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FULL-LENGTH ORIGINAL RESEARCH

Effective connectivity differs between focal cortical dysplasia types I and II

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Abstract

Objective: To determine whether brain connectivity differs between focal cortical dysplasia (FCD) types I and II.

Methods: We compared cortico-cortical evoked potentials (CCEPs) as measures of effective brain connectivity in 25 FCD patients with drug-resistant focal epilepsy who underwent intracranial evaluation with stereo-electroencephalography (SEEG). We analyzed the amplitude and latency of CCEP responses following ictal-onset single-pulse electrical stimulation (iSPES).

Results: In comparison to FCD type II, patients with type I demonstrated significantly larger responses in the electrodes near the ictal-onset zone (<50 mm). These findings persisted when controlling for the location of the epileptogenic zone, as noted in patients with temporal lobe epilepsies, as well as controlling for seizure type, as noted in patients with focal to bilateral tonic-clonic seizures (FBTCS). In type II, the root mean square (RMS) of CCEP responses dropped substantially from the early segment (10–60 ms) to the middle and late segments (60–600 ms). The middle and late CCEP latency segments showed the largest differences between FCD types I and II.

Significance: Focal cortical dysplasia type I may have a greater degree of cortical hyperexcitability as compared with FCD type II. In addition, FCD type II displays a more restrictive area of hyperexcitability in both temporal and spatial domains. In patients with FBTCS and type I FCD, the increased amplitudes of RMS in the middle and late CCEP periods appear consistent with the cortico-thalamo-cortical network involvement of FBTCS. The notable differences in degree and extent of hyperexcitability may contribute to the different postsurgical seizure outcomes noted between these two pathological substrates.

KEYWORDS
brain networks, cortico-cortical evoked potentials, epilepsy, focal cortical dysplasia, SEEG

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1 | INTRODUCTION

Focal cortical dysplasia (FCD) is a common pathological substrate in epilepsy surgery.[1] FCD type II is characterized by architectural disorganization as well as the presence of dysmorphic neurons with (type IIB) or without (type IIA) balloon cells.[2] Magnetic resonance imaging (MRI) abnormalities in FCD type II include increased cortical thickness, increased signal on fluid-attenuated inversion recovery (FLAIR), and gray-white matter blurring. The "transmantle" sign, a hallmark MRI finding in FCD, suggests the presence of FCD IIB.[3] Type I, which is not as well defined, is characterized mainly by architectural columnar and/or laminar disorganization in the absence of clear morphological cellular abnormalities. However, the MRI is often normal in the majority of patients with FCD type I.[2,3] FCD type I can be associated with nonspecific MRI differences including reduced white matter volume and subtly increased signal on FLAIR and T2 images.[4]

As with other substrates of focal epilepsy, a notable challenge in FCD is to determine the extent of the epileptogenic zone, even in MRI-positive lesions. Intracranial electrode monitoring may reveal epileptogenicity that extends beyond the nidus of the MRI abnormality.[5] Due to this characteristic of FCD, surgical failure can occur if only the MRI lesion is removed.[6] On the other hand, MRI-negative or nonlesional epilepsy poses a significant challenge in surgical management,[7] often requiring the use of intracranial electrode monitoring.[8]

Recent studies of focal epilepsy analyzing brain imaging, electrophysiology, and modeling techniques have shown evidence of multiple brain regions involved in epileptogenicity rather than a discrete area of dysfunction.[9,10] One of the posited reasons for surgical failure is that the given epileptic network is widely distributed.[11] This finding is supported by the observation that few patients achieve good outcomes following a small surgical resection.[12,13] The concept of epilepsy as a network-based disease has gained widespread acceptance from studies analyzing structural connectivity,[14] functional connectivity,[15] and effective connectivity.[16,17]

Effective connectivity aims to establish a causal or directed relationship between separate brain regions.[18] One approach to measuring effective connectivity involves recording cortico-cortical evoked potentials (CCEPs)[19] which can be undertaken in patients undergoing intracranial electrode evaluation with either subdural electrodes or stereo-electroencephalography (SEEG). CCEPs are recorded by applying single-pulse direct electrical cortical stimulation (SPES) to pairs of intracranial electrodes and averaging the evoked potentials in the remaining electrodes. In this way, CCEPs can directly study pathological and functional large-scale brain networks in vivo with a high degree of spatiotemporal resolution[16,19] in the regions of the implanted intracranial electrodes. A larger amplitude of CCEPs following stimulation of the ictal-onset zones has been shown to reflect an increased excitability of the cortex.[20] In addition, SPES and CCEPs have been employed to map the degree of epileptogenicity by measuring the level of neuronal excitability.[20,21] These studies suggested that either an increased amplitude of the early response of CCEPs or the presence of a delayed response following SPES can localize the epileptic cortex.

