ORIGINAL ARTICLE

Cortical Excitability in Temporal Lobe Epilepsy with Bilateral Tonic-Clonic Seizures

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ABSTRACT: ***Objective:*** We investigated motor cortical excitability (CE) in unilateral temporal lobe epilepsy (TLE) and its relationship to bilateral tonic-clonic seizure (BTCS) using paired-pulse transcranial magnetic stimulation (TMS). ***Methods:*** In this cross-sectional study, we enrolled 46 unilateral TLE patients and 16 age-and sex-matched healthy controls. Resting motor thresholds (RMT); short-interval intracortical inhibition (SICI, $GABA_A$ receptor-mediated); facilitation (ICF, glutamatergic-mediated) with interstimulus intervals (ISIs) of 2, 5, 10, and 15 ms; and long-interval intracortical inhibition (LICI, $GABA_B$ receptor-mediated) with ISIs of 200–400 ms were measured via paired-pulse TMS. Comparisons were made between controls and patients with TLE, and then among the TLE subgroups (no BTCS, infrequent BTCS and frequent BTCS subgroup). ***Results:*** Compared with controls, TLE patients had higher RMT, lower SICI and higher LICI in both hemispheres, and higher ICF in the ipsilateral hemisphere. In patients with frequent BTCS, cortical hyperexcitability in the ipsilateral hemisphere was found in a parameter-dependent manner (SICI decreased at a stimulation interval of 5 ms, and ICF increased at a stimulation interval of 15 ms) compared with patients with infrequent or no BTCS. ***Conclusions:*** Our results demonstrate that motor cortical hyper-excitability in the ipsilateral hemisphere underlies the epileptogenic network of patients with active BTCS, which is more extensive than those with infrequent or no BTCS.

RÉSUMÉ : L'excitabilité corticale dans l'épilepsie du lobe temporal, accompagnée de crises tonico-cloniques bilatérales. ***Objectif*** **:** L'étude portait sur l'excitabilité corticale (EC) motrice dans l'épilepsie du lobe temporal (ELT) unilatérale et sur la relation avec les crises tonico-cloniques bilatérales (CTCB), à l'aide de la stimulation magnétique transcrânienne (SMT) à impulsion double. ***Méthode*** **:** Il s'agit d'une étude transversale, à laquelle ont participé 46 patients atteints d'ELT unilatérale et 16 témoins en bonne santé, appariés selon l'âge et le sexe. Ont été mesurés, à l'aide de la SMT à impulsion double, les seuils moteurs au repos (RMT), l'inhibition intracorticale à intervalles courts (IICIC; médiée par les récepteurs du $GABA_A$), la facilitation intracorticale (FIC; à médiation glutamatergique) à des intervalles inter-stimuli (IIS) de 2, 5, 10 et 15 ms ainsi que l'inhibition intracorticale à intervalles longs (IICIL; médiée par les récepteurs du $GABA_B$) à des IIS variant de 200 à 400 ms. Des comparaisons ont été établies entre les témoins et les patients atteints d'ELT, puis entre les sous-groupes de sujets atteints d'ELT (pas de CTCB; peu de CTCB; beaucoup de CTCB). ***Résultats*** **:** Comparativement aux témoins, les patients atteints d'ELT avaient des RMT plus élevés, une IICIC plus basse et une IICIL plus élevée dans les deux hémisphères ainsi qu'une FIC plus élevée dans l'hémisphère ipsilatéral. Chez les patients présentant beaucoup de CTCB, l'hyperexcitabilité corticale dans l'hémisphère ipsilatéral s'est révélée dépendante des paramètres (diminution de l'IICIC à un intervalle de stimulation de 5 ms, et augmentation de la FIC à un intervalle de stimulation de 15 ms) comparativement aux patients présentant peu ou pas de CTCB. ***Conclusion*** **:** Les résultats de l'étude ont démontré que l'hyperexcitabilité corticale motrice dans l'hémisphère ipsilatéral est sous-jacente au réseau épileptogène chez les patients atteints de CTCB actives, réseau plus étendu dans ce dernier sous-groupe que dans ceux ayant peu ou pas de CTCB.

