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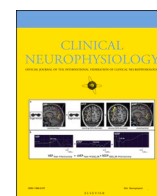
（もやもや病の一過性神経症状は頭皮上脳
波の Infralow と密接に関係している）

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Infraslow scalp electroencephalogram is closely linked to transient neurological events in Moyamoya disease

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ABSTRACT

Background: Transient neurological events (TNEs) commonly occur following direct revascularization for moyamoya disease (MMD). Although changes in the cerebral blood flow (CBF) may be linked to TNEs, the underlying mechanism remains unclear. Herein, we investigated the relationship between TNEs and EEG to elucidate the underlying mechanisms and pursue the clinical utility of EEG as a TNE biomarker.

Methods: Twenty-six hemispheres in 22 patients with MMD aged ≥ 15 years who underwent revascularization were analyzed. Scalp electroencephalography (EEG) and single-photon emission computed tomography (SPECT) performed within 7 days postoperatively were analyzed using the clinical information.

Results: Sixteen of 26 hemispheres developed TNEs, of which 12 demonstrated an increased frequency of delta waves (> 0.5 , < 4 Hz) on postoperative EEG ($P = 0.0002$), which was located in an area consistent with each symptom. Infraslow activity (ISA, < 0.33 Hz) was observed in all 4 hemispheres on the day of TNE development. More frequent occurrence of delta wave on postoperative EEG preceded onset in 2 hemispheres. CBF did not differ between the patients with and without TNEs.

Conclusions: ISA may be associated with the pathophysiology of TNEs. Delta waves can be used as clinical biomarkers to predict TNEs.

Significance: Slow waves on scalp EEG have the potential can predict and elucidate TNEs.

Non-standard Abbreviations and Acronyms.

TNEs, transient neurological events; MMD, Moyamoya disease; ISA, infraslow activity; SD, spreading depolarization; TC, time constant.

1. Introduction

Transient focal neurological episodes (TFNEs) are observed in various situations, including transient ischemic attack (TIA), epileptic seizures, migraine aura, and cerebral amyloid angiopathy-related TFNEs (Smith et al., 2021). TFNEs are not uncommon; however, diagnosis is challenging as some patients may be asymptomatic, while the

underlying abnormal findings may not be detected easily by conventional clinical methods. Further, it is currently difficult to define and delineate underlying causes. TFNEs share many common features with transient neurological symptoms observed in the postoperative state of moyamoya disease (MMD), referred to as transient neurological events (TNEs).

MMD is a cerebrovascular disease characterized by the progressive

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occlusion of the internal carotid arteries, resulting in the abnormal development of compensatory vascular networks with tiny blood vessels (Ihara et al., 2022). Surgical revascularization (superficial temporal artery (STA)-middle cerebral artery (MCA) direct bypass surgery) is effective in improving cerebral perfusion TNEs that occur in 40–60 % of patients with MMD after revascularization surgery in adults (Araki et al., 2021, Chen and Tu, 2022, Lu et al., 2019). Their clinical symptoms may vary (aphasia, hemiparesis, facial palsy, paresthesia, dysarthria, etc.), and may occasionally progress slowly, shift in time and location, and last for 5–30 min, as opposed to epileptic seizures that typically end in <2–3 min (Lu et al., 2019, Smith et al., 2021). TNEs exhibit various cerebral blood flow (CBF) changes, including transient hyperperfusion (Fujimura et al., 2007), transient hypoperfusion (Mukerji et al., 2015) and, more rarely, persistent ischemia (Araki et al., 2021). However, the mechanisms underlying these CBF changes remain unclear.

One of the main clinical problems of TNEs is the lack of clinical biomarkers. Although TNEs are reversible, a previous study suggested that TNEs may be a risk factor for cerebral infarction after surgery (Araki et al., 2021). Hence, TNEs could serve as a clinical biomarker for the prediction and prevention of cerebral infarction. Previous studies on TNEs have primarily employed imaging using radioisotopes, which detect changes in cerebral blood flow (CBF) (Kazumata et al., 2018, Tashiro et al., 2019). These imaging studies have a weak point in the research of such fluctuating and dynamic symptoms for a rather short period as TNEs because they are often not examined during active symptoms. Moreover, repeated examinations should increase radiation exposure.

Electrophysiological techniques such as electroencephalography (EEG) or electrocorticography (ECoG) have an advantage in terms of time resolution, attracting attention in the evaluation of brain function in addition to CBF changes. Extremely slow EEG waves have been observed in epileptic seizures (Ikeda et al., 1999, Kanazawa et al., 2015) and stroke (Dohmen et al., 2008, Takano et al., 1996). In epileptic seizures, ictal DC shifts are defined as sustained negative or positive potential changes lasting longer than 3 s observed around seizures (Ikeda et al., 1999) (Kanazawa et al., 2015). In stroke, SD is characterized by a relatively abrupt onset, and a large negative slow potential as measured in the low-frequency or direct current range of the ECoG (Drenckhahn et al., 2012).

SD is a reversible electrophysiological phenomenon associated with near-complete depolarization of virtually all the main cell types in the brain tissues, that is, neurons and astrocytes, which may affect the vasculature (Ayata and Lauritzen, 2015, Leao, 1944). SD can cause a transient increase or decrease in CBF, resulting in irreversible ischemia in a cluster (Dreier et al., 2022). These CBF changes resemble those observed in TNEs. The characteristic symptoms of TNEs may be associated with SD, as they are similar to migraines, which are believed to be triggered by SD (Charles and Baca, 2013, Hadjikhani et al., 2001, Woods et al., 1994). Although several reports have indicated an association between SD and the pathophysiology of TNEs (Domer et al., 2024, Phi et al., 2018), the precise relationship between SD and TNEs remains unknown.

We hypothesized that slow waves and more, including those below the Berger band (< 0.5–1 Hz), which have similar mechanisms to SD, would be associated with the pathophysiology of TNEs. Thus, we conducted this study with the aim of clarifying the relationship between slow waves and TNEs and identify clinical EEG biomarker candidates for TNEs. In the present study, we retrospectively investigated the relationship between scalp wideband EEG and TNEs in patients with MMD who underwent bypass surgery.

Our laboratory has been studying the role of slow waves in scalp EEG in various conditions, including critical care EEG (Togo et al., 2018), migraine (Hosokawa et al., 2024), neurofeedback (NFB) methods to regulate scalp-recorded slow cortical potential (SCP) and seizure suppression (Fumuro et al., 2024), and physiological motor readiness potential (Ikeda et al., 1992). Further, we believe that valuable insights can

also be obtained from the scalp EEG in this study. Finally, we investigated wide-band EEG, that is, slow and very slow waves (< 0.5 Hz), in addition to epileptiform discharges, focusing on underrecognized or fragmented possible SD, as mentioned above.

