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Case Report

Incremental changes in interhemispheric functional connectivity after two-stage corpus callosotomy in a patient with subcortical band heterotopia

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ABSTRACT

Corpus callosotomy (CC) has been reported to be effective in reducing generalized seizures in patients with drug-resistant epilepsies. However, efficacy is measured only by seizure frequency, without any electrophysiological guidance. Herein, we conducted a quantitative analysis of interhemispheric functional connectivity using inter-electrode coherence of scalp electroencephalogram (EEG) in a clinical case of subcortical band heterotopia to evaluate its relationship with seizure frequency. In our case, seizure frequency decreased significantly after posterior CC but not after anterior CC. Inter-electrode coherence also decreased after posterior CC, suggesting it correlated with seizure frequency. This case study supports the use of inter-electrode coherence as an electrophysiological tool that is useful as predictive factor in evaluating the effectiveness of CC.

Introduction

Corpus callosotomy (CC) is a palliative surgical procedure that limits the spread of epileptogenic activity between both cerebral hemispheres. Generalized atonic seizures are the most responsive seizure type to surgeries involving CC [1]. CC is also performed for bilateral subcortical band heterotopia with generalized seizures, which is a rare neuronal migrational disorder caused by disruption in the normal movement of neurons from their original position at birth to their final location during brain development [2–5].

Previous literature reported CC to be an effective treatment to alleviate generalized seizures [1,3,6–9]. However, efficacy is measured primarily by an outcome focused on reduction in seizure frequency without quantitative metrics. Here, we conducted an analysis of interhemispheric functional connectivity, utilizing inter-electrode coherence on electroencephalogram (EEG) in a patient with drug-resistant epilepsy and subcortical band heterotopia. Coherence is a correlation coefficient that estimates consistency of the relative amplitude and phase between any pair of signals within each frequency band [10]. Analysis of this case suggests that inter-electrode coherence may be a valid electrophysiological measure to predict outcome of the clinical effectiveness after a staged CC in patients with subcortical band heterotopia.

Methods

A patient with subcortical band heterotopia underwent total disconnection of the corpus callosum in a two-stage procedure. The patient had several types of debilitating seizures. The frequency reduction of seizures was compared over three stages. Assessment was made after each operation that involved anterior CC and subsequently after posterior CC. Inter-electrode coherence on EEG was analyzed at each stages. The relationship between inter-electrode coherence and seizure frequency was also investigated.

Case presentation

A 23-year-old female with band heterotopia underwent anterior and posterior CC at the Tokyo Metropolitan Neurological Hospital. She originally presented with afebrile seizures at the age of four years and had bilateral epileptiform discharges on EEG. She was started on antiseizure medication, but the seizures were drug-resistant. Magnetic resonance imaging (MRI) showed a continuous bilateral subcortical heterotopic band in the frontal, parietal, and occipital lobes (Fig. 1). The band thickness was

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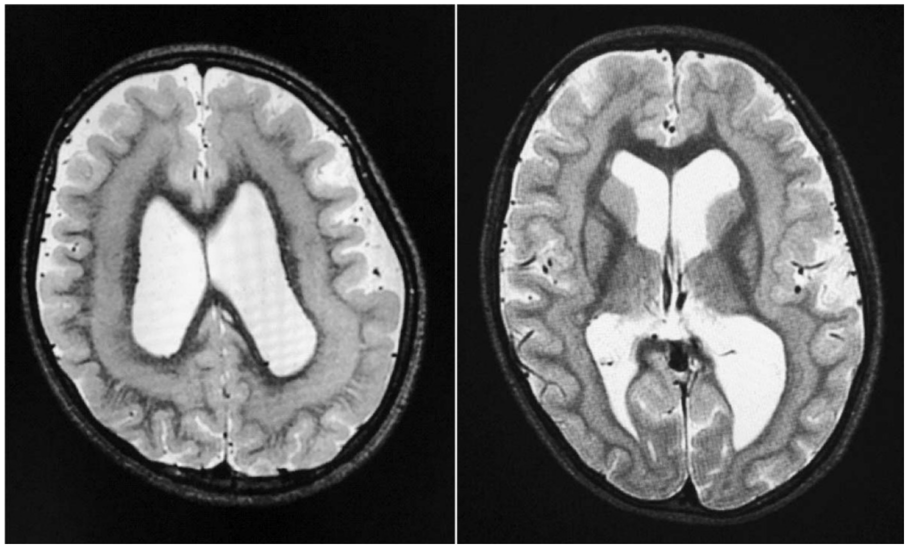