Keywords: Temporal lobe epilepsy, Bilateral tonic-clonic seizure, Motor threshold, Cortical excitability, Short-interval intracortical inhibition and facilitation, Long-interval intracortical inhibition

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Introduction

Temporal lobe epilepsy (TLE) is a common type of focal epilepsy, and the global incidence of pharmacoresistant epilepsy is about 20–30%.[1] About 70% of patients with TLE experience bilateral tonic-clonic seizures (BTCS), which is the most debilitating seizure type.[2] BTCS prominently impair cognition and social function[3] and results in a lower quality of life.[4] Frequent BTCS are likely linked to suffering from postictal cardiac autonomic disturbance[5] and generalized electroencephalograph (EEG) suppression,[6] which increases the risk of sudden unexpected death in epilepsy.

Resective surgery has a favorable prognosis in pharmacoresistant TLE, while a history of BTCS is a negative predictor for seizure freedom after surgery. About 36–81% of patients

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with BTCS experience seizure recurrence within 1–2 years after anterior temporal lobectomy,[7-10] suggesting that patients with BTCS had a more extensive epileptogenic network compared to those without BTCS.[9,11] Hence, identifying the potential abnormal network or pathways of TLE with BTCS may provide useful information in planning surgery and improving the surgical outcome. Many studies have identified functional and structural changes beyond the epileptogenic zone in patients with BTCS.[2,5,6,12,13] One cerebral blood flow study found that cortical (the fronto-parietal cortex) and subcortical structures (cerebellum, basal ganglia, brainstem and thalamus) were involved in the transition from focal seizures to BTCS in patients with TLE and extra-TLE.[2] Some intracranial electrophysiological and neuroimaging studies have also demonstrated that BTCS affected specific cortical structures, such as the fronto-parietal cortex and temporal lobe, while other structures were relatively spared.[2,14] Our previous studies based on structural neuroimaging have shown that TLE patients with BTCS had an additional atrophy in the medial thalamus and a disrupted hippocampal-thalamic pathway;[12,13] however, cortical structural abnormality was not prominent using a voxel-based morphometry study in our cohort.[13] These subtle cortical alterations await further examination.

Transcranial magnetic stimulation (TMS) is applied to detect the relatively subtle changes of physiological state,[15] and has long been used to assess motor cortical excitability (CE) in epilepsy, both to investigate the pathophysiologic process of disease and effects of antiepileptic drugs (AEDs).[16] TMS can noninvasively measure both inhibition and excitation of cortical functions separately using different stimulation parameters.[15] Here, we aimed to explore the motor CE in TLE and to investigate its alteration related to the occurrence of BTCS using TMS, which may give insights into the BTCS network in TLE.

MATERIALS AND METHODS

Patients

This prospective, cross-sectional study was approved by the Ethics Committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University and all participants provided informed consent. Consecutive patients with unilateral TLE were enrolled in our epilepsy center from June 2015 to July 2017. They were diagnosed by at least two experienced epileptologists based on their history, seizure semiology, long-term scalp video-EEG monitoring, and imaging findings. Typical focal seizures to BTCS was identified by at least two epileptologists based on a review of the seizure video. Accordingly, the whole cohort was categorized into BTCS and non-BTCS groups. Subsequently, the frequency of seizures was estimated using seizure diaries and family reports, and the BTCS group was further subdivided into frequent-BTCS (at least 3 times per year) or infrequent-BTCS subgroups (< 3 times per year).[12] Patients aged 15–37 years were included to maintain homogeneity across groups. Patients were excluded for the following reasons: 1) history of brain trauma or surgery, or other massive structural lesion in the brain; 2) ambiguous history of BTCS; 3) seizures arising from the temporal lobe, contralateral to the imaging lesion; 4) bilateral TLE; and 5) dual pathology.