2. Methods

2.1. Patients

This study prospectively recruited patients aged ≥ 15 years, diagnosed with MMD according to the guidelines (Hashimoto et al., 2012), and they underwent direct revascularization (STA–MCA bypass) between June 2019 and June 2022 at our institution. We investigated patients whose EEG were examined within 1 week postoperatively as baseline reference data or for routine evaluations of neurological function.

To precisely evaluate the presence or absence of TNEs, patients were excluded if they had any of the following: severe paralysis (MMT ≤ 3) or sensory impairment throughout the entire hemibody of the contralateral surgical side; impairment of higher brain dysfunction that would make identifying symptoms impossible (i.e., aphasia or memory impairment); or a currently active psychiatric disorder (i.e., anxiety disorder and panic disorder). The Wechsler Memory Scale-Revised was applied for patients with suspected memory impairment, and those with scores < 70 were excluded.

TNEs were defined as follows (Lu et al., 2019): any reversible neurological deficits observed objectively, or recognized subjectively in the body contralateral to the side of revascularization, with no sign of acute hemorrhage or cerebral infarction on radiological imaging.

The study protocol conformed to the Declaration of Helsinki, and was approved by the Institutional Ethics Committee (IRB R2149-1). Written informed consent was obtained from all recruited patients.

2.2. Wide-band, scalp EEG recording

Scalp-recorded EEG data were clinically obtained using a multi-channel commercially available EEG machine (AC amplifier; Nihon Kohden, Tokyo, Japan) with 21 Ag–AgCl electrodes and an international 10–20 system. EEG analysis was performed strictly using epochs during wakefulness. The sampling rate was set to 500 Hz. Recording did not utilize any high-frequency cut filter (HFF). The low-frequency cut filter (LFF) was set to 0.079 Hz (time constant (TC) = 2 s) or 0.016 Hz (TC = 10 s). The Notch filter was removed during recording. Contact impedance of each electrode was kept at least < 10 k Ω . The EEGs were recorded for approximately 30 min. A reference system was placed on the parasagittal side of the scalp (C3 and C4).

2.3. Conventional EEG analysis

First, each EEG was analyzed for the presence and frequency of spikes and delta waves (0.5 < , < 4 Hz) by two certified neurophysiologists blinded to the clinical data. The analysis condition was set as follows: LFF 0.57 Hz (TC 0.3 s), HFF 150 Hz, Notch filter off.

In addition, the two neurophysiologists compared the difference in the frequency of occurrence of spike and delta waves between pre- and post-operative EEGs. When a clear difference in frequency was observed at the same electrodes, the electrode with the highest frequency of occurrence was identified. Throughout this process, the two neurophysiologists were blind about whether EEGs were performed preoperatively or postoperatively. The final evaluation was performed using a binary method (“increase” or “no increase”), with reference to the date when EEG performed.

Such a comparison is important, because some patients show delta waves on preoperative EEG, probably due to a previous stroke. Findings with amplitudes < 50 mV or bilateral findings with higher amplitudes on the surgical side were excluded due to increases in amplitude near the

area of craniotomy.

To further determine the difference between pre- and post-operative EEG recordings, the rate of power spectral density was calculated for each frequency band. First, several segments (5–10 s each) were extracted from the EEG during the awake resting state with eyes closed. Second, the power spectral density of the temporal electrode on the operative side (T3 or T4) was calculated at each frequency (delta 1–3.5 Hz, theta 4–7.5 Hz, alpha 8–13.5 Hz, and beta 14–20 Hz) by Fourier transform using MATLAB-R2019a (Mathworks, Natick, MA, USA) with pre- and postoperative EEG. Third, the ratio was calculated and logged using the following formula: $\log(\text{postoperation/preoperative power spectral density})$. All recruited patients had similar bone defects under temporal electrodes (T3 or T4) using an established surgical method. Thus, no critical bias exists when the power spectral density of slow activity at the temporal electrodes is compared across patients.

2.4. Wideband EEG analysis

Because there are no previous reports of SD observed only in scalp recordings, we defined infraslow activity (ISA) as very slow waves in this study, as previously performed in our laboratory (Togo et al., 2018; Hosokawa et al., 2024). The definition of ISA varies in previous reports (Hashimoto et al., 2020, Joshi et al., 2018, van Putten et al., 2015, Vanhatalo et al., 2005). Based on our previous studies of critical care EEG (Togo et al., 2018) and patients with migraine (Hosokawa et al., 2024), ISA in scalp EEG was defined as sustained negative and/or positive potentials lasting > 3 s (< 0.33 Hz), and peak to peak amplitude of > 100 μV in TC 2 s. Analysis with a TC of 2 s can detect very slow waves in epileptic seizures (ictal DC shifts)(Izumi et al., 2023, Kajikawa et al., 2022, Murai et al., 2020) and patients needing critical care and migraine.

ISA was analyzed using at least two montages (an earlobe electrode referential montage and an average reference) to verify its reproducibility. The analysis conditions were as follows: LFF, 0.079 Hz (TC 2 s); HFF, 150 Hz, Notch filter off. To avoid misjudging slow artifacts, such as movement artifacts and galvanic skin response, suspicious waveforms limited to a single scalp electrode or having a bizarre morphology, that is, excessively large, extremely small, rapid, and large fluctuations of amplitude, strongly suggesting artifacts were excluded, as performed in the usual clinical EEG interpretation (Fig. S1). However, we did not evaluate the power spectrum density in the slow band (< 0.5 Hz) because horizontal eye-movement artifacts are included in the T3 and T4, and it is difficult to distinguish between the power spectrum density originating from the cortical-origin waveform and that from eye-movement artifacts (Fig. S1).

Finally, we compared the clinical characteristics of TNEs and EEG findings between the two TNE-positive subgroups (with and without ISA).

2.5. SPECT analysis

^{123}I -IMP single-photon emission computed tomography (IMP-SPECT) was also performed to evaluate CBF changes in the patients preoperatively and postoperatively. We evaluated these results qualitatively and quantitatively. For qualitative evaluation, two neurosurgeons, who were blinded to the clinical information, judged whether there was an increase or decrease in local blood flow postoperatively. For quantitative evaluation, the CBF change ratio was defined as follows (Tashiro et al., 2019), and the relationship between the obtained values and the presence or absence of TNEs was evaluated:

$$\text{CBF change ratio} = \frac{\text{post} - \text{QVMCA}/\text{post} - \text{QVcerebellar}}{\text{pre} - \text{QVMCA}/\text{pre} - \text{QVcerebellar}}$$

A quantitative value (QV) was obtained from the region of interest (ROI) which was automatically set using Neuroflexer (Nihon Medi-Physics Co., Ltd, Tokyo, Japan). Clinically, the cortical area supplied

by the MCA is separated into the anterior and posterior MCA areas. The highest value was selected as the $\text{QV}_{(\text{MCA})}$.