Epilepsy surgery is more successful in FCD type II,[22] possibly due to its association with MRI lesions. In contrast, there is a greater risk of epilepsy surgical failure in patients with FCD type I.[23] One reason for the failure may relate to the difference in the extent of epileptogenicity. We hypothesize that the extent of epileptogenicity is greater in FCD type I and more restricted in type II. We test our hypothesis using CCEP, a marker of hyperexcitability, among patients who underwent SEEG for epilepsy surgical localization. We expect the above differences between FCD types to result in distinctive patterns of hyperexcitability that can be assessed by ictal-onset single-pulse electrical stimulation (iSPES) of the suspected ictal-onset zone This difference would be an important consideration when planning epilepsy surgery guided by SEEG.

Key Points

- Focal cortical dysplasia (FCD) type I is associated with a larger degree of hyperexcitability in comparison to type II.
- FCD type II shows a more restrictive area of hyperexcitability compared with type I.
- Patients with FCD type II and Engel class I outcomes have a more restricted region of hyperexcitability than those with Engel class II.

2 | METHODS

2.1 | Demographic and SEEG data of participants

Patients were recruited with approval from our institutional review board (IRB protocol #12-857). Consecutive patients were identified from 2015 to 2018 who had undergone SEEG and had FCD type II. A total of 10 patients

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(age range: 5–47, two female) were identified, including seven type IIa and three type IIb. For each FCD type II patient, we matched at least one FCD type I, with a similar epilepsy localization and age range. To ensure an accurate comparison of epilepsy localization, we chose FCD type I patients with the best seizure-free outcomes. As a result, 15 FCD type I patients (age range: 5–69, eight female) were selected (Table 1). The iSPES was performed in 58 pairs for type I and 32 pairs for type II. On average, each participant had 3.6 iSPES sites (type I: 3.9, type II: 3.2), 13 implanted electrodes (type I: 14, type II: 12), and 116 contacts in gray matter (type I: 124, type II: 105). We performed t tests to compare these variables between FCD types I and II. However, no significant difference was observed in these four features: age, iSPES sites, implanted electrodes, and contacts in the gray matter after correcting for multiple comparisons (family-wise error [FWER] $< \alpha = .05$ using the Hochberg technique).

2.2 | Recording and anatomical labeling

A description of SEEG methodology and CCEP recording can be found online (Supporting Information).

2.3 | MRI and SEEG findings

We have provided presurgical MRI and ictal and interictal SEEG findings in Table S1 in the Supporting Information. Briefly, four patients with FCD type I and five participants with type II showed lesions consistent with FCD. There were four patients (two type I and two type II) who had previously failed epilepsy surgery with no other lesions visible on MRI. One patient in each group had MRI findings related to a previous ischemic event. As a result, 8 of 15 patients with type I (53%) and 2 of 10 with type II (20%) were identified as nonlesional. Interictal SEEG showed (near) continuous spikes in four patients with FCD type I and four cases with type II. Based on our observations, there was no clear pattern or distribution of ictal activity that can differentiate the two FCD types.

2.4 | The extent of the resection

We coregistered presurgical and post-resection MR images to compute the volume of resection. This was then normalized to the cerebral volume for each patient. We have described details of the analysis in the Supporting Information. Results demonstrated a relatively larger resected volume for patients with FCD type I when compared with type II ($p \approx .06$, marginally significant when comparing means).