Fig. 1. Preoperative magnetic resonance imaging (MRI). Axial T2-weighted images show bilateral subcortical heterotopic bands.

symmetric. She had her follow-up in the pediatric outpatient clinic at our institute. Despite frequent adjustments to antiseizure medication; focal atonic seizures, generalized atonic seizures, and focal onset impaired awareness seizures (FIAS) persisted. Delayed development was also observed.

At the age of 22, before surgical intervention, she worked at a sheltered workshop five days a week. Her developmental status was equivalent to that of a 6-year-old, and her neuropsychological evaluation showed an IQ of less than 69. She was treated with valproate, phenytoin, levetiracetam, perampanel, and lamotrigine, but focal atonic seizures and FIASs occurred multiple times daily and generalized atonic seizures occurred multiple times per month, which frequently caused physical injuries. She had three to five physical injuries per month due to falling. Her preoperative EEG showed diffuse, rhythmic, slow and high-voltage sharp waves in the bilateral frontal and parietal lobes (Fig. 2a, Supplementary Fig. 1a).

She was referred to the neurosurgical department and underwent CC in a two-stage procedure, initially anterior CC followed by posterior CC five months later to achieve total disconnection. Considering that her age was 22, a two-stage total CC instead of single-stage was chosen to minimize risk for complications including a severe disconnection syndrome [11].

She exhibited transient exacerbation of fine motor dysfunction and speech dysfunction after posterior CC, both of which returned to the preoperative baseline within one month. Postoperative EEGs and MRIs were obtained (Fig. 2b and c, Supplementary Fig. 1b and c, Supplementary Fig. 2). Frequent antiseizure medication changes were conducted before anterior CC in an attempt to control seizures, but none were made thereafter. Six months after posterior CC, no generalized atonic seizures were observed, and the frequencies of focal atonic seizures and FIASs decreased significantly. Furthermore, the patient has not experienced any physical injuries after surgery. Her developmental status also did not change and her IQ was less than 69.

Data acquisition and statistical analysis

Data on the incidence of seizures was obtained from the daily records kept by her family. Standard chi-square test was used to compare the seizure frequencies in three stages: before operation at baseline, after anterior CC, and after posterior CC. $p < 0.05$ was considered statistically significant.

In-house MATLAB codes (MathWorks, Natick, MA, USA), with statistical and signal processing toolboxes, were used for the data analysis of inter-electrode coherence on EEG. Five minutes of interictal EEG during awake resting state were selected from EEGs before operation, after anterior CC, and after posterior CC. Five-minute-EEGs were selected to avoid artifacts as much as possible, without being arbitrary. Using the 10–20 system of electrode placement and linked ears reference montage, five-minute-EEGs were binned into 300 one-second waveforms, and each second was assigned as either 'baseline', 'discharge', or 'artifact' [12]. The number of one-second segments of EEG used for statistical analysis for 'baseline' were 180, 105, and 103 for before surgery, after anterior CC, and after posterior CC, respectively. Relative to a 'discharge', one-second segments of EEG were used for analysis lasting 48 seconds, 101 seconds, and 71 seconds respectively for each time period. Each second labeled as 'baseline' was collected and sorted into six frequency bands: delta, theta, alpha, beta, gamma, and high-gamma. Inter-electrode coherence for every two electrodes was calculated for each frequency band. Interhemispheric inter-electrode coherence was calculated as the coherence of combinations of the following electrodes: Fp1 and Fp2, F3 and F4, C3 and C4, P3 and P4, O1 and O2. The same process was done for each second identified as 'discharge', and inter-electrode coherence for discharges were calculated as well. Inter-electrode coherence in the three stages was compared using analysis of variance with Bonferroni correction, and $p < 0.05$ was considered significant.