2.6. Statistics

Spike, ISA, and delta wave occurrences were evaluated as binary measures (presence or absence). EEG and CBF changes were further assessed based on predefined conditions, making them binary measures. The rate of power spectrum density and the CBF change ratio are expressed as ratios and thus do not have specific units.

The number of hemispheres in the clinical profiles, EEG results (spike, delta wave, and ISA), and Single-photon emission computed tomography (SPECT) results (hyperperfusion and hypoperfusion) were compared between the patient groups with and without TNEs using Fisher's exact test. SPECT (CBF change ratio) and EEG (the rate of power spectral density) results underwent univariate analysis using the Wilcoxon signed-rank test. To control for multiple comparisons, we further applied Bonferroni correction by dividing the original threshold ($P = 0.05$) by the number of comparisons ($n = 13$). The adjusted significance threshold was set at $P < 0.0038$.

Subsequent comparison of the clinical characteristics of TNEs and EEG findings between TNE-positive subgroups (with and without ISA) was performed using the Fisher's exact test.

3. Results

3.1. Patient profile

Overall, 36 patients with MMD (45 hemispheres) underwent surgery at our hospital between June 2019 and July 2022. Of these patients, 25 (31 hemispheres) underwent EEG within 7 days postoperatively and 24 (30 of 31 hemispheres) underwent preoperative EEG within 6 months. After two patients were excluded due to memory impairment, 22 patients (26 hemispheres) were included in the analysis (Table 1).

TNEs occurred in 61 % of the hemispheres (16/26 hemispheres with TNEs, and 10/26 hemispheres without TNE). Of the 16 hemispheres with TNE, 12 had daily clusters of TNE, and among these, 6 hemispheres had clusters in one day. All hemispheres in which clusters of TNEs occurred during the day exhibited symptoms the following day. Clustered symptoms, except those in one hemisphere (#3), resolved during the intermittent period. In the remaining hemisphere (#3), paresthesia persisted until 10 days postoperatively and then disappeared. Isolated TNE were observed in four of the 16 hemispheres (Fig. 1).

The symptoms of TNEs included paresthesia of the upper extremities in 13 hemispheres, paresthesia of the mouth in 4 hemispheres, paresis of the upper and lower extremities in 1 hemisphere, dysarthria in 5 hemispheres, and aphasia in 5 hemispheres, with durations of 5–60 min

Table 1
Clinical characteristics of all patients.

Clinical features	TNEs+ (n = 16)	TNEs- (n = 10)	Total (n = 26)	
Age, y (mean $\pm$ SD)	35 $\pm$ 11.7	45.8 $\pm$ 15.4	39.4 $\pm$ 13.6	$P = 0.06^*$
Female, n	15	9	24	$P = 0.63$
Side of operation, n				
L	9	5	14	$P = 0.53$
Type of MMD, n				
Ischemic Stroke	14	6	20	$P = 0.16$
Hemorrhage	1	2	3	$P = 0.54$
Others	1	2	3	$P = 0.54$

Abbreviations: TNEs: transient neurological events, MMD: moyamoya disease. Ischemic Stroke includes TIA patients. Numbers are based on hemisphere counts. *P values were calculated using Student's t -test. Other P values were calculated using the Fisher's test.

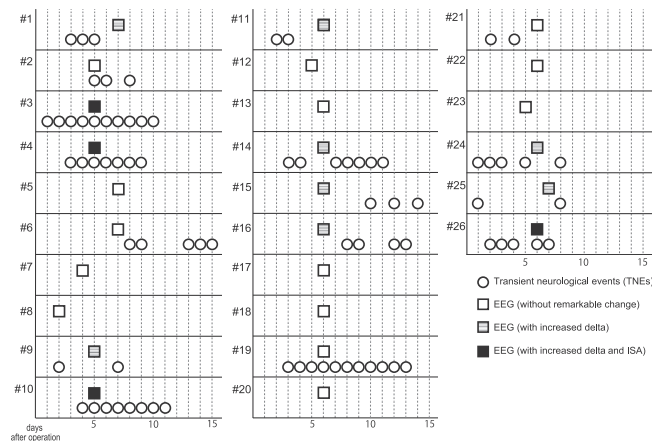


Fig. 1. Summary of the clinical course of transient neurological events (TNEs) and electroencephalogram (EEG) in all hemispheres. ISA was observed in EEGs on the same days of TNE (#3, #4, #10, and #26). Focusing on cases in which EEG was performed before TNE appearance (#6, #15, #16), #15 and #16 demonstrated increased occurrence rates of delta wave.

(Tables 2 and 3). Most of them (14 of 16 hemispheres) were self-reported because symptoms did not last long enough to be noticed by other health professionals or symptoms were only sensory. A representative patient sample is presented in Fig. 2.

During the perioperative period, the systolic blood pressure was maintained at 100–140 mmHg. Antiplatelet drugs were discontinued 3 days before surgery, and restarted with aspirin 100 mg/day or cilostazol 200 mg/day 3 days postoperatively.

ASMs were administered to 13 of the 26 hemispheres (phenytoin (PHT) in 12 hemispheres and levetiracetam in one hemisphere) post-operatively. Of the 13 hemispheres, eight that were administered ASM developed TNE. No significant difference in TNE appearance was

Table 2
Results of EEG and SPECT.

	TNEs+ (n = 16)	TNEs- (n = 10)	Total (n = 26)	
Preoperative EEG, n				
Spike/sharp transients	0	0	0	—
Delta waves	5	2	7	$P = 0.67$
ISA	0	0	0	—
Postoperative EEG, n				
Spike/sharp transients	1	1	2	$P = 0.86$
Delta wave	13	5	18	$P = 0.19$
ISA	4	0	4	$P = 0.14$
EEG change [†]				
Spike/sharp transients increase	0	0	0	—
Delta increase	12	0	12	$P = 0.0002$
ISA increase	4	0	4	$P = 0.14$
SPECT				
CBF ratio, (mean ± SD)	1.21 ± 0.03	1.15 ± 0.04	1.19 ± 0.01	$P = 0.45^*$
CBF change, n	6	1	7	$P = 0.35$
Hyperperfusion	4	1	5	$P = 0.62$
Hypoperfusion	2	0	2	$P = 0.52$

ISA, infraslow activity; SPECT, single-photon emission computed tomography; CBF, cerebral blood flow.