2.5 | CCEP analysis

In this study we considered only contacts in gray matter. The electrocorticography data containing the SPES periods were processed using Brainstorm.[24] Trials were visually inspected and those containing excessive noise were removed from further analysis. The remaining trials were averaged to obtain the evoked potential from all other cortical SEEG electrodes for each recording site. We analyzed these waveforms either in their entire response period (10–600 ms after the stimulation onset) or divided them into three intervals: early latency (10–60 ms), middle latency (60–250 ms), and late latency (250–600 ms).

2.6 | Statistical analysis

2.6.1 | Significant CCEP responses

The early, middle, and late latency periods of the averaged CCEP responses were assessed for statistical significance by employing a sign permutation test as described in our recent work.[25] The test operates by randomly multiplying the responses of each trial by +1 or −1 and forming a new average evoked response for each contact. Under the assumption that no response has been recorded, there should be no effect on the distribution of the evoked response. When a latency period is identified as significant using this method, the root mean square (RMS) of the response can be calculated to represent the strength of connectivity. In this section, we employed SAS 9.3 software (SAS Institute) to perform statistical analyses on a complete-case basis ($\alpha = .05$). The averaged CCEP responses and results of applying the sign permutation test are depicted in Figure 1B. Similarly, the sign permutation test was also performed for the entire period (10–600 ms). We limited further analyses to statistically significant responses. Thereafter, the CCEPs were divided into two groups based on the Euclidean distance from the midpoint of the stimulating pair to the recorded contact. These groups were labeled as near (<50 mm) and far (>50 mm).

2.6.2 | Comparing RMS of CCEPs between two FCD types

Statistical analysis between RMS responses of types I and II in the period of 10–600 ms was conducted by percentile bootstrap on trimmed means ($B = 10^4$ bootstraps, with

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TABLE 1 Clinical characteristics of patients

ID	Sex	Age (year)	FCD	Implanted electrodes	Gray matter contacts	Ictal stim pairs	SEEG classification	Resective surgery	Outcomes Engel class	Duration of epilepsy (Years)	Focal to bilateral tonic-clonic seizures	Region
M1977J4I	M	37	Type IIA	8	69	4	Right peri-Rolandic (face)	Right subcentral and Right caudal precentral gyrus	IA	32	+	Extra
F1996J57	F	19	Type IIA	10	47	2	Right precuneus and post cingulate	Right precuneus, ant/mid/post cingulate	IIB	19	−	Extra
M1968H92	M	47	Type IIB	11	73	2	Left temporo-perisylvian (posterior)	Left posterior temporal	IA	43	+	Temporal
M2000H77	M	16	Type IIA	15	113	4	Left frontoparietal operculum	Left frontoparietal	IA	10	+	Extra
M1986H8I	M	30	Type IIA	14	138	7	Left basomesial frontal	Left orbitofrontal	IA	21	+	Extra
M1987I2S	M	30	Type IIA	14	129	4	Left lateral temporal	Left temporal	N/A	26	+	Temporal
M1992I2F	M	25	Type IIA	14	156	2	Left superior & Middle frontal gyrus	Left superior frontal gyrus and mid cingulate	IIB	25	-	Extra
M2000H8Q	M	16	Type IIA	14	138	2	Left frontal epilepsy	Left dorsal lateral frontal	IIB	11	−	Extra
M1979H8J	M	38	Type IIB	10	87	4	Left neocortical temporal epilepsy	Left posterior lateral/basal temporal	IB	36	+	Temporal
F2012H8C	F	5	Type IIB	9	98	1	Left mesial frontal epilepsy	Left mesial frontal resection	N/A	3	−	Extra
F1982I2H	F	35	Type I	14	140	2	Left mesial frontal epilepsy	Left superior frontal gyrus as well as the motor cingulate	IIB	24	+	Extra
F1983I26	F	34	Type I	10	116	6	Right precentral and inferior-frontal gyrus	Right frontal	IA	26	+	Extra
M1960GAP	M	56	Type I	10	74	10	Left caudal postcentral gyrus	Left parietal	IA	36	+	Extra