Results

Seizure frequency

The patient preoperatively suffered from focal atonic seizures, generalized atonic seizures, and FIASs. The average number of focal atonic seizures that did not result in generalized atonic seizures averaged 36.5 times per month before surgical interventions, 38.75 times after anterior CC, and 6.75 times after posterior CC ($p < 1.00 \times 10^{-20}$). The average number of generalized atonic seizures was 2.5 times per month before surgical interventions, 2.5 times after anterior CC, and 0 times after posterior CC ($p = 0.007$). The average number of FIASs was 22.75 times per month before surgeries, 25.75 times after anterior CC, and 12.75 times after posterior CC ($p < 1.00 \times 10^{-3}$) (Supplementary Fig. 3).

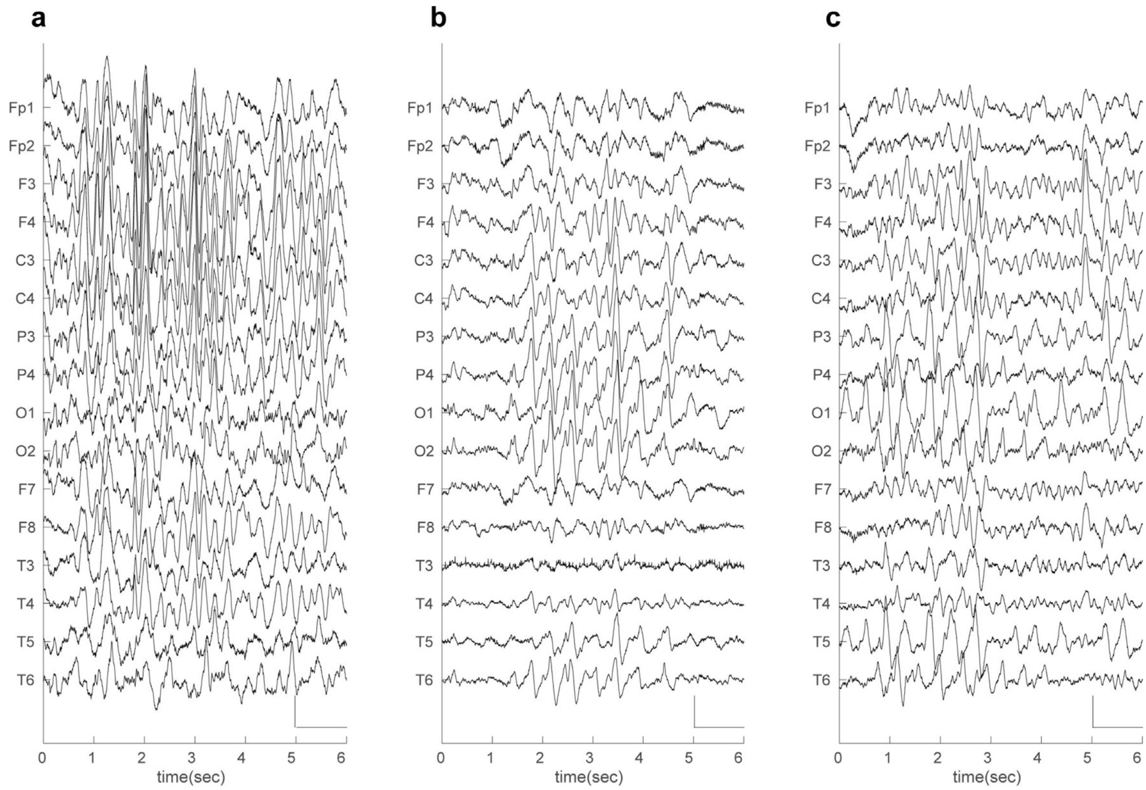

Fig. 2. Electroencephalogram (EEG) using standard ipsilateral ear reference montage in each stage. Before surgical interventions, EEG showed high-voltage sharp waves in bilateral frontal and parietal lobes (a). After anterior corpus callosotomy (CC), high-voltage sharp waves and slow waves in bilateral frontal and parietal lobes still persisted (b). After posterior CC, EEG showed high-voltage slow waves without bilateral synchrony (c).