CBF ratio was calculated by quantitative values. There were 21 quantitative data points (TNEs+: 13; TNEs-: 8). Changes in CBF, hyperperfusion, and hypoperfusion were visually determined by two neurosurgeons using qualitative data. The number of qualitative data points was 25 (TNEs+: 16; TNEs-: 9).

* P values were calculated using the Wilcoxon rank-sum test. Other P values were calculated using the Fisher's test.

[†] Occurrence frequency in the postoperative state compared with the preoperative state.

Table 3
Symptoms of TNEs and location of EEG slow.

	Side	Detailed symptoms of TNEs	Location of delta wave	Location of ISA
#1	Lt	Paresthesia (Rt. Upper limb) and aphasia	T3, F7, T5	—
#2	Lt	Paresthesia (Rt. Upper limb) and dysarthria	—	—
#3	Lt	Paresthesia (Rt. Upper limb) and aphasia	C3, F3, F7	C3, F7
#4	Rt	Paresthesia (Lt. Face and hand)	T6, F8, C4, T4, P4	T6, T4
#6	Lt	Paresis (Rt. Upper limb)	—	—
#9	Lt	Aphasia and dysarthria	T3, F7	—
#10	Rt	Paresthesia (Lt. Upper limb)	C4, T4, F4	C4, T4
#11	Lt	Clumsy hand (Rt.) and aphasia	T3, F3, F7, C3	—
#14	Rt	Paresthesia (Lt. Upper limb) and dysarthria	T6, P4	—
#15	Rt	Paresthesia (Lt. Face and upper limb)	C4, P4, T6, T4	—
#16	Lt	Paresthesia (Rt. Upper limb) and dysarthria	T3, F7, F3, C3, T5	—
#19	Rt	Paresthesia (Lt. Face and upper limb)	—	—
#21	Rt	Paresthesia (Lt. Upper limb)	T4, F8, F4, C4	—
#24	Rt	Paresthesia (Lt. Upper and lower limbs)	T4, F8, T6	—
#25	Lt	Paresthesia (Rt. Face and upper limb)	C3, P3, T3	—
#26	Lt	Paresthesia (Rt. Upper limb) and aphasia	T3, F7, C3, T5	T3, T5, C3

Side: side of operation, Rt: right, Lt: left.

observed between the groups with and without ASM (13 hemispheres vs. 13 hemispheres) ($P = 0.612$, Fisher's exact test (Table S1)).

3.2. Results of EEG and SPECT (Table 2)

Postoperative EEG demonstrated delta waves in 16 hemispheres; none exhibited spikes and two demonstrated sharp transients (Table 2). We compared the EEG signals between preoperative and postoperative states in all 16 hemispheres.

3.3. ISA vs. TNE as the novel finding

The occurrence frequency of delta waves in the postoperative state increased in 12 of 26 hemispheres (12/16 TNE hemispheres and 0/10 no TNE hemispheres) (Table 2). All patients who exhibited an increase in delta waves developed TNE. Among the 13 parameters analyzed in the present study, including spike, delta wave, ISA (EEG), and CBF changes (SPECT) (Table 2), only the increase in the frequency of delta wave occurrence in the postoperative state showed a statistically significant association with TNE ($P = 0.0002$, Fisher's test, $\alpha = 0.05/13 = 0.0038$, Bonferroni correction) (See Fig. S2 for the occurrence frequency data of pre- and post-operative EEG findings). No specific temporal relationship was found between increased delta waves on the EEG and the timing of TNEs onset. However, when we focused on the utility of an increase of delta waves on the postoperative state for the diagnosis of TNEs, the sensitivity was 0.75 (95 % CI: 0.48–0.93) and the specificity was 1.00 (95 % CI: 0.69–1.00). An increase in delta wave was detected prior to the onset of TNEs in the two hemispheres, during clusters of TNEs in the four hemispheres, during intervals of TNEs in four and after the disappearance of TNEs in the two hemispheres (Fig. 1). With regard to the presence of TNEs during EEG recording, 1 hemisphere (#10) exhibited TNEs. In the other hemispheres, no information on clinical symptoms was obtained during EEG.

The delta waves were primarily observed in the central to mid-temporal areas (Table 3). When symptoms were subdivided into motor, sensory, and aphasia categories and their relationships with delta