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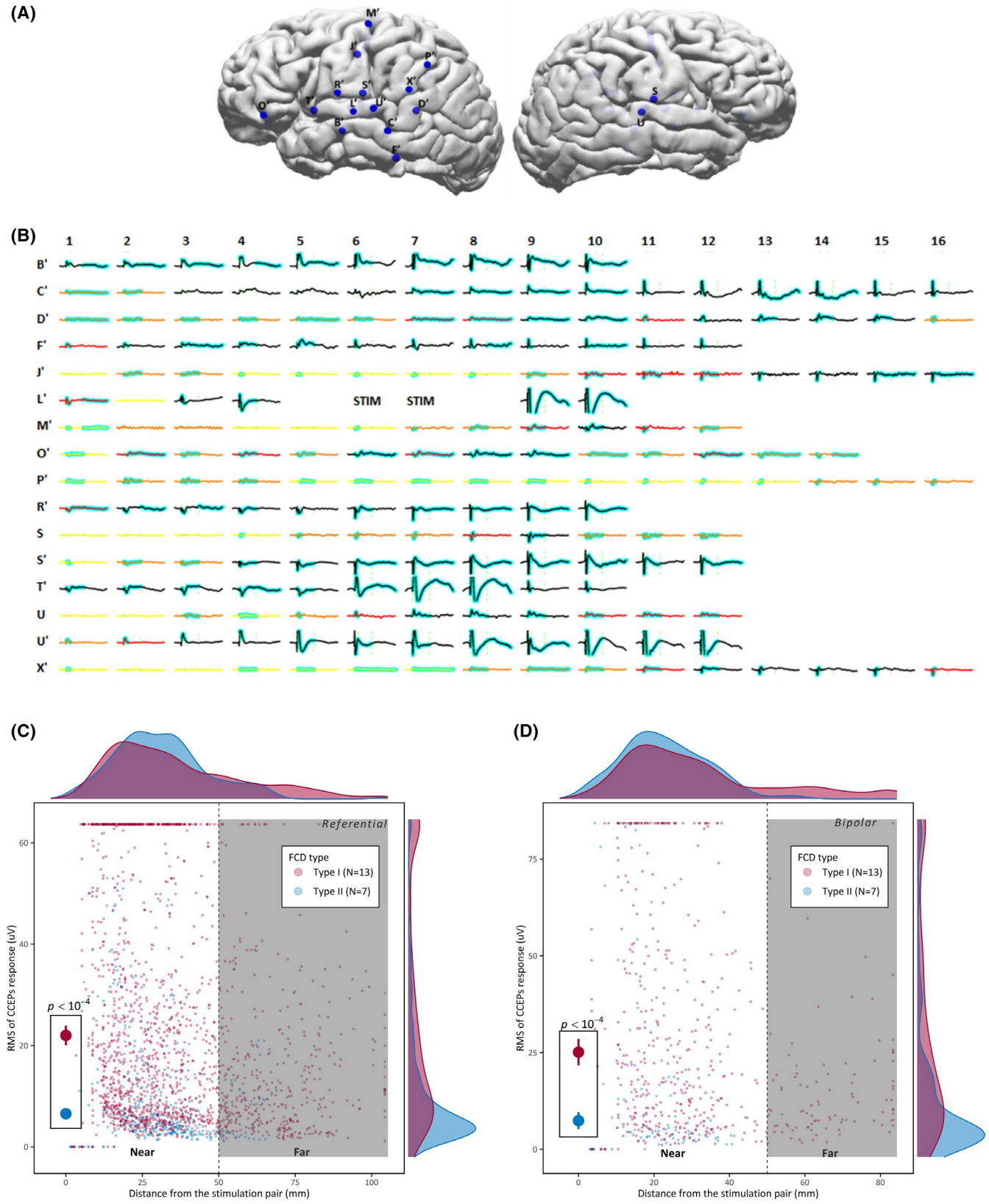
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TABLE 1 (Continued)

