

Is a cortical spike discharge “transferred” to the contralateral cortex via the corpus callosum? : An intraoperative observation of electrocorticogram and callosal compound action potentials

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Abstract

Purpose: By means of the intraoperative electrophysiological observation, the authors reevaluated the “transfer” theory that a transcallosal volley invoked by a cortical spike discharge in one hemisphere directly causes its contralateral counterpart via the corpus callosum (CC).

Methods: Twenty-six patients who underwent corpus callosotomy were the subjects of this study. Intraoperatively, electrocorticograms from both hemispheres were simultaneously monitored with callosal compound action potentials (CCAPs) from the CC. Analysis was conducted on (a) the interhemispheric delay of bilaterally synchronous spike and wave discharges (BSSWs), and (b) the chronological relationship between BSSWs and CCAPs.

Results: The side of prior spike discharges was never fixed but was occasionally reversed. Interhemispheric delays between the BSSWs were not constant regardless of direction, and fluctuated in all patients. Most of the interhemispheric delays were distributed within 20 ms with a mode of 0 ms. The waveform of the CCAP was characterized by slow-rising negative potential change that attained its peak following a cortical spike discharge. These findings were identical in all the patients regardless of whether the BSSWs were changed or unchanged after callosotomy.

Conclusions: If the “transfer” role of the CC is true, interhemispheric delays between BSSWs must be longer than interhemispheric axonal conduction time (about 20 ms), and a preceding cortical spike discharge must produce a CCAP and then a contralateral one in order of time. However, this hypothesis was not confirmed in the present study. The authors propose the interhemispheric recruitment of epileptogenic state as a different role of the CC on epileptogenesis.

Introduction

In the epileptic brain, the corpus callosum (CC) is assumed to play a role in the bilateral synchronization of seizure discharge (1-6). In this scenario, the fundamental neural mechanism is expressed as “transfer” of seizure discharges via the CC (1, 2, 6). Other terms, such as “propagation”, “transmission”, “travel”, or “spread” have also been used. However, the meaning of the term “transfer” has not been clearly defined. Some studies have attempted to differentiate between primary and secondary bilateral synchrony by measuring the small time differences between bilaterally synchronous spike and wave discharges (BSSWs) recorded from the two hemispheres (7, 8). The methodological rationale appears to represent a notion that a unilateral cortical spike is transcallosally “transferred” to the contralateral hemisphere as an evoked potential. This view is partly consistent with the post-callosotomy observation of the transformation of BSSWs to lateralized or desynchronized discharge. However, the theory does not explain why and how a reduction or disappearance of BSSWs occurs in some patients (9-11). This raises a serious question as to the validity of the “transfer” theory that the CC is responsible for the bilateral discharge resulting presumably from a unilateral discharge. Thus, a fundamental question of whether a unilateral cortical spike discharge directly produces a contralateral one via the CC remains unanswered.

The CC is a bundle of axons originating from neurons widely distributed but clustered throughout the cortical hemispheres (12). The CC is one of the prominent structures in the brain, and the total number of callosal fibers is estimated at approximately 200 million (13). However, taking into consideration the fact that the cerebral cortex consists of over 15 billion neurons, callosally projecting neurons are no more than a small percentage of the entire pyramidal cell count. Thus, it is reasonable to doubt that a callosal volley may not be adequate to induce a contralateral seizure response. Since scalp EEG spike discharges become visible only if the spatial extent of synchronized activities of cortical neurons

extends more than 6 cm² (14), callosal involvement in cortical spike discharges may not be evident on the EEG. In this context, one approach to critically test the “transfer” theory would be a direct recording of the callosal compound action potentials (CCAPs) during cortical seizure discharges to reveal the extent of callosal participation in cortical seizure discharges.