Data Acquisition and Analyses

Clinical, imaging, EEG, histopathology, and surgical outcome data were collected. Focal seizure frequency was categorized as frequent (at least once a week) or infrequent (less than once a week). Video-EEG was performed, with scalp electrodes placed according to the international 10–20 systems, and the findings were analyzed by epileptologists and EEG technicians. The final report was prepared by epileptologists. All patients underwent MRI using an epilepsy protocol (3.0 T). The findings of the noninvasive evaluation and surgical plans were discussed during a routine multidisciplinary patient management conference.

Because AEDs, especially sodium channel-blocker AEDs, influence motor CE,[16,17] we employed three indicators to measure the AED dose: total drug load; sodium channel drug load; and number of currently prescribed AEDs. Drug load for each drug was computed as the percentage of prescribed daily dose (PDD) divided by defined daily dose (DDD) according to WHO guidelines.[18] DDD is an average maintenance dose per day for a drug in adults; the data is available at http://www.whocc.no/atc_ddd_index/. Total drug load was estimated by the sum of all AED loads per patient.[16] Sodium channel blockers included carbamazepine, lamotrigine, phenytoin, and oxcarbazepine. Sodium channel drug load was estimated by the sum of all sodium channel-blocker AED loads per patient.

Transcranial Magnetic Stimulation

Both hemispheres were examined in each participant. In order to reduce lateralization differences, we showed the results of both dominant and non-dominant hemispheres as a reference for analysis and compared the findings in our patients. All participants sat in a comfortable, reclining chair. Surface electromyographic (EMG) recordings were obtained from the abductor pollicis brevis muscle (APB). The contralateral cerebral hemisphere was stimulated by applying flow in the appropriate direction for the coil current (i.e. if right hemisphere was dominant, the direction of the current in the coil was clockwise; while the direction was anticlockwise if the left hemisphere was dominant), using a 12.6-cm diameter parabolic circular MMC-140-II coil (Magventure) with the center of the coil positioned over the vertex and held in a plane tangential to it using a pair of MagPro X100 magnetic stimulators (MagVenture, Farum, Denmark). Paired magnetic stimulation at various interstimulus intervals (ISIs) was applied using a Bistim module to connect 2 stimulators to the coil.

To avoid any effect of diurnal variation in CE, all studies were performed between 10 am and 3 pm. Similarly, to avoid any hormonal effects across the menstrual cycle, female participants were enrolled during their luteal and follicular periods. All participants were requested to maintain regular sleep patterns with 7–9 hours of sleep the night before the test, and the results were only analyzed after a minimum of 3 days of freedom from seizures and 14 days from the last BTCS on either side.

Resting motor thresholds (RMT) were determined for each hemisphere while the participant was at rest and were verified by continuous visual and auditory EMG feedback. Stimulation commenced at 30% of the maximum output and was increased

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Table 1: Demographics of TLE patients included in each group

Variables	All (N = 46)	Non-BTCS (N = 21)	Infrequent-BTCS (N = 14)	Frequent-BTCS (N = 11)	*p* value
Gender, F	17	8	5	4	0.299
Age at onset	17.56 ± 8.15	18.19 ± 8.09	16.86 ± 8.16	17.26 ± 9.71	0.946
Epilepsy duration, Y	10.45 ± 8.13	10.34 ± 8.04	11.36 ± 9.27	10.18 ± 5.58	0.513
Lateralization, L	24	11	8	5	0.482
Frequency of partial seizures (frequent)	23	12	7	4	0.512
MRI findings (HS)	22	9	6	6	0.819
Subsequent surgery	19	8	6	5	0.870
Total drug load	1.33 ± 1.09	1.25 ± 0.70	1.19 ± 1.14	1.63 ± 1.59	0.570
Sodium channel drug load	0.53 ± 0.46	0.54 ± 0.37	0.55 ± 0.62	0.52 ± 0.43	0.991
Number of AEDs	1.91 ± 0.95	2.04 ± 1.02	1.76 ± 0.83	1.82 ± 0.98	0.67

TLE = temporal lobe epilepsy; BTCS = bilateral tonic-clonic seizure; F = female; Y = year; L = left; HS = hippocampal sclerosis; AEDs = antiepileptic drugs.