Multiple comparison analysis showed that generalized atonic seizures significantly decreased after posterior CC (generalized atonic seizures, $p = 0.002$), but not after anterior CC. The same could be said for focal atonic seizures and FIAS as well (focal atonic seizures: $p < 1.00 \times 10^{-18}$; FIAS, $p < 1.00 \times 10^{-3}$). The statistical measures for each stage are shown in Supplementary Table 1. It is worth noting the patient did not experience generalized atonic seizures for six months following posterior CC.

Inter-electrode coherence

Coherence was calculated from the five minute-EEGs as described above. After anterior CC, the patient's EEG showed high-voltage sharp waves and slow waves in the bilateral frontal and parietal lobes. The voltages of interictal epileptiform discharges were sometimes higher in the right hemisphere and at other times over the left. After posterior CC, the patient's EEG showed high-voltage slow waves in the right frontal lobe or left frontal and parietal lobes, but did not demonstrate secondary bilateral synchrony. Inter-electrode coherence was calculated between every electrode and in every frequency band, but interhemispheric inter-electrode coherence showed significant incremental changes only in the delta, theta, and alpha frequency bands. Inter-electrode coherence showed significant changes in both baseline EEG and discharge waves. We focused on the analysis of delta, theta, and alpha frequency bands because most baseline waves were alpha waves (8–13 Hz) (Fig. 3a, b), and discharge waves were delta or theta waves (1–7 Hz) (Fig. 3c, d). After anterior CC, inter-electrode coherence in delta and theta waves decreased significantly between electrodes Fp1-Fp2, F3-F4, and C3-C4; but not between P3-P4 and O3-O4 in discharge waves, which suggests that disconnection of anterior corpus callosum decreased inter-electrode coherence in the anterior area, but not in the posterior area. However, it decreased significantly in all areas after posterior CC (discharge theta waves: Fp1-Fp2, $p < 1.00 \times 10^{-21}$; F3-F4, $p < 1.00 \times 10^{-13}$; C3-C4, $p < 1.00 \times 10^{-10}$; P3-P4, $p < 1.00 \times 10^{-26}$; O1-O2, $p < 1.00 \times 10^{-18}$) (Fig. 4, Supplementary Table 2), which is consistent with the clinical outcome that seizure frequency significantly decreased after posterior CC, but not after anterior CC.

Discussion

Desynchronization of interhemispheric activities in the acute phase of CC was supported by measuring intraoperative coherence [13,14]. However, long-term outcome of CC is determined by clinical endpoints. Our results showed a significant decrease in seizure frequency and bilateral synchronization after total disconnection, but not after anterior CC alone.

Seizure frequency

Ten previous studies reported on patients with subcortical band heterotopia who underwent CC (Supplementary Table 3). Three patients underwent total CC [6–8], while seven underwent anterior CC only [1,3,9,15,16]. All patients who underwent total CC had a significant decrease in seizure frequency, whereas patients who underwent anterior CC were not responsive in five of seven cases. Another report noted 77.8 % of children undergoing total CC had a notable reduction of generalized atonic seizures, whereas only 45.4% of those undergoing anterior CC alone had a reduced number of generalized atonic seizures [17]. Cases where anterior CC is sufficient for seizure control exist; however, these cases are less commonly seen that our case with complete disconnection. Moreover,