In this study, the authors carried out intraoperative simultaneous recordings of electrocorticograms (ECoG) and CCAPs in patients with intractable epilepsy undergoing callosotomy. If the hypothesis that a unilateral cortical spike discharge directly produces its contralateral counterpart via the CC is true, the massive transcallosal volley must be invoked by the preceding cortical spike discharge in one hemisphere, and then the contralateral one must be triggered. In this scenario, three findings in relation to ECoG and CCAP would be expected: (a) a unilateral cortical spike discharge must produce firstly a CCAP and then a contralateral one in chronological order, (b) there must be a reasonably constant interhemispheric delay between BSSWs regardless of the laterality of prior spike discharges and (c) the delay must be longer than the minimal value expected from axonal conduction velocity (approximately 20 ms, see below).

Materials and Methods

Patient Selection

Twenty-six patients, 16 male and 10 female, who underwent callosotomy for medically intractable generalized epilepsy were the subjects of this study. In all patients, preoperative EEG showed widespread and, most often, generalized BSSWs. The age at seizure onset ranged from 0.3 to 20 years (mean: 4.9 years), and the age at the time of operation ranged from 2 to 51 years (mean: 16 years). Based on the seizure semiology, neuroimaging study and long-term video-EEG monitoring, the preoperative diagnosis was either symptomatic generalized epilepsy (SGE, 22 cases), or severe myoclonic epilepsy (SME, 2 cases), or frontal lobe epilepsy (FLE, 2 cases). In patients with SGE, four had been diagnosed as West syndrome and eight had characteristic features of Lennox-Gastaut syndrome. In addition to BSSWs, preoperative EEG demonstrated independent multifocal epileptiform

Table 1. Overall patient characteristics.

Gender	
Male	16 (62.5 %)
Female	10 (38.5 %)
Age at seizure onset ^a	4.9 (0.3-15) yr
Age at operation ^{a, b}	16 (2-51) yr
Preoperative diagnosis ^c	
SGE	22 (84.6 %)
SME	2 (7.7 %)
FLE	2 (7.7 %)
Preoperative epileptic activity (EEG) ^d	
BSSW	26 (100 %)
Multi focal discharges	4 (15.4 %)
Operation	
Anterior callosotomy	22 (84.6 %)
Staged total callosotomy	4 (15.4 %)
Postoperative seizure reduction	
> 80 %	14 (53.8 %)
50-80 %	7 (26.9 %)
< 50 %	5 (19.2 %)
Postoperative epileptic activity (EEG) ^d	
BSSW-changed	21 (80.8 %)
No discharge	3 (11.5 %)
Lateralized discharges	10 (38.5 %)
Asynchronous discharges	8 (30.8 %)
BSSW-unchanged	5 (19.2 %)

^a Mean age (range) years.

^b Age at the first operation in 5 patients of staged total callosotomy.

^c SGE, symptomatic generalized epilepsy; SME, severe myoclonic epilepsy; FLE, frontal lobe epilepsy.

^d BSSW, bilateral synchronous spike and wave discharge.