in 5% increments until the motor-evoked potential (MEP) was established. Changes in intensity by 1% were then used to measure the threshold value. RMT was defined as the lowest level of stimulus intensity that produced a MEP of peak-to-peak amplitude >100 μV in the target muscle on ≥50% of 10 trials.[19,20]

Intracortical inhibition and facilitation: short interval intracortical inhibition (SICI), intracortical facilitation (ICF) and long-interval intracortical inhibition (LICI) were measured, using pairs of conditioning and test stimuli provided in a random order at each ISI (SICI at ISIs 2 ms/5 ms, ICF at 10 ms/15 ms, LICI at 200 ms/250 ms/300 ms/350 ms/400 ms). The conditioning stimulus was delivered at 80% of the RMT and the test stimulus was delivered at 20% above the RMT. Ten stimuli were also delivered at 20% above the RMT without a preconditioning stimulus. For longer ISIs, the stimulation intensity was set at 20% above the RMT using paired stimuli in 50 ms increments at ISIs of 200–400 ms. A minimum delay of 15 s was ensured between each pair of stimuli. Stimuli were delivered at randomly selected ISIs until ten samples for each ISI were obtained.

Curves at short ISIs (2–15 ms) were constructed for each hemisphere using the ratio of the mean peak-to-peak amplitude of the response (termed the test response [TR]) observed at each ISI after the conditioning stimulus (given below the RMT); the measurements were expressed as the percentage of the mean MEP when the test stimulus was given alone without a preconditioning stimulus (TR/MEP%). Curves at longer ISIs (200–400 ms) were constructed for each hemisphere using the ratio of the mean peak-to-peak amplitude of the response to the test stimulus (termed the test response [TR]) and the response to the conditioning stimulus (termed the conditioning response [CR]) at each ISI; the measurements were indicated as a percentage (TR/CR%). Ratios <100% indicate inhibition and ratios >100% indicate facilitation.

In addition, none of the patients experienced seizures during or up to 8 hours after the TMS study. The results from the controls were analyzed according to the dominant hemisphere (e.g. left hemisphere for right-hand dominance). In patients, the results were analyzed based on the ipsilateral (hemisphere with presumed seizure focus) and contralateral hemispheres according to the electro-clinical and neuroimaging findings.

Statistical Methods

SPSS 24.0 software was used for statistical analysis. All continuous variables were first tested using a homogeneity test for variance and a test of normality. According to the results, normal variables were presented as mean±standard deviation (SD); non-normal variables were reported as medians (interquartile range). Categorical variables were expressed as frequencies. Comparisons between two groups were made using Student's *t*-test or nonparametric Mann-Whitney U test; comparisons among three or more groups were analyzed with one-way analysis of variance (ANOVA) or nonparametric Kruskal-Wallis test. A Chi-square test was used for categorical variables (Table 1). For the RMT, SICI, ICF, and LICI values, between-group differences were evaluated using one-way ANOVA followed by the post-hoc LSD pair-wise comparison test if the data were normally distributed and the variance was homogeneous; in other cases, Kruskal-Wallis analyses were used. A p value of < 0.05 was considered statistically significant.

Results

Patient Demographics

A total of 46 TLE patients and 16 healthy controls were enrolled. There was no difference between healthy controls and patients with TLE in terms of gender (male %: 56.3 % vs. 60.9 %, $p = 0.774$) or age (24.31 ± 5.15 vs. 27.93 ± 7.37 years, $p = 0.075$). There were also no differences among the non-BTCS, infrequent-BTCS and frequent-BTCS subgroups in TLE, in terms of the age at onset, epilepsy duration, seizure lateralization, seizure frequency, MRI findings or AED treatment (Table 1). Of 46 patients, 17 were female and 19 patients underwent subsequent anterior temporal lobectomy. The mean age at seizure

