Hemispheric asymmetry of the callosal involvement in bilaterally synchronous epileptiform discharges revealed by direct recording of callosal compound action potentials

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Background

Bilaterally synchronous spike-and-wave discharge may be generated through interhemispheric recruitment via the corpus callosum.

So far, while the callosal participation in some generalized epilepsies has long been supposed, selective activities of the callosal neurons have not been studied in relation to the epileptic seizures. Our recent study (2) of intraoperative electrocorticogram (ECoG) and callosal compound action potential (CCAP) suggested that, as some sort of concerted action between both hemispheres, a gradual recruitment of callosal and other cortical neurons in widely extended areas are built up to a supra-threshold level via the transcallosal facilitatory mechanism, thereby epileptiform discharges are elicited in both hemispheres at nearly same moment.

Asymmetry of pre-existing cortical epileptogenic susceptibility states between two hemispheres may explain outcomes after callosotomy.

EEGs after callosotomy show various changes of preoperatively observed bilaterally synchronous spike and wave discharges (BSSWs), i.e., desynchronization, lateralization or disappearance, and it may be construed as disparity in potentiality of preexisting hemispheric epileptogenesis. Post-callosotomy emergence of hemispheric asymmetry in the amount of residual epileptiform discharges found between two hemispheres could differentiate the dominant hemisphere from the non-dominant one with respect to the presumed epileptogenesis (3). This finding leads us to postulate putative asymmetry of pre-existing cortical epileptogenic susceptibility states between two hemispheres, even in the case that almost identical epileptiform discharges in both hemispheres are preoperatively manifested.

Working hypothesis

The pre-existing cortical epileptogenic susceptibility may be reflected in the CCAP (Predictability of the postoperative lateralization).

In spite of apparently symmetrical BSSWs, the extent of the callosal involvement in BSSW genesis would be greater in the epileptogenicity-dominant hemisphere than in the non-dominant one. In this study, we devised an averaging-based method to estimate separately the component proper to each hemisphere (hemispheric CCAP) from the observed CCAPs synchronized to BSSWs (those essentially include bi-directional activation). Then laterality of hemispheric CCAP was correlated with postoperative EEG and clinical seizure outcomes.

Methods

Elecrophysiologic procedure

Intraoperative CCAP and electrocorticogram (ECoG) recordings were performed in 19 patients who submitted corpus callosotomy for medically intractable generalized epilepsy. All patients were preoperatively informed and consented the aim of surgery and the intraoperative electrophysiologic studies. Their common interictal EEG abnormality was characterized by bilaterally synchronous (almost symmetrical) spike-and-wave discharges (BSSWs).

Prior to dissection of the CC, simultaneous recordings of ECoG and CCAP were performed for about 15 minutes under 1-2% sevoflurane general anesthesia. ECoGs were recorded from two strip electrodes (4-6 channels at intervals of 1 cm) over the exposed frontal lobe (direct recording from the cerebral cortex) and from the non-exposed one (epidural recording). CCAPs were recorded from either a strip electrode (2-6 channels at intervals of 3 mm) or a pair of bipolar needle electrodes placed on the CC. The transcallosal responses were evoked by direct callosal stimuli in order to confirm the extent of the callosal projection and to place cortical electrodes correctly corresponding to the callosal site.

Data processing

The electrophysiologic data were digitized at a sampling interval of 5 ms through a carefully tuned antialiasing low-pass filter, and the following data processing was performed under a visually guided graphical environment using a home-made computer system as follows:

(1)A pair of homotopically located channels of ECoG from which more prominent BSSW were recorded, and a channel of CCAP corresponding to the selected cortical channels were chosen;

(2)One-second long epochs in which those midpoints were visually aligned to a negative peak of BSSWs were extracted from recorded ECoGs and CCAPs;

(3)All epochs were averaged with a time-alignment to the negative peak of referenced (right or left) cortical spike discharges, thereby CCAPs synchronized with cortical spike discharges were estimated. In the present study, we refer the term CCAP to the callosal activities synchronized with

cortical BSSW.