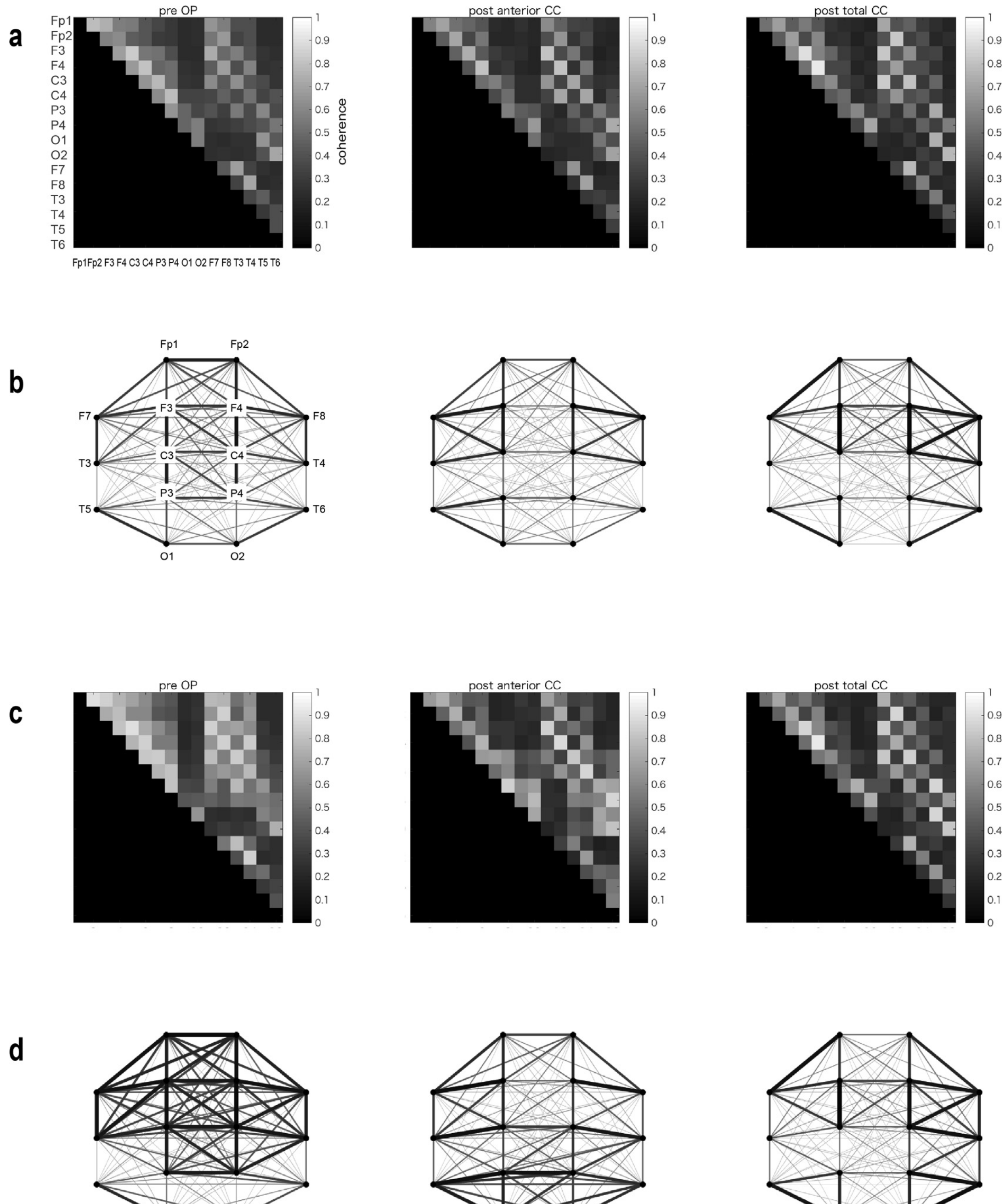

Fig. 3. Coherence calculated from the five-minute-EEGs extracted from each stage: before operation, after anterior corpus callosotomy (CC), and after posterior CC. Electrodes (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6) are lined up vertically and horizontally, and inter-electrode coherence between any two electrodes is represented by the color shown on the vertical bar on the right (a, c). A scheme of the brain: the lines connecting each electrode representing the coherence between two electrodes. Thick and wide lines represent stronger coherence (b, d). After anterior CC, inter-electrode coherence calculated for the two electrodes in symmetric positions is not decreased. After posterior CC, inter-electrode coherence between the two electrodes in symmetric positions is decreased, but inter-electrode coherence between the two electrodes in the same hemisphere is preserved. Inter-electrode coherence was calculated in all frequency bands in both baseline EEG and discharges. Representative data of baseline alpha waves (a, b) and discharge and theta waves (c, d) are shown in the figure.