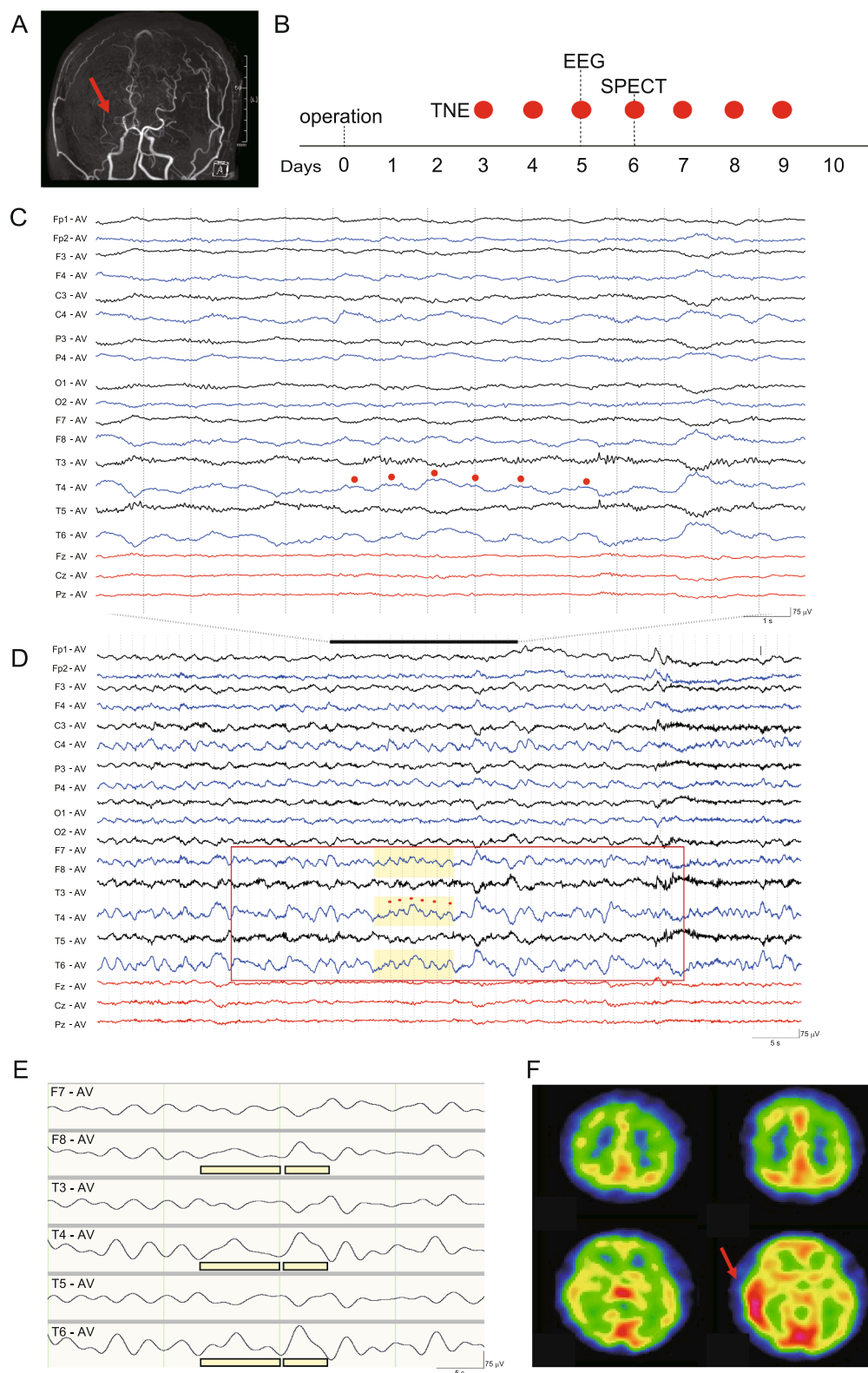


Fig. 2. Overview of a representative hemisphere (#4). **A.** Preoperative magnetic resonance angiography (MRA) scan demonstrating the disappearance of signals of the right middle cerebral artery (MCA) (red arrow). The patient had undergone a superficial temporal artery–MCA bypass on the left side 3 months before. **B.** Clinical course. She had dysarthria and paresthesia in the Lt. hand, which lasted 15–30 min each day. **C.** Postoperative electroencephalogram (EEG) (width of 15 s). Rhythmic delta activity was observed in C4, T4, and T6. **D.** Postoperative EEG (width of 60 s). The black bold line is the same part as the width of C. Infraslow activity (ISA) was observed in F8, T4 and T6 (yellow band area). **E.** Representative wave form of ISA. The red square in D is the same area, and the yellow bar highlights ISA area. This was produced solely for the presentation by using wide-band EEG analysis program with low pass filter of 0.5 Hz from the Nihon-Koden EEG 1260 software. **F.** Single photon emission computed tomography (SPECT). Preoperative SPECT on the left and postoperative ones on the right. The red arrow indicates the region of increased cerebral blood flow (CBF). The CBF ratio was $1.22 < 1.5$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

waves were investigated, delta waves tended to increase in cases of aphasia (sensory, 10/13 hemispheres; motor, 3/5 hemispheres; aphasia, 5/5 hemispheres).

The ratio of the power spectral density between the preoperative and postoperative EEGs indicated that all bands (delta, theta, alpha, and beta) tended to be high in the TNEs group. However, only the delta wave showed a statically significant increase (*P*-value: delta = 0.0042, theta = 0.025, alpha = 0.1, and beta = 0.034, Wilcoxon rank-sum test, $\alpha = 0.05/4 = 0.013$, Bonferroni correction) (Fig. S3). We did not evaluate the power in the slow band (< 0.5 Hz), especially in the ISA, because dissociating eye movement artifacts from real EEG waveforms is difficult.

ISA was observed only in 4 hemispheres (#3,4,10, and 26), all of which developed TNEs. When the presence of ISA on the postoperative state was used to diagnose TNEs, the sensitivity was 0.25 (95 % CI: 0.073–0.52) and the specificity was 1.00 (95 % CI: 0.69–1.00). TNEs in all four hemispheres occurred for > 5 days postoperatively and demonstrated continuous delta activity on the EEG (Table 4). The ISA lasted for up to 7 s and propagation to the adjacent area was absent. The ISA was observed mainly in the unilateral central and temporal areas. In three of the four hemispheres (#3, 10, and 26), the location of the EEG changes corresponded to those responsible for the clinical neurological symptoms (Table 3). In the #4 hemisphere, the ISA was observed in the parieto-temporal electrodes (T4 and T6), although the region responsible for the paresthesia was believed to be located in the postcentral gyrus. Regarding the temporal relationship between EEG and TNEs (Fig. 1), ISA was observed on the same day when TNEs appeared, whereas delta waves were observed after and before appearance of TNEs (–4 to + 4 days). Two (#2 and #19) hemispheres also underwent EEG on the same day as the TNE occurred. However, ISA was not observed in these hemispheres. When comparing the clinical symptoms, the severity of the symptoms was greater in the four hemispheres with ISA (#3,4,10, and 26) than in those without ISA (#2 and #19).

In all hemispheres, CBF increased on the operated side rather than on the other side when analyzed quantitatively. However, the degree of increase was not significantly different between TNEs + and TNEs – (1.17 ± 0.08 , TNEs +; 1.21 ± 0.03 , TNEs –; 1.15 ± 0.04 , *P* = 0.29, Wilcoxon rank-sum test, Table 2). Qualitative analysis of CBF changes was observed in seven patients (6 patients with TNEs and 1 patient without TNEs, *P* = 0.35). Local hyperperfusion was observed in five patients (four patients with TNEs and one patient without TNEs). Local hypoperfusion was observed in two patients (both with TNEs).

In the present study, we included both the right and left hemispheres in which surgery was performed in the same patient at separate times with appropriate intervals; based on these criteria, four eligible patients were identified. The intervals between hemisphere surgeries were 2, 3, 8, and 12 months. Second, contralateral surgeries were performed after confirming the disappearance of acute postoperative hemodynamic changes. For further analysis, we focused on the first surgery. The results remained unchanged from those described previously (Table S2), indicating that our findings are applicable to patients who had undergone

bilateral surgery.

4. Discussion

4.1. Postoperative EEG findings in TNEs

TNEs were observed in 16 of 26 hemispheres (61 %). In 12 of 16 hemispheres with TNE, the occurrence frequency of delta waves increased postoperatively. Four of the 16 hemispheres with TNE and all patients without TNE did not have an increased delta wave (10 hemispheres). ISA were observed in four hemispheres that suffered from TNEs on the same day as the EEG examination.