Outcome evaluation

According to our routine procedure, EEG and seizure outcome after callosotomy were evaluated one month after the operation. Seizure reduction at least as great as 80% was obtained in 12 patients including three of complete disappearance (excellent outcome group, Group E). The rest of patients remained at the unsatisfactory reduction less than 80% (not-excellent outcome group, Group NE). As to the interictal EEG outcome by visual inspection of long-term EEGs, a dramatic modification of preoperatively observed BSSWs was unexceptional. No epileptiform discharge was seen in three (discharge-free group, Group F), epileptiform discharges were largely confined to only one hemisphere in eight (unilateral discharge group, Group U), and bilaterally independent epileptiform discharges became evident in eight patients (bilateral discharge group, Group B).

Estimation of the hemispheric CCAP

Fig. 1 represents an example of the estimated CCAPs, where r-CCAP and l-CCAP were referenced or synchronized to the right and left cortical spike discharges, respectively (observed CCAPs). However, because of quasi-synchronous activities of the contralateral hemisphere (as shown by Cont-LSCD or Cont-RCSD in Fig. 1 and bi-directional property of the CC, each CCAP inevitably includes not only the ipsilateral component to the referenced spike activity but also a certain amount of contamination by the contralateral activities. Therefore, say that the hemispheric CCAP to the right hemisphere and quasi-synchronous contralateral one from the left hemisphere are $CCAP_{RR}$ and $CCAP_{RL}$, respectively, and vice versa as shown in Fig. 2, we can formularize as follows;

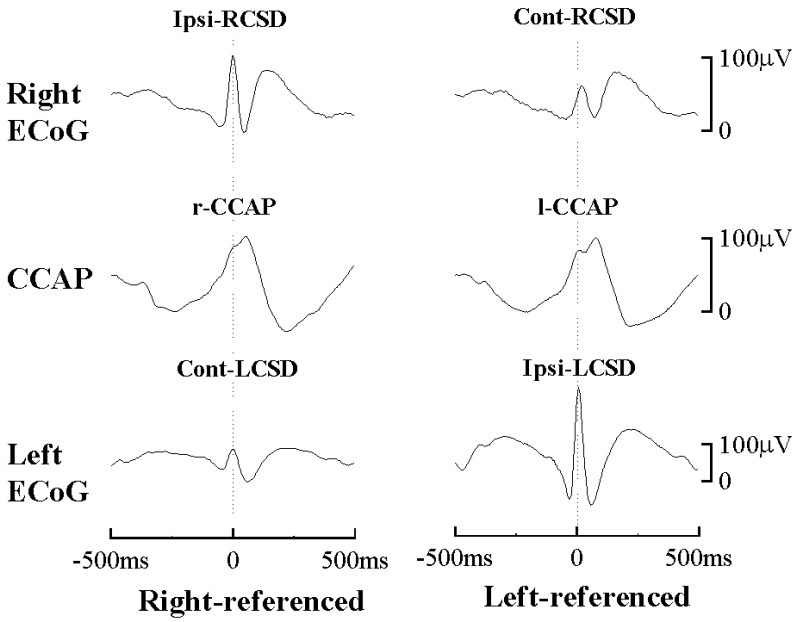

Figure 1. Averaged ECoG and CCAP with a time-alignment to the negative peak of referenced (right or left) cortical spike discharges.