ID	Sex	Age (year)	FCD	Implanted electrodes	Gray matter contacts	Ictal stim pairs	SEEG classification	Resective surgery	Outcomes Engel class	Duration of epilepsy (Years)	Focal to bilateral tonic-clonic seizures	Region
M1997J5C	M	18	Type I	15	113	3	Left precuneus, posterior cingulate, occipital	Left parieto-occipital	IIA	18	+	Extra
F1987I33	F	31	Type I	16	142	3	Left superior temporal gyrus & Heschl's gyrus	Left superior temporal gyrus & Heschl's gyrus	IA	25	−	Temporal
F2005H33	F	11	Type I	14	132	1	Left orbitofrontal & Frontal operculum	Left orbito-frontal	IA	10	−	Extra
M1984J4H	M	30	Type I	14	98	4	Right basal temporo-Occipital	Right extensive temporal	IA	12	+	Temporal
M1984GBB	M	32	Type I	15	125	5	Left antero-lateral-basal temporal	Left temporal	IA	3	+	Temporal
F1988H88	F	29	Type I	16	131	4	Right temporal & Collateral sulcus	Right temporal	IA	16	+	Temporal
M1990J42	M	24	Type I	16	133	2	Right temporal pole, inferior & middle temporal gyrus	Right temporal	IA	17	+	Temporal
M1984I2P	M	33	Type I	14	117	3	Right superior frontal gyrus	Right superior & Middle frontal gyrus	ID	32	+	Extra
F1965HAA	F	52	Type I	15	149	7	Right mesial frontal	Right frontal	IA	4	+	Extra
F2005HC8	F	12	Type I	14	134	4	Right frontal (mesial and lateral)	Right frontal	IA	10	+	Extra
M1999J4J	M	16	Type I	15	139	1	Left temporal pole	Left anterior temporal	IA	4	+	Temporal
F1949G4Q	F	69	Type I	14	112	3	Right frontal	Right frontal pole	IA	50	+	Extra

Abbreviation: FCD, focal cortical dysplasia; N/A, Not available.

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20% trimming on each side). This method can deal with the possible non-normality and heteroscedasticity of the sampled data.[26] The test was performed using the *trimpb2* function in the WRS2 package[26] for R (R Foundation for Statistical Computing). We contrasted the RMS values between the two FCD types for near distances, since FCD type II significant responses were seen predominantly within 50 mm of the stimulation site.

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FIGURE 1 Recording paradigm and cortico-cortical evoked potential (CCEP) responses in two reference montages. (A) A schematic representation of electrode implantation. Each electrode can include up to 16 contacts. (B) CCEP responses by stimulating the L′6–L′7 pair. Cyan highlighted waveforms indicate significant responses after the permutation test (see Section 2). (C) Significant root mean square (RMS) values of CCEPs (in referential montage) are depicted for the 10–600 ms latency period. Each point in the scatter plot represents a unique recording contact from a stimulation site. Hypothesis testing was conducted using contacts in near distances (<50 mm). The box at the bottom left displays the trimmed mean and confidence interval for each group and the *p*-value for their comparison. For illustration purposes, data points larger than four median absolute deviations above the median were Winsorized in each axis, independently. Marginal distributions depict the increased connectivity for focal cortical dysplasia (FCD) type I in comparison to FCD type II. *N* denotes the number of patients in each category. (D) The data displayed using a bipolar montage illustrates consistent findings between FCD types I and II

2.6.3 | Latency analysis

We used a between-by-within test to assess the effects of two main factors: FCD type (Factor A with two independent levels: types I and II) and latency (Factor B with three dependent levels: early, middle, and late), and their possible interaction on CCEP responses. This 2-by-3 design was evaluated using a robust bootstrap-t method on trimmed means ($B = 10^4$ bootstraps, with 20% trimming on each side using the *bwmcp* function in WRS2 package[26]). All *p*-values, including the post hoc analysis, were collectively corrected using the Hochberg technique (FWER <0.05).

3 | RESULTS

3.1 | RMS of CCEPs in FCD types I and II

We analyzed electrodes with significant RMS values of CCEP responses based on the sign permutation test following SPES of the ictal-onset zone. Figure 1C illustrates the RMS of CCEP responses in the entire analysis period (10–600 ms) for FCD types I and II, using a referential montage (midline scalp reference). The *x*-axis represents the distance of each contact from the stimulated pair. Five (two with type I and three with type II) of 25 patients were discarded in this section, since none of their contacts