Our results suggest that the emergence of delta waves and ISA in postoperative EEG and the more frequent occurrence of delta waves compared to the preoperative EEG were associated with TNEs. Few case series have reported EEG findings of TNEs in MMD(Huguenard et al., 2021, Phi et al., 2018, Zhang et al., 2022). To the best of our knowledge, this is the first case–control study to investigate delta waves and ISA during TNEs.

Our findings regarding delta waves in patients with TNE are comparable to those of previous reports. Since most symptoms of TNEs are self-reported, reporting bias needs to be considered; thus, we certainly need more objective parameters for TNEs. Importantly, delta waves were identified in the area responsible for TNE symptoms, suggesting that delta waves in TNEs could be a candidate biomarker.

In addition to the focal delta wave, the findings of ISA observed during TNEs may help elucidate the pathogenesis of TNEs. ISA were observed only on the day when TNEs appeared, whereas delta waves were observed very close to the TNEs either before or after. Therefore, ISA may be generated independently of the delta wave. However, considering the high spatial proximity between the delta waves and the ISA, repeatedly occurring delta waves in time and space may be related to the appearance of the ISA. Repeatedly occurring delta waves may lead to the accumulation of abnormal brain activity, which may result in ISA on EEG and TNEs in semiology. Considering that the ISA was observed in a region adjacent to the area responsible for TNEs symptoms in one patient (#4), it could be hypothesized that the ISA spatially spreads and moves like an SD propagation, or originates from a rather deeply seated brain structure.

4.2. Generator mechanism of TNEs

Prior studies have suggested two primary hypotheses regarding the mechanism of TNEs: hyperperfusion caused by increased CBF after bypass surgery(Fujimura et al., 2011) and hypoperfusion caused by decreased anterograde flow from the MCA(Mukerji et al., 2015). Both conditions may trigger disruption of the blood–brain barrier(Yang and Rosenberg, 2011), cause impairment of ion homeostasis (including potassium) and amino acid transporter distribution, and may finally induce depolarization of astrocytes and abnormally excited neuronal activity (Armbruster et al., 2022, Heinemann et al., 2012).

Our findings regarding delta waves and ISA did not directly clarify the relationship between TNEs and SD. However, these EEG changes (delta wave and ISA) may reflect impairment of the complex system of astrocytes and neuronal changes caused by CBF changes, which may be a common underlying mechanism of SD.

Both qualitative and quantitative evaluations of SPECT indicated that the TNEs + group showed large degree of CBF changes than the TNEs – group, but the results were preliminary due to small number of patients. In the future, a more detailed evaluation of cerebrovascular disorders with reversible CBF changes may be possible by increasing the number of patients and correlating the timings of SPECT and EEG, both of which can track changes over time. This approach may also be useful for elucidating the underlying mechanisms.

Appropriate treatment or prevention of TNEs has not yet been established. Blood pressure control may be important and minocycline

Table 4
Relationship between clinical information and ISA.

	ISA+ (n = 4)	ISA- (n = 12)	
Clinical symptoms of TNEs			
Days (> 5 days)	4 (100 %)	4 (33.3 %)	<i>P</i> = 0.038
Time (> 30 min)	3 (75 %)	4 (33.3 %)	<i>P</i> = 0.26
Frequency (>1 /day)	3 (75 %)	3 (25 %)	<i>P</i> = 0.12
EEG findings (other than ISA)			
Continuous delta (> 70 %)	3 (75 %)	2 (16.7 %)	<i>P</i> = 0.063
High amplitude delta (>100 μV)	1 (25 %)	1 (8.3 %)	<i>P</i> = 0.45

ISA, infraslow activity; ISA+, patients with TNEs who showed ISA on postoperative EEG; ISA-, patients with TNEs who did not show ISA on postoperative EEG.

P values were calculated by fisher's test.

(Fujimura et al., 2014) has been reported to be effective. In the present study, PHT, known as ASM, was administered postoperatively in some recruited hemispheres but did not prevent TNEs. Valproic acid may be a candidate ASM for prevention because it exerts neuroprotective effects on neurons and astrocytes protective effects (Gao et al., 2022, Mukai et al., 2018).

4.3. Limitations

Our study demonstrates that scalp EEG could be more clinically useful than general recognition for detecting TNEs. Delta waves on postoperative EEG have high sensitivity and specificity for the diagnosis of TNE, although augmented slow and fast activity due to craniotomy should not be misinterpreted as a breach rhythm (Brigo et al., 2011), defined as a focal increase in the amplitude of 6–11 Hz activities through craniotomy. Delta waves associated with the breach rhythm raise the suspicion of minute brain damage (Brigo et al., 2011). In this study, we considered that the delta wave observed through craniotomy was associated with the pathology of TNEs but not with past brain damage revealed by craniotomy.

Moreover, only three hemispheres underwent EEG before the onset of symptoms after surgery, suggesting that delta waves may be useful predictive markers of TNE. Although EEG has mainly been used to diagnose epileptic seizures, focusing on slow waves, as in this study, could widen the utility of clinical EEG in delineating abnormal brain conditions other than epilepsy, such as stroke-mimicking events.

5. Conclusion

This study suggests that the slow wave (delta) on EEG of TC 2 s is a useful biomarker of TNEs, and that ISA may be further helpful in elucidating the pathophysiology of TNE. Because TNEs are transient symptoms, continuous or frequent EEG of TC 2 s is important for investigating its pathophysiology, predicting its occurrence, and determining the effect of treatment.

CRediT authorship contribution statement

Kozue Hayashi: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Kiyohide Usami:** Methodology, Formal analysis, Investigation, Writing – review & editing, Funding acquisition. **Masaya Togo:** Methodology. **Yukihiro Yamao:** Methodology, Formal analysis, Investigation, Writing – review & editing, Resources. **Takeshi Funaki:** Methodology, Formal analysis, Investigation, Resources. **Takefumi Hitomi:** Formal analysis, Investigation, Resources. **Takayuki Kikuchi:** Conceptualization, Resources. **Masao Matsuhashi:** Formal analysis, Investigation. **Kazumichi Yoshida:** Conceptualization, Resources. **Yoshiki Arakawa:** Resources. **Ryosuke Takahashi:** Supervision. **Susumu Miyamoto:** Resources, Supervision. **Akio Ikeda:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [The author declares that the following potential conflict of interest with respect to the research, authorship, and/or publication of this article: K. H, M.M and A.I. belong to the Department of Epilepsy, Movement Disorders, and Physiology, Kyoto University Graduate School of Medicine. This department was an Industry-Academia Collaboration Courses, supported by Eisai Co., Ltd., Nihon Kohden Corporation, Otsuka Pharmaceutical Co., Ltd. and UCB Japan Co. Ltd. from June 2018 to May 2023, and has been supported by Sumitomo Pharma Co., Ltd. and Nihon Kohden Corporation since June 2023.]