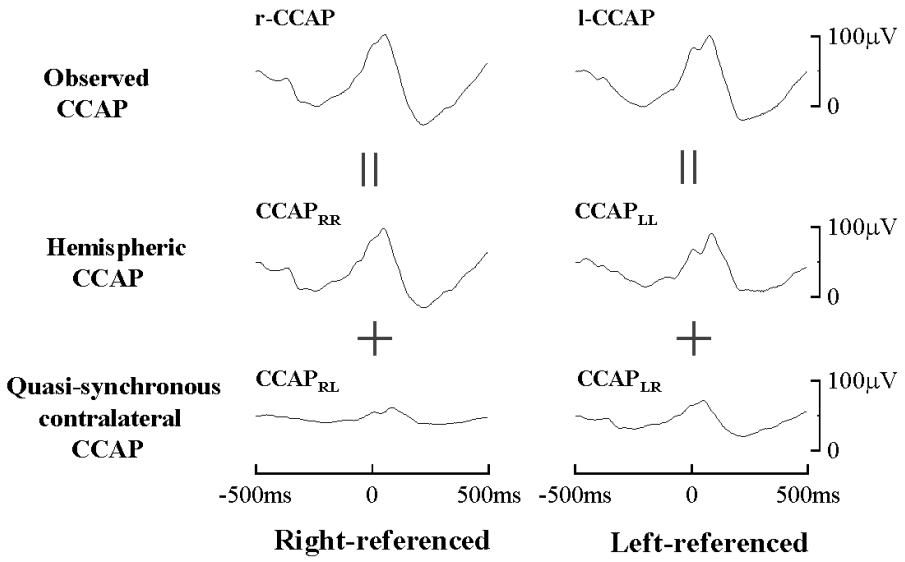

Figure 2. Observed CCAP inevitably includes not only the ipsilateral component to the referenced spike activity but also a certain amount of contamination by the contralateral activities.

$$\text{r-CCAP} = \text{CCAP}_{RR} + \text{CCAP}_{RL}$$
$$\text{l-CCAP} = \text{CCAP}_{LL} + \text{CCAP}_{LR} \quad (1)$$

Then we can assume that the contralateral contribution may be proportional to the magnitude of the contralateral CCAP and the degree of quasi-synchrony, or

$$\text{CCAP}_{LR} = S_{LR} \cdot \text{CCAP}_{RR}$$
$$\text{CCAP}_{RL} = S_{RL} \cdot \text{CCAP}_{LL} \quad (2)$$

The averaged amplitude of the contralaterally referenced cortical spikes (quasi-synchronous Cont-RCSD and Cont-LCSD) is appreciably small by comparison with that of ipsilaterally referenced cortical spikes (completely synchronous Ipsi-RCSD and Ipsi-RCSD). This is due to a considerable fluctuation of the interhemispheric delay of BSSWs, and thus reflects a probability of synchrony. Therefore we can utilize those ratios as the degree of contralateral quasi-synchrony (Synchrony index, SI), that is,

$$S_{LR} = \text{Cont-LCSD / Ipsi-LCSD}$$
$$S_{RL} = \text{Cont-RCSD / Ipsi-RCSD} \quad (3)$$

Solving the simultaneous equations (1) with (2) and (3), the uncontaminated hemispheric CCAPs (CCAP_{RR} and CCAP_{LL}) can be estimated (Fig. 2). They should reflect the neuronal activity of the callosal system specific to each hemisphere during bilateral synchronous epileptiform discharges. Hemispheric difference was assessed with a laterality index (LI) defined as

$$\text{LI} = |(\text{CCAP}_{RR} - \text{CCAP}_{LL}) / (\text{CCAP}_{RR} + \text{CCAP}_{LL})| \quad (4)$$

Under our working hypothesis that the larger number of callosal neurons may be involved during

bilaterally synchronous epileptiform discharges in the more epileptogenic hemisphere, we attempted to correlate LI with seizure outcome and EEG changes after callosotomy. For statistical analysis, Fisher's exact test and Mann-Whitney's U-test was applied to compare groups.

Results

1. Onset age of epilepsy was significantly lower in Seizure-outcome Group NE than group E ($p < 0.05$), but was not significantly different between EEG-outcome Groups (Mann-Whitney's U-test).
2. EEG-outcome Group U+F had significantly higher rate of excellent seizure outcome ($p<0.01$, Fisher's exact test).
3. LI of EEG-outcome Group U+F was significantly higher than that of Group B ($p<0.05$, Mann-Whitney's U-test).
4. LI of Seizure-outcome Group E was significantly higher than that of Group NE ($p<0.01$, Mann-Whitney's U-test).
5. The side of larger CCAP was coincident with the side of postoperative lateralization.

Discussion

Why and How does callosotomy affect seizures?