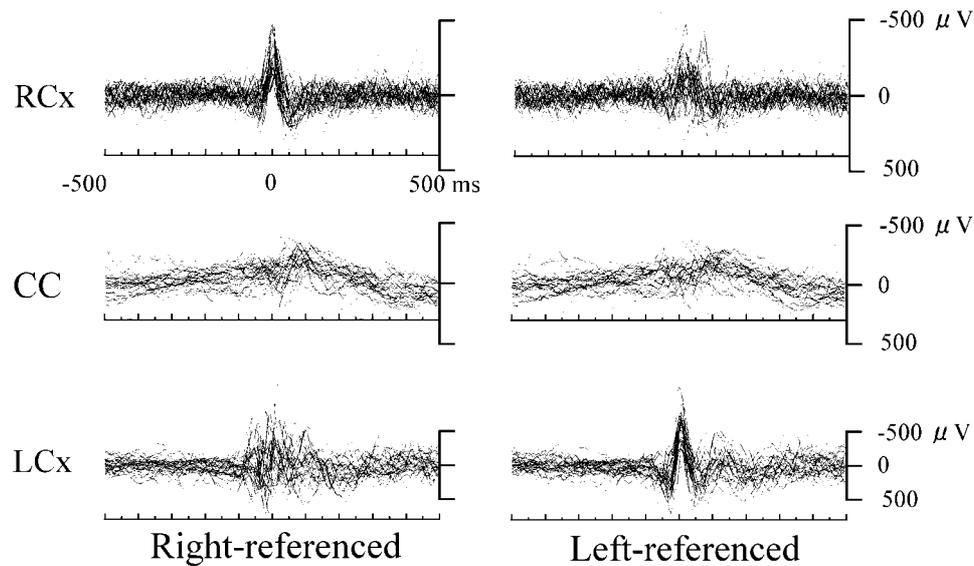


Fig. 1. An example of the superimposed one-second long epochs extracted from ECoGs and CCAPs in which those midpoints were aligned to the referenced negative peak of the cortical spike discharges (right or left). Regardless of the side of reference, interhemispheric delay of the BSSWs was not constant but fluctuated to a considerable degree. The preceding side was not fixed but occasionally reversed. Amplitude difference between left and right hemispheres was due to whether the electrode placement was on the cortex or the dura mater. RCx, right cortex; CC, corpus callosum; LCx, left cortex.

discharges in four patients (2 SGEs and 2 FLEs). Anterior callosotomy was performed in all patients. Of the 26 patients, four had a second operation for posterior callosotomy, i.e., staged total callosotomy, at 5 to 66 months after the first operation, because of insufficient seizure control. Postoperative follow-up periods ranged from 2 to 91 months (mean: 34 months). According to our rating criteria for postoperative seizure frequency as described in a previous paper (15), seizure reduction of at least 80% was obtained in 14 patients, including three with complete disappearance. A reduction of 50-80% or a poor reduction of less than 50% was obtained in seven and five patients, respectively. In all but five patients, postoperative EEG showed dramatic transformation of its BSSWs (BSSW-changed group), as well as no seizure discharge in three, seizure discharges lateralized to one hemisphere only in ten, and bilateral asynchronous independent seizure discharges in eight patients. In the remaining five patients, no apparent postoperative EEG changes were seen (BSSW-unchanged group). Overall patient characteristics are summarized in Table 1.

Surgery and intraoperative electrophysiological study

All patients and their wardship families consented to the surgery and intraoperative electrophysiological study. At anterior callosotomy, a right frontal rectangular craniotomy crossing over the midline was usually performed, but left craniotomy was chosen in two patients, based on angiographical findings. After the dura was reflected medially, both cerebral hemispheres were separated, and the CC was exposed for the length of about 5 cm from the genu of the CC. 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 transcalsal responses were evoked by direct callosal stimuli in order to confirm the extent of the callosal projection and to place cortical electrodes corresponding to the callosal site. At posterior callosotomy, a medial frontoparietal craniotomy was done, and ECoGs from the bilateral frontoparietal lobe and CCAPs from the splenium of the CC were recorded by a similar method. Then, electrophysiological study consisting of simultaneous recordings of ECoG and CCAP was continued for about 15 minutes under 1-2 % sevoflurane general anesthesia. Finally, dissection of the CC according to the preoperative plan was followed.