selective posterior CC is known to be safe and effective in controlling drop attacks, raising the possibility that fibers crossing the posterior callosum may be specifically relevant to seizure-induced falls [18]. No obvious clinical or radiological factors have been suggested to predict the sufficiency of anterior CC.

Inter-electrode coherence

Inter-electrode coherence was analyzed before and after CC in a few previous reports [6,13,14,19,20]. Inter-electrode coherence was evaluated intraoperatively in the acute phase under general anesthesia [13]; however, it was unknown whether the same result occurred in normal conditions. Our results suggest that the findings of Okumura et al. could also be applied in the chronic state. Bilateral functional connectivity is likely driven by complex network interactions and is maintained by a few indirect structural connections beyond the anatomical fibers [20]. In our case, disconnection of the anterior corpus callosum did not significantly reduce the inter-electrode coherence in the anterior part of the brain, but total disconnection reduced the inter-electrode coherence in all

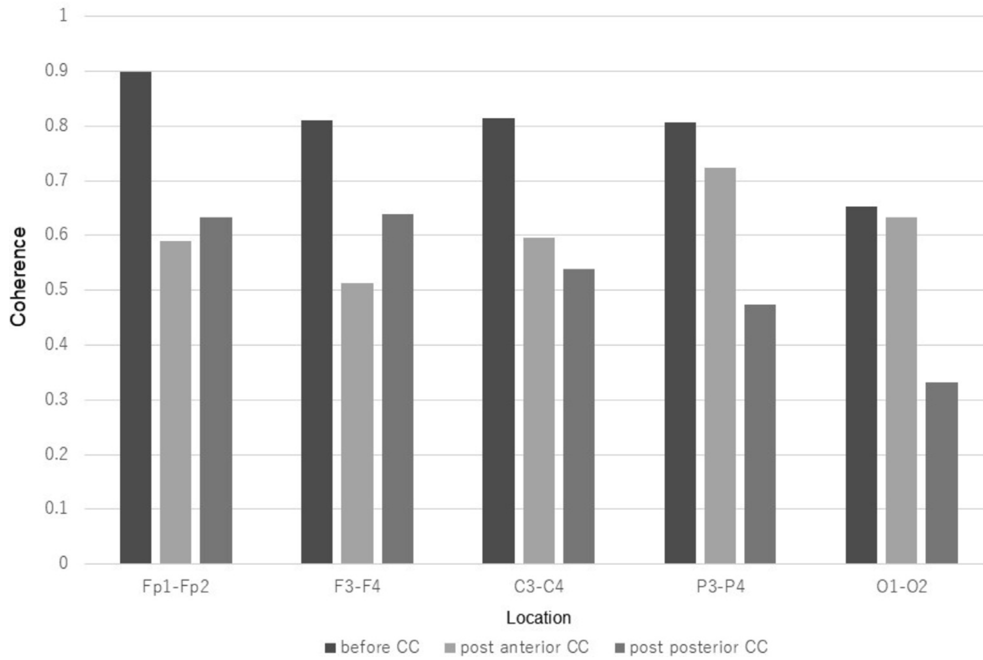

Fig. 4. Incremental changes of inter-electrode coherence for discharge theta waves in three stages are shown. Inter-electrode coherence calculated for the two electrodes in symmetric positions decreased only in anterior area after anterior corpus callosotomy (CC), and significantly decreased in all areas after posterior CC.

areas, which implies that the extent of reduction of inter-electrode coherence does not necessarily correlate with the extent of structural disconnection.