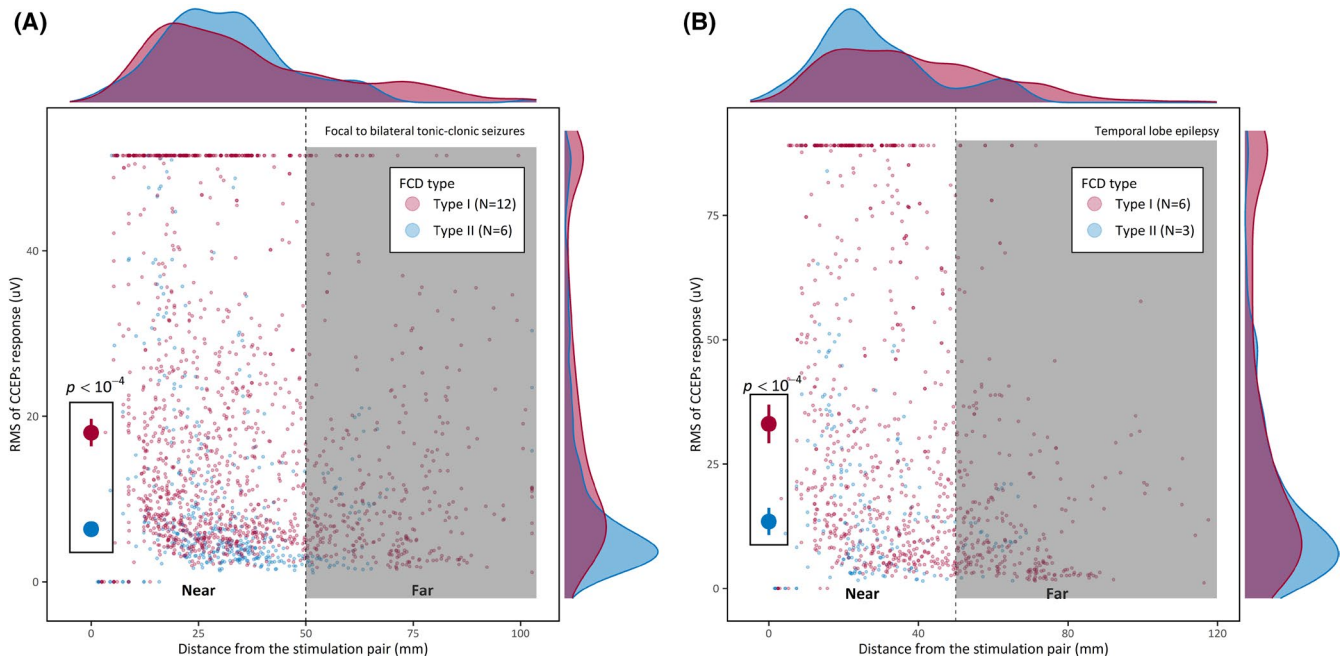


FIGURE 2 Cortico-cortical evoked potential (CCEP) response in two subcategories. (A) Root mean square (RMS) values of CCEPs (in referential montage) in the 10–600 ms latency period. Here, only patients with focal to bilateral tonic-clonic seizures (FBTCS) were considered. Each point in the scatter plot represents a unique recording contact from a stimulation site. Hypothesis testing was conducted using contacts in near distances (<50 mm). The box at the bottom left displays the trimmed mean and confidence interval for each group and the *p*-value for their comparison. For illustration purposes, data points larger than four median absolute deviations above the median were Winsorized in each axis, independently. Marginal distributions depict the increased connectivity for focal cortical dysplasia (FCD) type I in comparison to FCD type II. *N* represents the number of patients in each category. (B) The equivalent plot for patients with temporal lobe epilepsy