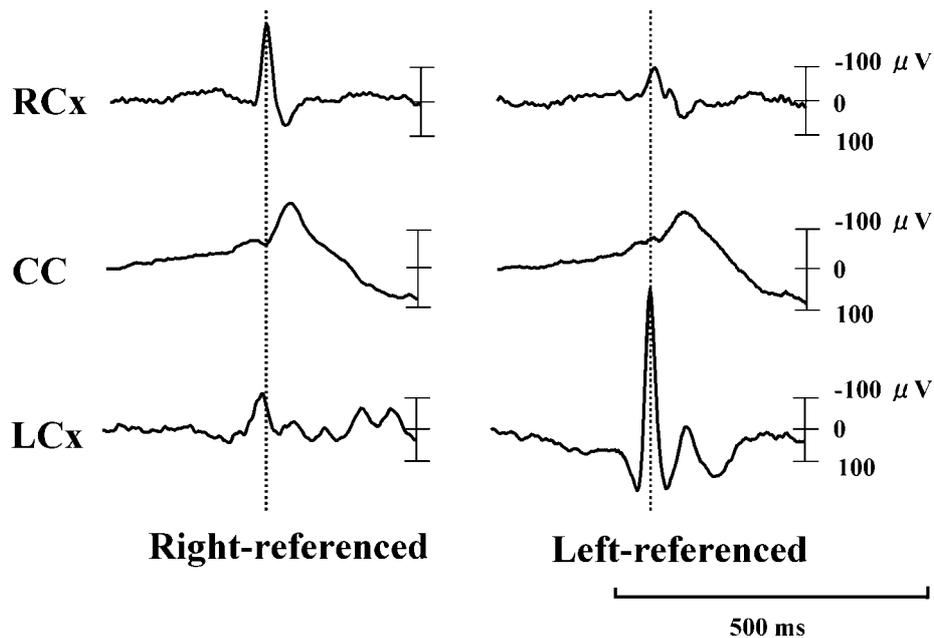


Fig. 2. Averaged patterns of cortical spikes and CCAPs with a time reference to the negative peak of the right or left cortical spike discharges. Irrespective of the side of reference, the waveform of the CCAP was characterized by a slow-rising negative potential change that precedes the cortical spike discharge and continues to increase after it occurs. Amplitude of the contralateral spike discharge was dwarfed because of their fluctuation as shown in Fig. 1. RCx, right cortex; CC, corpus callosum; LCx, left cortex.

Analysis of intraoperative electrophysiological study

The data from the anterior callosotomy were used in 22 patients. In the remaining four patients who underwent the two-staged total callosotomy, intraoperative studies were performed at the second operation (posterior callosotomy). In all patients, the electrophysiological 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 recording from which more prominent cortical spike discharges were recorded (we assigned them RCx and LCx, respectively), and a channel of CCAP recording corresponding to the selected cortical channels were chosen; (2) fifteen to 157 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 superimposed (Fig. 1) and (4) averaged with a time-alignment to the negative peak of referenced (right or left) cortical spike discharges (Fig. 2). Interhemispheric delay was measured for all BSSWs. To depict the fluctuation of delays, a histogram was made up with a 5 ms bin using the values referenced to a peak of the right cortical spike discharge. Concurrent CCAPs with cortical spike discharges were averaged, and the patterns of temporal interrelationship with cortical spike discharges were evaluated. Histograms of interhemispheric delay and the waveforms of CCAP were then compared between the BSSW-changed group (21 patients) and the BSSW-unchanged group (5 patients) to gain insight into the putative pathophysiological differences in generation of BSSWs as suggested by surgical outcome. When possible, non-parametric statistical procedures, such as the Wilcoxon Signed Rank test or the Mann-Whitney U-test, or ridit (relative to an identified distribution) analysis were applied according to need. The results were then evaluated as to whether the working hypothesis described above was fully consistent.

Results

Transcallosal responses by direct CC stimulation

Transcallosal response by direct stimuli to the CC consisted of a positive-negative biphasic potential in all 26 patients. The latency of positive peak was 9.6 ± 1.2 ms and that of negative peak was 32.8 ± 4.4 ms (mean \pm SE), respectively. The length of the callosal fiber from the mid-CC to the intraoperative recording sites measured with magnetic resonance imaging was 5 cm on average.