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2025.2110748>.

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Figure S1

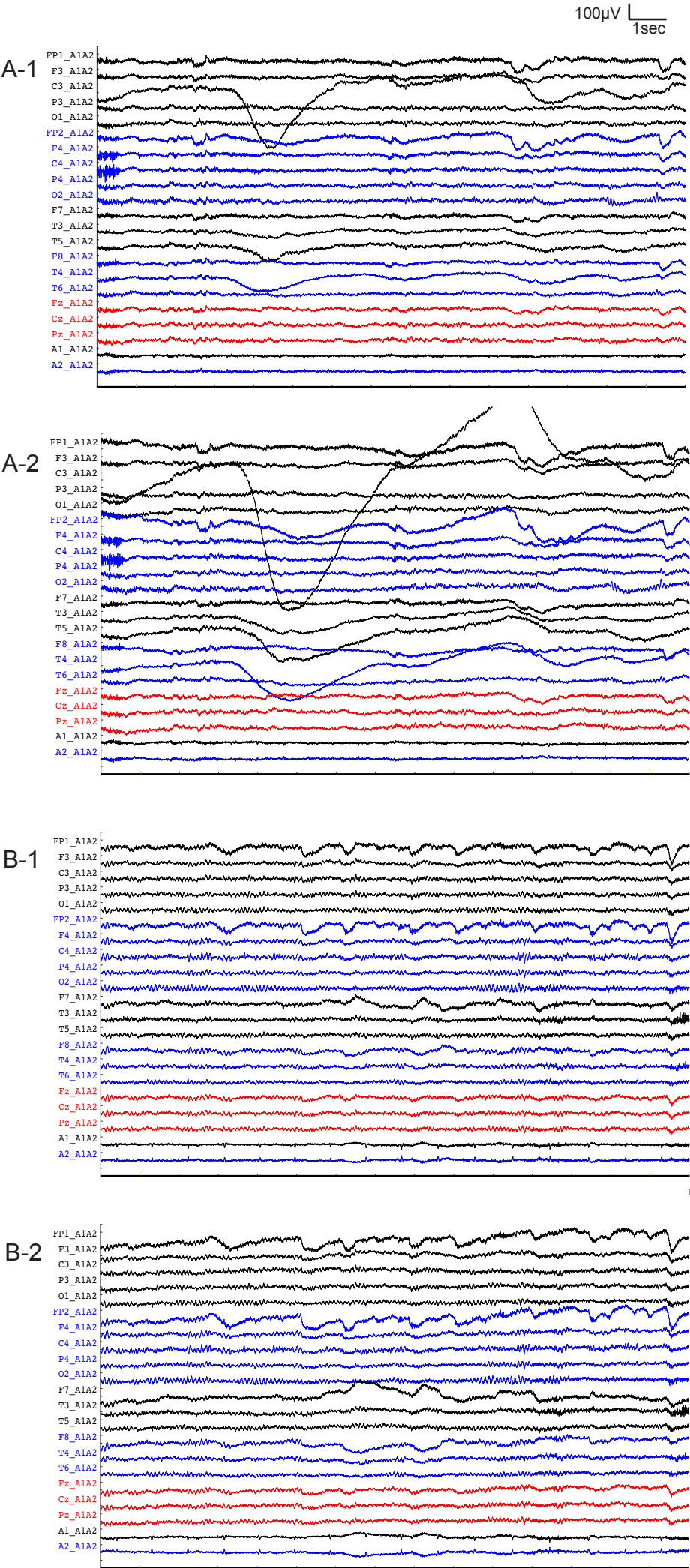


Figure S2

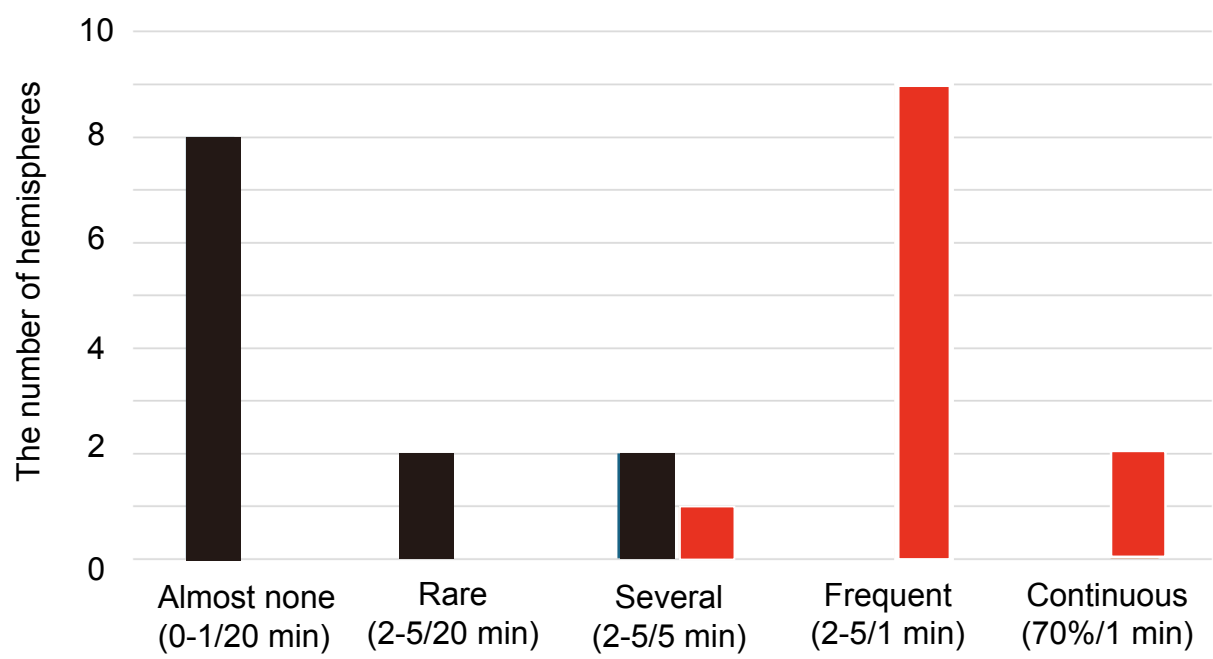
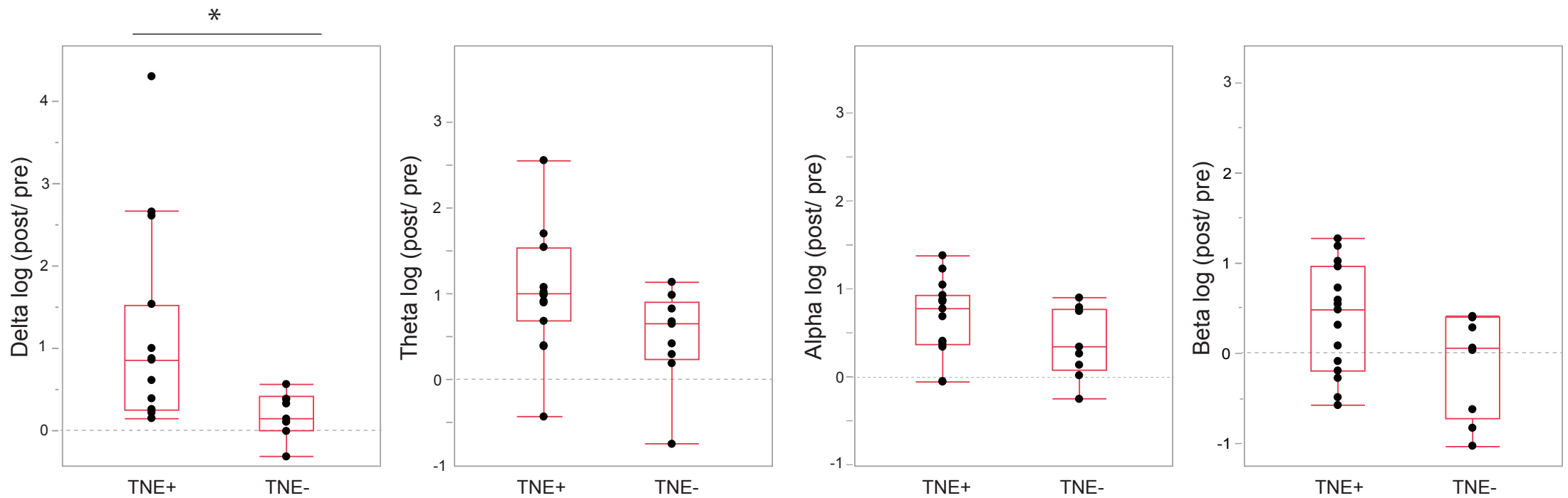