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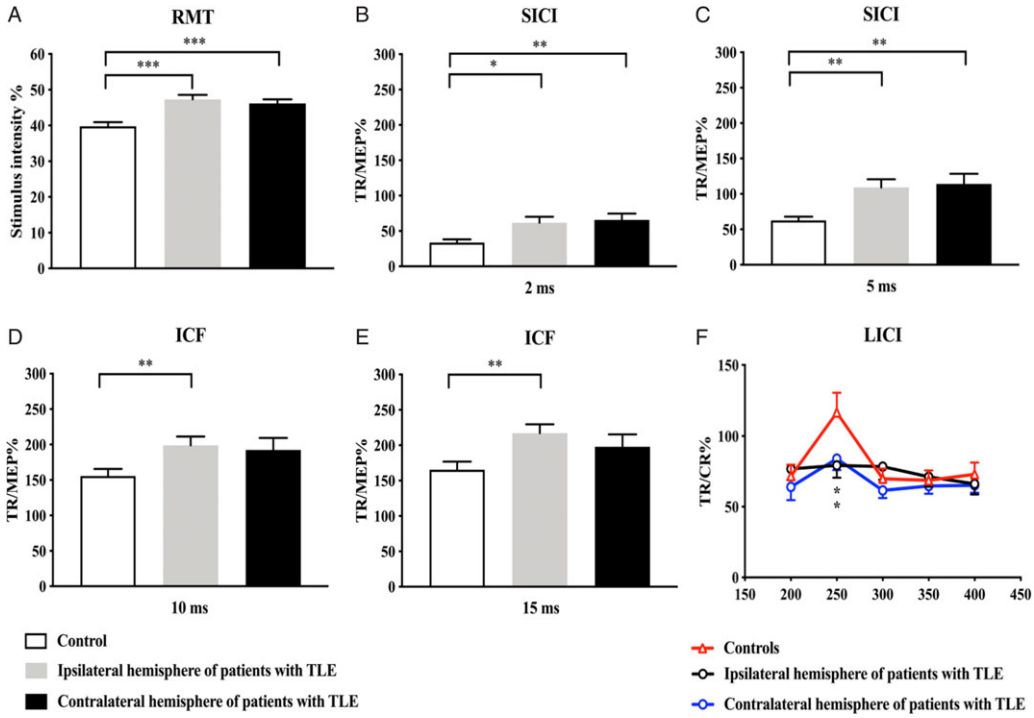

Figure 1: *Cortical excitability in TLE patients and healthy controls.* ***A.*** *Resting motor threshold.* ***B.*** *Short-interval intracortical inhibition (ISI 2 ms).* ***C.*** *Short-interval intracortical inhibition (ISI 5 ms).* ***D.*** *Intracortical facilitation (ISI 10 ms).* ***E.*** *Intracortical facilitation (ISI 15 ms).* ***F.*** *Long-interval intracortical inhibition (ISI 200–400 ms). ISI = interstimulus interval. Data are presented as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001.*

onset was 17.56 ± 8.15 years, mean epilepsy duration at surgery was 10.45 ± 8.13 years, and the age at TMS measurement ranged from 15 to 37 years. The MRI findings were as follows: hippocampal sclerosis in 22 patients, small tumor in five patients, amygdala enlargement in six patients, negative result in eight patients, vascular malformation in one patient, cysts or malacia in two patients, focal cortical dysplasia in one patient, and encephalocele in one patient. There was no significant difference in the presence of BTCS between patients with hippocampal sclerosis versus other etiologies ($p = 0.819$).

Comparison between Controls and Patients with TLE

Compared to the healthy controls, among TLE patients, the RMT was greater in both hemispheres (both $p < 0.001$, Figure 1A), the SICI was lower at ISIs of 2 ms ($p = 0.016$, Figure 1B) and 5 ms ($p = 0.002$, Figure 1C), and the ICF was higher at ISIs of 10 ms ($p = 0.009$, Figure 1D) and 15 ms ($p = 0.003$, Figure 1E) in the ipsilateral hemisphere, whereas the SICI was lower at ISIs of 2 ms ($p = 0.002$, Figure 1B) and 5 ms ($p = 0.007$, Figure 1C) in the contralateral hemisphere. A higher LICI was observed in both hemispheres at an ISI of 250 ms (both $p < 0.05$, Figure 1F).