Distribution of the interhemispheric delay

Superimposed BSSWs consisting of 15-157 (mean: 52.4) epochs were analyzed in every patient. An illustrative case is shown in Fig. 1. Interhemispheric delays were not constant but fluctuated to a considerable degree and always distributed on both sides across 0 ms in all patient. In each individual, maximal and mean interhemispheric absolute delays ranged 40-95 ms (mean: 67.3 ms) and 6.9-30.1 ms

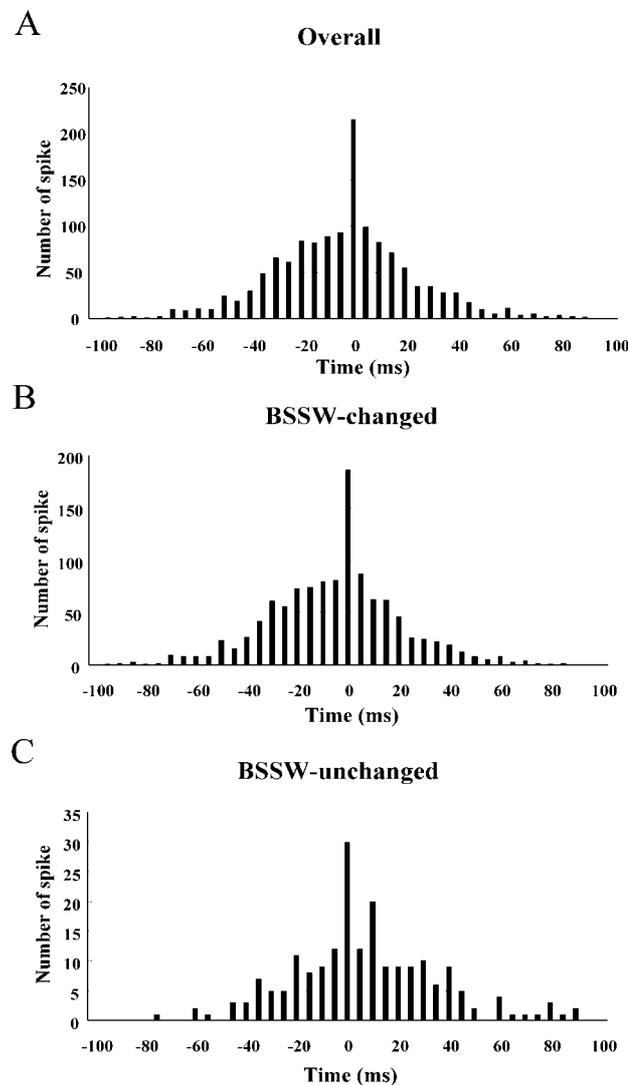


Fig. 3. Grand total histograms of overall (A), BSSW-changed (B) and BSSW-unchanged (C) groups, showing the distribution of interhemispheric delays referenced to a peak of the right cortical spike discharges. All graphs were almost identical and had a mode of 0 ms. Note that a considerable number of spike discharges contralateral to the reference massed within ± 20 ms. There was no significant difference of distribution between BSSW-changed and BSSW-unchanged groups ($p = 0.103$).

(mean: 21.2 ms), respectively. The grand total histogram consisted of 1363 spikes in all 26 patients is shown in Fig. 3A, where the mode of interhemispheric delay was 0 ms, and many spike discharges massed within ± 20 ms. In fact, the mode of individual histograms was 0 ms in all but five patients where it was -30, -10, -5, 5, or 10 ms, respectively. Consequently, there were no case in which the interhemispheric delays distributed around ± 20 ms with no value around 0 ms, as would be expected if the current working hypothesis, i.e., a cortical spike discharge in one hemisphere directly cause the contralateral one, was true.