Relationship between seizure frequency and inter-electrode coherence

The inter-electrode coherence calculated for the two electrodes in symmetric positions reflects the functional connectivity of the right and left hemispheres mediated by the corpus callosum and has been used to discriminate changes in hemispheric relationships [19,21]. The statistical analysis of inter-electrode coherence before operation, after anterior CC, and after posterior CC was consistent with the clinical outcome, suggesting a positive correlation between inter-electrode coherence and seizure frequency. Coherence is superior to visual analysis of EEG because it can be measured quantitatively. Visual analysis of EEG needs to be evaluated by an experienced evaluator, and the evaluation may differ depending on the evaluator, whereas coherence can be used as a standardized measurement. We hypothesized inter-electrode coherence would be predictive of long-term improvement in seizure frequency and could be used to assess whether a patient who underwent anterior CC might experience clinical improvement.

Limitations

We analyzed intra-hemispheric inter-electrode coherence in this study as well and found coherence in delta and theta waves increased in some but not all areas after staged CC. Therefore, an increase in coherence cannot be interpreted as a significant change for every frequency and in every region of the brain and further research in this area is warranted.

A single case report is insufficient to propose inter-electrode coherence as a predictive factor for long-term clinical outcomes after CC. Further studies involving larger cohorts with bihemispheric malformations as well as cases without structural abnormalities are needed to validate inter-electrode coherence as a general predictive factor of clinical improvement after anterior CC.

Conclusion

Our patient with subcortical band heterotopia demonstrated a correlation between changes in inter-electrode coherence and reduction in baseline seizure frequency. We suggest that inter-electrode coherence could be utilized as a predive factor to judge clinical outcomes after anterior CC and recommend further studies be considered to evaluate the efficiency of this technique.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2022.100525.

References

[1] Landy HJ, Curless RG, Ramsay RE, Slater J, Ajmone-Marsan C, Quencer RM. Corpus callosotomy for seizures associated with band heterotopia. Epilepsia 1993;34(1):79–83. https://doi.org/10.1111/j.1528-1157.1993.tb02379.x.

[2] Bahi-Buisson N, Souville I, Fourniol FJ, Toussaint A, Moores CA, Houdusse A, et al. New insights into genotype–phenotype correlations for the doublecortin-related lissencephaly spectrum. Brain 2013;136(1):223–44. https://doi.org/10.1093/brain/aws323.

[3] Bernasconi A, Martinez V, Rosa-Neto P, D'Agostino D, Bernasconi N, Berkovic S, et al. Surgical resection for intractable epilepsy in "double cortex" syndrome yields inadequate results. Epilepsia 2001;42(9):1124–9. https://doi.org/10.1046/j.1528-1157.2001.39900.x.

[4] González-Morón D, Vishnopolska S, Consalvo D, Medina N, Marti M, Córdoba M, et al. Germline and somatic mutations in cortical malformations: Molecular