Comparison of Subgroups in TLE

There were no intergroup differences in the RMT, SICI at an ISI of 2 ms, ICF at an ISI of 10 ms or LICI (not presented) (Figure 2A-B, D). In ipsilateral hemispheres of frequent BTCS, the SICI at an ISI of 5 ms was lower than that in ipsilateral hemispheres of infrequent-BTCS ($p = 0.003$, Figure 2C) and non-BTCS subgroups ($p = 0.014$, Figure 2C), while the ICF at an ISI of 15 ms was greater than that in ipsilateral hemispheres of non-BTCS ($p = 0.017$, Figure 2E). Moreover, in contralateral hemispheres of frequent BTCS, the SICI at an ISI of 5 ms was lower ($p = 0.01$, Figure 2C), and the ICF at an ISI of 15 ms was greater, as compared to that in the contralateral hemisphere of infrequent-BTCS ($p = 0.022$, Figure 2E).

Discussion

Transcranial magnetic stimulation (TMS) has been widely used to measure CE in epilepsy patients.[15] CE in genetic generalized and focal epilepsy has been extensively reported, predominantly in terms of the pathophysiologic process of disease and the drug response.[21] Although TMS parameters vary somewhat between studies, cortical hyperexcitability appears to be a common feature in epilepsy.[21] However, to our knowledge, the studies on CE of BTCS in focal epilepsy are limited. Here, we present the first demonstration of different patterns of motor CE across different BTCS susceptibilities in TLE.

In the present study, the RMT was greater in both hemispheres of TLE patients compared to non-epilepsy controls, consistent with results from previous studies in patients with chronic epilepsy.[19,20] RMT value primarily reflects the neuronal membrane excitability and Na^+ channel conductivity.[19,22] The increased RMT observed in both genetic generalized and focal epilepsy could be interpreted as an antiepileptic mechanism due to the consequence of multiple AEDs.[19,23,24] This antiepileptic effect seems to increase the excitability threshold.

CE could be measured with other TMS parameters, such as SICI and ICF, most likely representing the $GABA_A$ receptor-mediated inhibition and glutamate receptor-mediated excitation,

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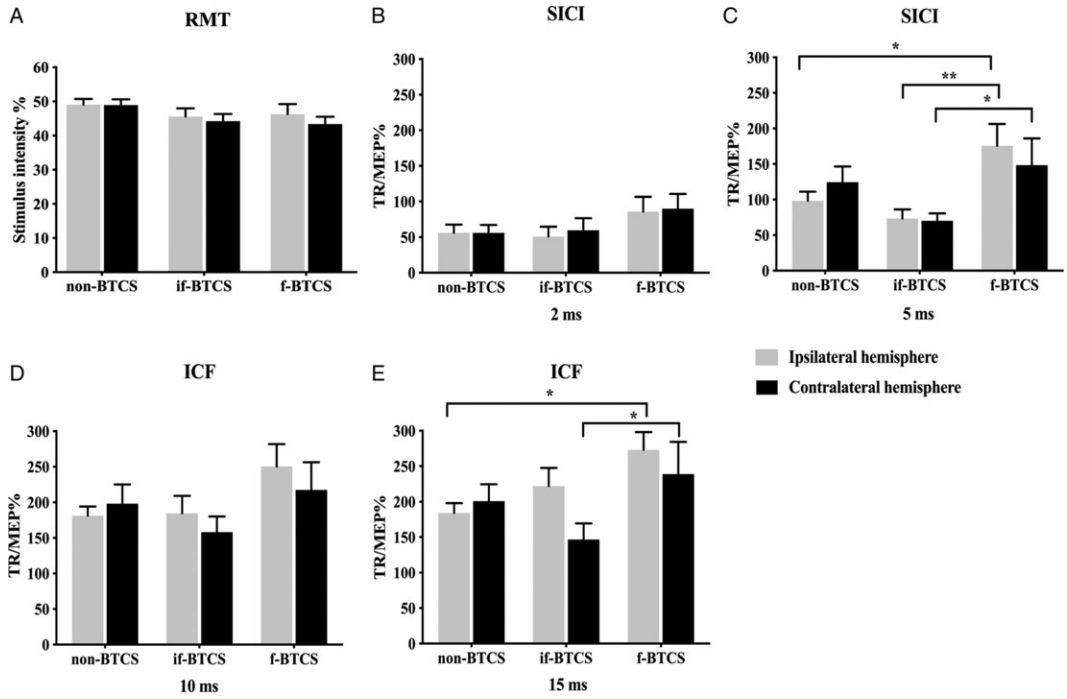