Waveform of concurrent CCAP with cortical spike discharges

Concurrent CCAPs with cortical spike discharges were identified in 20 patients through an averaging method referenced to cortical spike discharges. The waveform of CCAP was characterized by a slow-rising negative potential change that preceded the cortical spike discharge and continued to increase after it occurred (Fig. 2). As shown in Fig. 4, the following common features among all 20 patients were measured: CCAP preceding time from the onset of negative potential change to the negative peak of the referenced cortical spike discharge, and CCAP peak delay between the negative peak of the referenced cortical spike discharge and the negative peak of the CCAP. The results are summarized in Table 2. Means of right- and left- referenced CCAP preceding time were 117.8 ms (range 10-400 ms) and 114.8 ms (range 0-395 ms), respectively. In the same way, mean CCAP peak delays were 71.3 ms (range 40-110 ms) and 73.2 ms (range 30-115 ms), respectively. There was no significant difference between right- and left-referenced CCAP in terms of the CCAP preceding time and the CCAP peak delay ($p = 0.65$ and $p = 0.35$, respectively). As a result, the expected chronological sequence among bilateral cortical spike discharges and CCAP, i.e., preceding cortical spike - callosal volleys - contralateral cortical spike in chronological order, were not confirmed.

BSSW-changed group vs. BSSW-unchanged group

Interhemispheric delay (Fig. 3B and C) and CCAP waveform (Table 2) of the BSSW-changed and BSSW-unchanged groups were compared. The grand total histograms of interhemispheric delays in both groups were not significantly different (ridit = 0.53, $p = 0.10$) (Fig. 3B and 3C). Both groups showed a mode of 0 ms and interhemispheric delays distributed primarily within ± 20 ms. In 20 patients with a distinctly identified CCAP waveform, 16 were categorized into the BSSW-changed, and four were into the BSSW-unchanged group. The right- or left-referenced mean CCAP preceding time of the BSSW-changed group was 114.0 ms (range 10-400 ms) or 107.8 ms (range 0-395 ms), respectively. Similarly, the mean of BSSW-unchanged group was 132.5 ms (range 45-240 ms) or 142.5 ms (range 50-260 ms), respectively. Whether the referenced side was right or left, the CCAP preceding time was

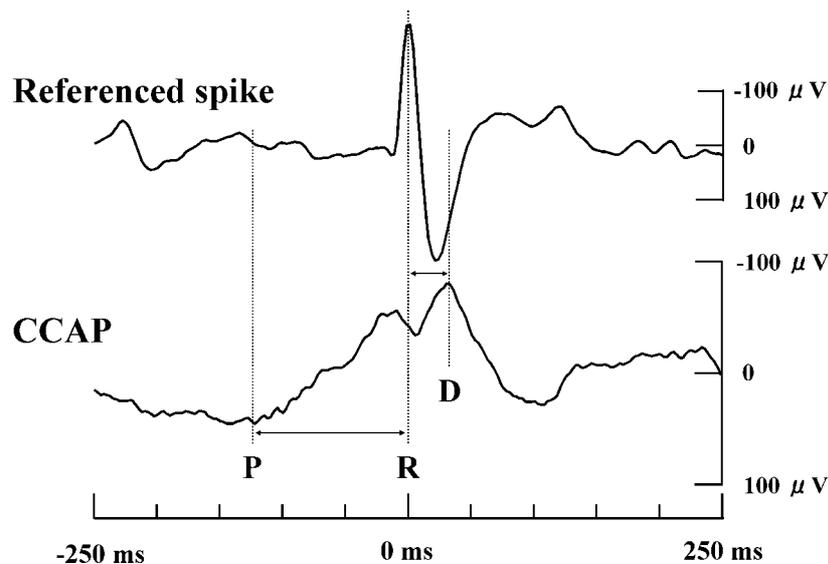


Fig. 4. Measurement of the CCAP preceding time and peak delay. They were defined as the time from the onset of the CCAP negative potential change (P) to the negative peak of the referenced cortical spike discharge (R), and from the negative peak of the referenced cortical spike discharge (R) to the negative peak of the CCAP (D), respectively.