defects in Argentinean patients with neuronal migration disorders. PLoS ONE 2017;12(9):e0185103. https://doi.org/10.1371/journal.pone.0185103.
[5] Kikuchi K, Hamano S-I, Goto F, Takahashi A, Ida H. Epileptic focus in a case of subcortical band heterotopia: SISCOM and ictal EEG findings. Epilepsy Seizure 2010;3(1):192–8. https://doi.org/10.3805/eands.3.192.
[6] Hur YJ, Kim HD. Predictive role of brain connectivity for resective surgery in Lennox-Gastaut syndrome. Clin Neurophysiol 2016;127(8):2862–8. https://doi.org/10.1016/j.clinph.2016.05.011.
[7] Kawai K, Shimizu H, Yagishita A, Maehara T, Tamagawa K. Clinical outcomes after corpus callosotomy in patients with bihemispheric malformations of cortical development. J Neurosurg Pediatr 2004;101(2):7–15. https://doi.org/10.3171/ped.2004.101.2.0007.
[8] Saito Y, Sugai K, Nakagawa E, Sakuma H, Komaki H, Sasaki M, et al. Treatment of epilepsy in severely disabled children with bilateral brain malformations. J Neurol Sci 2009;277(1-2):37–49. https://doi.org/10.1016/j.jns.2008.10.009.
[9] Vossler DG, Jung Kyo Lee, Tae Sung Ko. Treatment of seizures in subcortical laminar heterotopia with corpus callosotomy and lamotrigine. J Child Neurol 1999; 14:282–8. https://doi.org/10.1177/088307389901400503.
[10] Srinivasan R, Winter WR, Ding J, Nunez PL. EEG and MEG coherence: Measures of functional connectivity at distinct spatial scales of neocortical dynamics. J Neurosci Methods 2007;166(1):41–52. https://doi.org/10.1016/j.jneumeth.2007.06.026.
[11] Lassonde M, Sauerwein H, Chicoine A-J, Geoffroy G. Absence of disconnexion syndrome in callosal agenesis and early callosotomy: brain reorganization or lack of structural specificity during ontogeny? Neuropsychology 1991;29(6):481–95.
[12] Shrey DW, Kim McManus O, Rajaraman R, Ombao H, Hussain SA, Lopour BA. Strength and stability of EEG functional connectivity predict treatment response in infants with epileptic spasms. Clin Neurophysiol 2018;129(10):2137–48. https://doi.org/10.1016/j.clinph.2018.07.017.
[13] Okumura E, Iwasaki M, Sakuraba R, Itabashi I, Osawa S-I, Jin K, et al. Time-varying inter-hemispheric coherence during corpus callosotomy. Clin Neurophysiol 2013;124(11):2091–100. https://doi.org/10.1016/j.clinph.2013.05.004.
[14] Rojas-Ramos OA, Ondarza R, Ramos-Loyo J, Trejo-Martínez D, del Río-Portilla Y, Guevara MA, et al. Acute effect of callosotomy on cortical temporal coupling in humans: Intraoperative electrocorticographic recording. Clin Neurophysiol 2013;124(10):1959–69. https://doi.org/10.1016/j.clinph.2013.04.334.
[15] Pallini R, Aglioti S, Tassinari G, Berlucchi G, Colosimo C, Rossi GF. Callosotomy for intractable epilepsy from bihemispheric cortical dysplasias. Acta Neurochir 1995;132(1-3):79–86. https://doi.org/10.1007/BF01404852.
[16] Palmini A, Andermann F, Aicardi J, Dulac O, Chaves F, Ponsot G, et al. Diffuse cortical dyslasia, or the 'double cortex' syndrome: The clinical and epileptic spectrum in 10 patients. Neurol 1991;41:1656–62. https://doi.org/10.1212/wnl.41.10.1656.
[17] Graham D, Tisdall MM, Gill D. Corpus callosotomy outcomes in pediatric patients: A systematic review. Epilepsia 2016;57:1053–68. https://doi.org/10.1111/epi.13408.
[18] Paglioli E, Martins WA, Azambuja N, Portuguez M, Frigeri TM, Pinos L, et al. Selective posterior callosotomy for drop attacks: A new approach sparing prefrontal connectivity. Neurology 2016;87(19):1968–74.
[19] Montplaisir J, Nielsen T, Côté J, Boivin D, Rouleau I, Lapierre G. Interhemispheric EEG coherence before and after partial callosotomy. Clin Electroencephalogr 1990;21(1):42–7. https://doi.org/10.1177/155005949002100114.
[20] O'Reilly JX, Croxson PL, Jbabdi S, Sallet J, Noonan MP, Mars RB, et al. Causal effect of disconnection lesions on interhemispheric functional connectivity in rhesus monkeys. Proc Natl Acad Sci 2013;110(34):13982–7. https://doi.org/10.1073/pnas.1305062110.
[21] Corsi-Cabrera M, Trías G, Guevara MA, Haro R, Hernández A. EEG interhemispheric correlation after callosotomy: one case study. Percept Mot Skills 1995;80(2):504–6. https://doi.org/10.2466/pms.1995.80.2.504.