CC neurons could influence on the widespread cortical activities despite minimal direct contribution to the cortical EEG due to relative rarity of the CC neurons. Transcallosal activation of the CC neurons results in enhancement of the thalamo-cortical responses (1). This effect could be

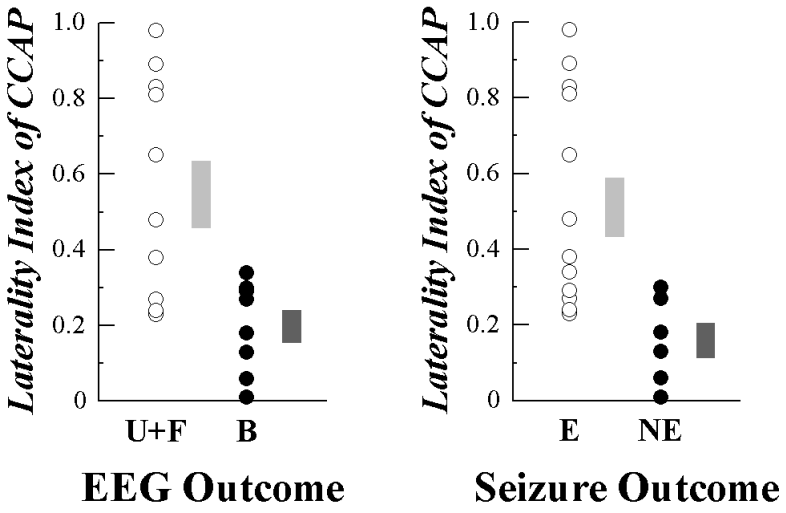

Figure 3. Laterality indices defined as the absolute value of $(CCAP_{RR} - CCAP_{LL}) / (CCAP_{RR} + CCAP_{LL})$ were plotted for each outcome group. Solid bars indicate 99% confidence interval for mean values.

manifested through the ipsilaterally projecting axons of the CC neurons to the thalamo-cortical column neurons. In this scenario, the CC is assumed to have a mutually facilitatory effect that enhances the susceptible state of both hemispheres, leading to bilateral symmetry and synchrony (or nearly so) of the epileptiform discharge (2). The latter could have augmented the tendency to generalized seizure emission. Thus, blockade of transcallosal volleys by callosotomy will reduce basal activities of the formerly CC projecting neurons, and thereby result in less facilitatory influences over the ipsilateral hemisphere through the surviving collaterals.

What does CCAP represent?

Since the corpus callosum simply consists of axonal fibers of callosal neurons, amplitude of hemispheric CCAP selectively reflects the maximal number of recruited callosal neurons during BSSW in each hemisphere, and enables us to determine in which hemisphere they are predominantly involved.

What does LI imply?

A higher LI implies larger hemispheric difference of callosal participation in BSSW, i.e., more callosal neurons are recruited in the more epileptogenic hemisphere during BSSW emission. The epileptogenicity-dominant hemisphere may produce larger transcallosal volleys, and may force contralateral hemisphere up to the susceptible state so as to generate epileptiform discharges synchronously. Results showed that postoperative lateralization of epileptiform discharges and excellent seizure suppression were well coincident and adequately predictable in terms of LI.

Potentiality of preexisting epileptogenicity governs outcomes.

In case that epileptogenicity in both hemispheres is potent enough to maintain irrespective of transcallosal recruitment, bilaterally independent epileptiform discharges would remain after callosotomy (Group B), and clinical seizures would persist (Group NE) as well. Bilaterally potent epileptogenicity may tend to precipitate neuronal recruitment, thereby result in a low LI.

Unilaterally confined potent epileptogenicity would secondarily build up contralateral epileptogenesis over time, and manifest bilateral synchrony through the interhemispheric recruitment mechanism. After callosotomy, the contralateral epileptogenicity would shrink, and epileptiform discharges would be confined to the primary side (Group U).

On the contrary, if the transcallosal facilitation maintains on bilaterally moderate epileptogenicity, callosotomy would completely suppress both clinical seizures and epileptiform discharges (Group F).

Clinical implications

CCAP recordings may give us some information to predict outcomes, though its clinical usability is limited. According to our results, excellent seizure outcome and lateralization of epileptiform discharges may be more expected in cases with higher LI. This finding indicates that outcomes may

be preoperatively predictable, and encourages seeking clinically more applicable factors. Moreover, diagnosis of hemispheric asymmetry in epileptogenesis may help subsequent treatment, e.g., resection of epileptogenic foci emerged after callosotomy.

References

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