Table 2. CCAP preceding time and peak delay^a

	Overall (n = 20)	BSSW-changed (n = 16)	BSSW-unchanged (n = 4)
Preceding time			
R-ref	117.8 ± 21.3	114.0 ± 25.0 ^b	132.5 ± 43.0 ^b
L-ref	114.8 ± 21.8	107.8 ± 25.3 ^c	142.5 ± 44.2 ^c
Peak delay			
R-ref	71.3 ± 4.5	69.7 ± 5.2 ^d	77.5 ± 9.2 ^d
L-ref	73.3 ± 4.7	73.4 ± 5.7 ^e	72.5 ± 8.3 ^e

R-ref, Right-referenced; L-ref, Left-referenced; BSSW, bilateral synchronous spike and wave discharge.

^a All values were mean ± SE (ms).

^{b-c} There was no significant difference between BSSW-changed and BSSW-unchanged groups (^bp = 0.37, ^cp = 0.45, ^dp = 0.57, ^ep = 0.74).

not significantly different between the two groups (p = 0.37 or 0.45, respectively). The right- or left-referenced mean CCAP peak delay of the BSSW-changed group was 69.7 ms (range 40-110 ms) or 73.4 ms (range 30-115 ms), respectively. Similarly, the mean of the BSSW-unchanged group was 77.5 ms (range 55-95 ms) or 72.5 ms (range 55-95 ms). In addition, the CCAP peak delay was not significantly different between the groups whether the referenced side was right or left (p = 0.57 or 0.74, respectively) (Table 2). Consequently, there was no difference between the groups in regard to interhemispheric delay and concurrent CCAP with BSSW.

Discussion

If a cortical spike discharge in one hemisphere directly causes its contralateral counterpart via the CC, as an evoked potential, the interhemispheric delay (time difference between BSSWs) must be reasonably constant and, at least, longer than an expected axonal conduction time. In our intraoperative study, transcallosal responses at the cortical surface evoked by stimuli to the CC showed positive-negative waveforms whose latency was about 10 ms and 30 ms, respectively. Moreover, the length of the callosal fiber from mid-CC to the intraoperative recording sites measured with magnetic resonance imaging was about 5 cm, and axonal conduction velocity of the human CC was reportedly about 5 mm/ms (13). These data suggest that the expected callosal conduction time should be approximately 20 ms or longer. Therefore, a histogram of the interhemispheric delays should show two symmetrical peaks about a delay longer than ±20 ms and with no value around 0 ms. Our results were not consistent with this expectation. A grand total histogram of all patients showed a relatively wide and single-peaked distribution with a mode of 0 ms, and a considerable number of spike discharges contralateral to the reference massed within ±20 ms. Similar findings were commonly confirmed in both the BSSW-changed and BSSW-unchanged groups. Therefore, it is improbable that a unilateral cortical spike discharge directly produces a contralateral one via the CC, in spite of clear callosal contribution to the generation of BSSW as revealed by callosal section at least in the BSSW-changed group. We may need an alternate explanation for the mechanism of callosally mediated secondary bilateral synchrony. In the BSSW-changed group, one must accept clear contribution of the CC for the transformation of BSSWs. Results of our novel approach by concurrent monitoring of CCAPs with cortical spike discharge casts a serious doubt about the validity of the “transfer” role of the CC. If the hypothesis that a transcallosal volley invoked by a cortical spike discharge in one hemisphere directly causes the contralateral counterpart is true, a unilateral cortical spike discharge must produce a CCAP and then a contralateral spike in order of sequence. However, waveforms of CCAP showed a slow-rising negative potential change that preceded the cortical spike discharge and continued to increase after it occurred. Although the preceding side of the cortical spike discharges was occasionally reversed in all the patients, the mean of the interhemispheric delays was about 20 ms, whereas mean CCAP preceding time and peak delay were about 110 ms and 70 ms, respectively. This indicated that callosal potential change, contrary to the hypothesis, led the cortical spike discharges. Because these findings were identical between the BSSW-changed and BSSW-unchanged groups, one cannot postulate a different contribution of the CC on BSSW generation between these two groups. The waveform of CCAP suggested that callosally projecting pyramidal neurons (probably in both hemispheres) begin to fire about 100 ms prior to the cortical spike discharges, and gradually recruit other allied neurons to a certain degree (slow-rising negative potential), resulting in bilateral cortical spike discharges. Callosal