Figure 2: *Cortical excitability in both hemispheres of subgroups in TLE.* ***A.*** *Resting motor threshold.* ***B.*** *Short-interval intracortical inhibition (ISI 2 ms).* ***C.*** *Short-interval intracortical inhibition (ISI 5 ms).* ***D.*** *Intracortical facilitation (ISI 10 ms).* ***E.*** *Intracortical facilitation (ISI 15 ms). ISI = interstimulus interval, if-BTCS = infrequent bilateral tonic-clonic seizure, f-BTCS = frequent bilateral tonic-clonic seizure. Data are presented as mean ± SEM. *p < 0.05, **p < 0.01.*

respectively.[17,19] In our cohort, increased CE was observed using SICI and ICF in both hemispheres of TLE compared to controls and was prominent in the ipsilateral hemisphere. These findings were in line with previous studies comparing CE in TLE patients with controls.[19] In addition, we also found a similarly increased CE in the ipsilateral hemisphere of the frequent-BTCS subgroup, relative to the infrequent-BTCS and non-BTCS subgroups. These results show that the changes of CE were likely to be influenced by BTCS in TLE, and CE increases with the seizure severity. Decreased SICI and increased ICF in this study represented the dysfunction of $GABA_A$ and glutamate receptors in the motor cortex. The epileptic process has been thought to be mediated by the disturbance of neuronal inhibitory/excitatory balance, leading to the formation of hyperexcitable networks.[25] The network beyond the epileptogenic zone has also influenced the motor cortex.[19] These findings have been supported by animal and human studies.

For example, in rat hippocampus, tonic-clonic seizures occurred when inhibitory GABA release decreased and excitatory glutamate release increased, and reduced GABA was responsible for the increase of glutamate levels.[26] Other studies have shown that promoting glutamate cycling contributed to progression from focal seizures to BTCS.[27] Furthermore, the GABA subunit mutation could induce increased ICF in humans,[28] which has been found to be associated with genetic generalized epilepsy.[29] Our previous study also reported that mesial TLE patients with uncontrolled BTCS showed more pronounced atrophy in the medial thalamus, relative to those with controlled BTCS.[12] In this context, frequent BTCS may cause irreversible damage in the cortical network, and the dysfunction in the cortex beyond the epileptogenic zone may consequently lead to the genesis of BTCS or to secondary progressive changes in TLE. Overall, our findings underscore that cortical hyperexcitability increases with the severity of disease in TLE. The cortical hyperexcitability in frequent-BTCS underlies the extensive epileptogenic network.

Interestingly, compared to controls, bilateral decreased CE was observed on LICI data (ISI at 250 ms) in TLE, possibly mediated by $GABA_B$ receptors. Differences in LICI between TLE and controls were reported in several studies previously. Consistent with our results, a recent article has shown that the CE was weakest for poorly controlled TLE, followed by well-controlled TLE and healthy individuals at 50, 150, and 200 ms, respectively.[30] The participant cohorts (patients with TLE and healthy individuals in China), coil type, and TMS protocol in the study were all similar to the present study, while another study found that the increased CE (at ISIs 250 and 300 ms) in patients with TLE at various stages of epilepsy compared to controls.[20] For these different findings, one potential explanation could be the disparity in disease status, recruited cohort, and stimulation protocols. First, we only included TLE patients with or without BTCS and controls and excluded TLE with ambiguous history of BTCS. In contrast, previous studies have included patients with TLE at various stages (drug naïve new onset epilepsy, refractory seizures, and seizure free).[20] Second, ethnic differences might influence the results of LICI. We focused on Asians while previous studies mainly enrolled Caucasians. Third, despite a similar protocol being used, the different stimulator (MagVenture vs Magstim) and coil type (parabolic circular vs flat circular) might result in different LICI responses. Lastly, epilepsy patients with psychiatric comorbidities were common. Disorder in attention and mood in healthy individuals and epilepsy patients with generalized seizures were associated with changes of LICI.[31,32]