Figure S3



Supplement Figure Legends

Figure S1. Sample of artifact data

A-1 (LFF 0.57 Hz (TC 0.3 s)), A-2 (LFF 0.079Hz (TC 2 s)). Artifact data (suspicious waveform). Post Lt. STA-MCA bypass surgery (#25). In A-1 and A-2, waveforms lasting longer than 2 s are observed at C3, T3, T5 and T4. Since the distribution is not topographic but rather discontinuous, these waveforms were determined to be an artifact.

B-1 (LFF 0.57 Hz (TC 0.3 s)), B-2 (LFF 0.079Hz (TC 2 s)). Artifact data (eye movement). Post Lt. STA-MCA bypass surgery (#12). In B-1, artifact caused by horizontal eye movements are localized to F7 and F8, whereas in B-2 they are also observed at T3 and T4.

Figure S2. The occurrence frequency of delta waves in EEG from 12 hemispheres with “more frequent occurrence of delta waves after surgery”

We assessed the occurrence frequency of delta waves based on a five-tier classification: (1) almost none (0-1/20 min), (2) rare (2-5/20 min), (3) several (2-5/5 min), (4) frequent (2-5/1 min), and (5) continuous (more than 70%). The frequency was averaged for each hemisphere and categorized into the nearest tier. Black bars represent the results of the preoperative EEG, and red bars represent the results of the postoperative EEG. Y-axis indicates the number of hemispheres per category.

Figure S3. Comparison of power (post/ pre) with transient neurological event (TNE) + and TNE– in each band.

All bands tended to be higher in the TNE+ group. However, statistical significant increase was observed only in delta wave (P -value: delta = 0.0042, theta = 0.025, alpha = 0.1, and beta = 0.034, Wilcoxon rank-sum test, $\alpha = 0.05/4 = 0.013$, Bonferroni correction). TNE+: cases with TNE, TNE–: cases without TNEs, * $P < 0.013$. Delta, 1–3.5 Hz; Theta, 4–7.5 Hz; Alpha, 8 –

26 13.5 Hz; and Beta, 14–20 Hz. Post: power calculated from postoperative EEG; and pre: power
27 calculated from preoperative EEG.

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Tables S1. Results of relationship between ASM and TNE

	TNE+ (n=16)	TNE- (n=10)	Total (n=26)	
PHT, n	8	4	12	<i>P</i> =0.70
LEV, n	0	1	1	<i>P</i> =0.43

PHT: phenytoin, LEV: levetiracetam.

P values were calculated by Fisher's test.

Table S2.**Revised Results of EEG and SPECT by excluding 4 hemispheres of bilateral surgery**

	TNEs+ (n=14)	TNEs- (n=8)	Total (n=22)	
Preoperative EEG, n				
Spike/sharp transient	0	0	0	-
Delta wave	4	1	5	<i>P</i> =0.61
ISA	0	0	0	-
Postoperative EEG, n				
Spike/sharp transient	1	1	2	<i>P</i> =0.86
Delta wave	11	4	15	<i>P</i> =0.34
ISA	2	0	2	<i>P</i> =0.52
EEG change (occurrence frequency), n				
Spike/sharp transients increase	0	0	0	-
Delta increase	10	0	10	<i>P</i> =0.0017
ISA increase	2	0	0	<i>P</i> =0.52
SPECT				
CBF ratio, (mean±SD)	1.21±0.12	1.15±0.08	1.19±0.01	<i>P</i> =0.58*
CBF change, n	5	1	6	<i>P</i> =0.25
Hyperperfusion	4	1	5	<i>P</i> =0.62
Hypoperfusion	0	0	0	-

ISA: infraslow activity, SPECT: single photon emission computed tomography, CBF: cerebral blood flow

CBF ratio was calculated by quantitative values. The number of quantitative data was 20 (TNEs+: 12, TNEs-: 8). CBF change, hyperperfusion and hypoperfusion were visually determined by two neurosurgeons on qualitative data. The number of qualitative dates was 21 (TNEs+: 14, TNEs-: 7).

**P* values were calculated by Wilcoxon rank sum test. Another *P* values were calculated by fisher's test. Bonferroni correction was applied for the multiple comparison. The adjusted significance threshold was set at $p < 0.0038$.