firing continues to increase thereafter for about 70 ms up to a maximum level (delayed peak). Anatomically, callosally projecting neurons are widely distributed but clustered according to the architectonic concept of columnar organization of the cerebral cortex (12, 16). Callosal neurons not only project contralaterally but also have rich collateral projections to the ipsilateral hemisphere (17). Therefore, it is reasonable to assume that this slow-rising negative potential of the CCAP reflects a gradual recruitment of callosal neurons and, at the same moment, other pyramidal neurons in widely extended areas of both hemispheres might also be built up to generate seizure discharges (interhemispheric recruitment).

As mentioned above, it was confirmed that a considerably large proportion of BSSWs occurs in both hemispheres at almost the same moment even in patients diagnosed, by definition, as the secondary generalized epilepsy. This raises the question: How do BSSWs take place virtually simultaneously over an extended space? There are some hypotheses that subcortical structures such as the thalamus or the brain stem play an important role in bilateral synchrony (1, 18-20). However, this would not explain the nature of post callosotomy change of BSSWs. Clinical and EEG outcomes of callosotomy clearly indicate that the CC must have played a major role in the BSSW-changed group at least. However, transfer of seizure discharges, as traditionally assumed, is not responsible for bilateral synchrony. We propose here our interhemispheric recruitment theory whereby preexistent epileptogenesis in both hemispheres mutually interact to recruit cortical neurons up to a spike-induction threshold via the CC, and then BSSWs are produced at almost the same moment. For this to occur, we assume cortical epileptogenesis must be present bilaterally regardless of its cause and temporal nature such as secondary epileptogenesis (21).

The “transfer” role of the CC has traditionally been supported by postoperative EEG changes after callosotomy, i.e., lateralization or desynchronization of preoperatively observed BSSWs (9-11, 22, 23). However, it does not explain reported marked reduction or disappearance of seizure discharges themselves in some patients (9-11). If the fundamental role of the CC on BSSW generation is not one of “transfer”, what are the alternative explanations for those postoperative EEG changes? Our proposed interhemispheric recruitment theory assumes pre-existence of a cortical epileptogenic susceptibility in both hemispheres. The degree and extent of susceptibility may be asymmetrical, but if they are sufficiently strong to maintain itself without transcallosal recruitment, unilateral or bilateral discharges would remain after callosotomy. On the other hand, in those patients whose hemispheric susceptibility may require transcallosal recruitment to maintain epileptogenesis, the BSSWs would be decreased or even abolished completely after callosotomy. It has been reported that the CC has a facilitatory as well as an inhibitory effect on epileptogenesis (24). Experimentally, coexisting multiple epileptic foci enhanced each other, and especially, bilateral symmetric foci displayed a mutual facilitation that resulted in the production of BSSWs (5, 25). Thus, the authors additionally consider that interhemispheric recruitment implies a transcallosal facilitatory effect. Taken together, we postulate that persistent neuronal volleys via the CC from both susceptible hemispheres mutually facilitate, modulate and maintain epileptogenesis in each hemisphere for emission of BSSWs (and possibly clinical seizures).

In conclusion, the “transfer” hypothesis that a transcallosal volley invoked during a cortical spike discharge in one hemisphere directly causes the contralateral one via the CC was not confirmed by the present study involving intraoperative observation of simultaneous ECoG and CCAP monitoring of BSSWs. The authors propose that an interhemispheric recruitment of epileptogenic state via the CC system accounts for the bilateral synchrony and postoperative EEG changes following callosotomy. In other words, the term “transfer” may not represent the transfer of seizure discharges but rather the facilitation of an epileptogenic susceptible state.

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