported that the majority of axons passing through the anterior third of the corpus callosum originate from the MF regions and that approximately 68.6 to 90.6% of them are myelinated axons with estimated diameters of 0.65 to 0.74 μm.

In this study about 8% of the spikes from the left MF region were preceded by contralateral spikes. In addition, occasional independent right MF spikes were observed.

Invasive recordings and the favourable outcome after a limited left mesial frontal resection suggest that the patient was suffering from left MF epilepsy. Right MF spikes could represent secondary epileptogenicity (mirror focus phenomenon) (Morrell and de Toledo-Morrell, 1999). In addition, we cannot exclude the possibility that earlier spikes from a left MF region, not covered by subdural electrodes, triggered contralateral right MF spikes.

Conclusion

This study supports the hypothesis that MF spikes propagate mainly in myelinated fibres between bilateral MF regions. The conduction velocity in this study was concordant with the data from other reports and anatomical estimations. From these results, we speculate that the cross correlation studies of this type could be a valuable tool for patients with MF spike foci in which seizure semiology, MRI and surface scalp EEG recordings do not permit reliable lateralization of the epileptogenic zone. □

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