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In addition, LICI variability was shown to be linked to the difference of AED response,[16] sleep-wake cycle,[33] age and hemispheric dominance.[34] These and possibly other unknown factors contribute to the evident interindividual variability of LICI and should be fully considered. To obtain a better understanding of LICI results, future research should require more homogenous cohorts and standardized stimulation protocols.

In our study, LICI increased but SICI decreased in TLE patients compared to controls, which suggests that different GABA subtypes in inhibitory circuits have very different effects on epilepsy. This conjecture is similar to the widely accepted hypothesis that generalized spike-wave discharges are triggered by the inhibition of $GABA_A$ receptor-mediated circuits and rely critically on the activation of thalamic $GABA_B$ receptor-mediated inhibitory postsynaptic potentials for their generation.[15,22] The hypothesis based on animal models of absence seizures does not necessarily apply to other epilepsy syndromes. Furthermore, competition may also occur in inhibitory circuits. A Triple-Pulse TMS study demonstrated that SICI is reduced during the action of LICI, which corresponds with an increase in net corticomotor excitability. The former is thought to be a disinhibition process, possibly by the activation of presynaptic $GABA_B$ receptors. When the disinhibition prevails over the postsynaptic inhibition, it likely leads to a period of late cortical disinhibition.[35,36] In general, the dysfunction of $GABA_A$ and $GABA_B$ receptor-mediated inhibitory network activity in epilepsy remains to be investigated.

A growing amount of evidence has accumulated showing that an abnormal interaction between cortical and subcortical structures was involved in pathogenesis of focal seizures to BTCS.[2,13,14] Recent studies highlighted the critical role of the thalamocortical circuit in generating BTCS.[2] He et al. further demonstrated that the basal ganglia–thalamus–cortex loops could inform the presence and effective control of focal seizures to BTCS.[37] Given that the motor cortex projects to the thalamus, corpus callosum, and striatum, it also receives projections from the thalamus.[38] Deep brain stimulation of the subthalamic nucleus and anterior thalamus has been reported to affect motor cortex excitability in Parkinson's disease or epilepsy.[24,39] These findings imply that subcortical structures, including the thalamus, striatum, and corpus callosum, may affect motor cortex hyperexcitability in BTCS. Thus, CE could also be influenced by subcortical structure and the severity and status of disease except for the effects of AEDs, which should be carefully considered when interpreting the results.

Limitations

Our study was cross-sectional in nature, and the altered CE between TLE with BTCS and non-BTCS groups needs to be further confirmed by a study with a longitudinal design including drug-naïve patients with BTCS. In addition, the postoperative changes between seizure-free and recurrent groups need further exploration. Different pathologies may also affect CE. While previous studies mainly focused on changes of CE among groups with various epileptic syndromes,[21] there is no such work on the impact of pathology in TMS studies, so this needed to be further explored. Our study was of interictal changes, while studying the dynamic changes in CE makes more sense around the time of the seizure. These problems need further study in order to understand the pathophysiological mechanism of BTCS.

Conclusions

To our knowledge, this is the first report on the correlation between altered CE within the motor cortex and the presence of active BTCS in TLE, which demonstrated that motor cortical hyperexcitability in the ipsilateral hemisphere underlies the extensive epileptogenic network of patients with active BTCS.

Conflicts of Interest

The authors have no conflicts of interest to disclose pertaining to this study.

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Statement of Authorship

SW* and MPD contributed to study conception and design. LLH, HMY, and LLY acquired the data. CC and CMH collated and analyzed the data. LLH and YC drafted the manuscript. YD, JMZ, SW, SW*, and MPD discussed, read, and revised the manuscript. All authors approved the publication of this manuscript.

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