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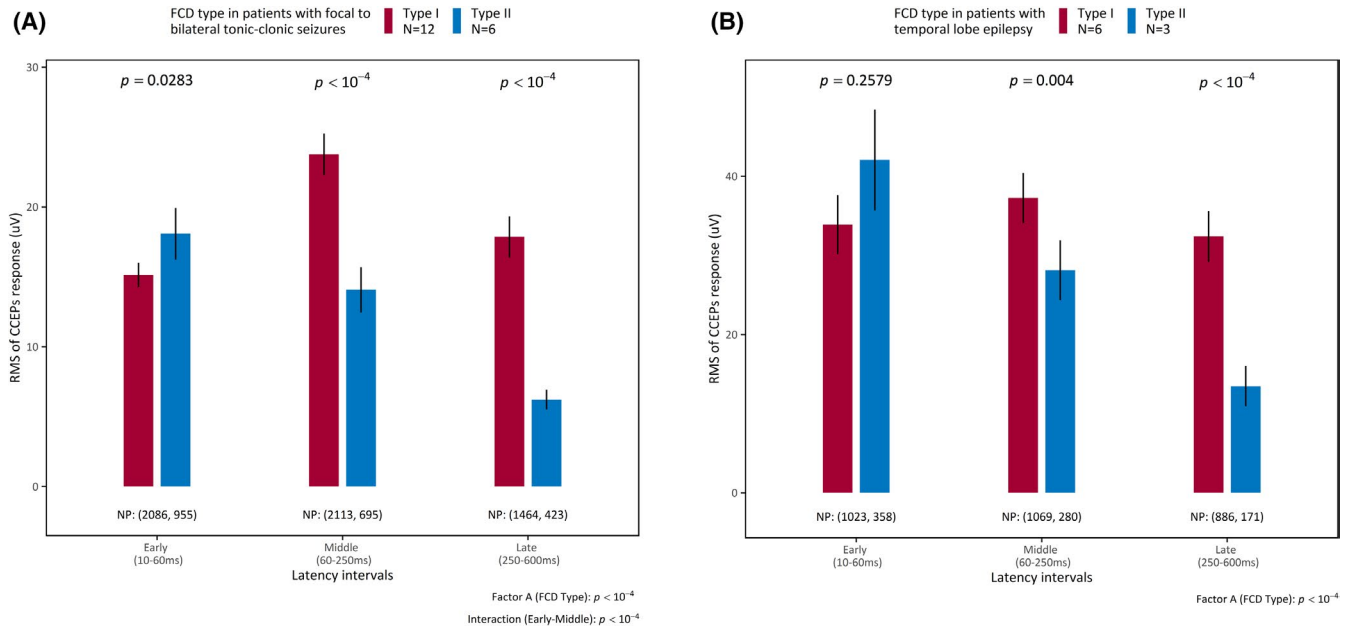


FIGURE 3 Cortico-cortical evoked potential (CCEP) responses in different latency intervals. (A) Root mean square (RMS) values of CCEPs are computed in early, middle, and late latencies in patients with focal to bilateral tonic-clonic seizures (FBTCS). The plot shows the trimmed mean (20% trimming on each side) with 95% confidence interval based on the trimmed mean. A robust between-by-within analysis presented a significant difference in Factor A (focal cortical dysplasia [FCD] type). Numerical *p*-values illustrate the distinction for each latency. Comparing FCD types in early and middle latencies revealed a disordinal interaction ($p < 10^{-4}$). *N* denotes the number of patients in each category. The variable NP represents the number of contacts that passed the permutation test for each latency. All *p*-values are corrected. (B) The same approach is illustrated for patients with temporal lobe epilepsy

showed a significant response. Comparing marginal distributions, FCD type II displays more restricted RMS values than type I in both axes. This was true when comparing absolute RMS values where FCD type I had greater values than FCD type II as well as RMS values measured from the distance to stimulation site where FCD type II had RMS values that dropped off more drastically than FCD type I in contacts farther away from the stimulation site. Similar results were observed for the bipolar montage (Figure 1D).

Based on the above statistical analysis, type I demonstrated significantly larger RMS values than type II, encompassing the entire analysis period (10–600 ms) after the stimulation ($p < 10^{-4}$ for both referential and bipolar montages). The similarity of results in Figure 1 among referential and bipolar montages argues against the possible influence of reference selection bias or far field potentials. For the scatter plots, marginal distributions, and statistical tests, the selection of bipolar or referential montage had no effect on our findings except that the bipolar montage showed a faster drop in the spatial distribution in FCD type II. For simplicity, we represent our findings in referential montage only after Figure 1.

3.2 | Focal to bilateral tonic-clonic seizures and epilepsy localization

In the prior section we pooled all patients independent of their seizure type or epilepsy localization. However, one can argue that these parameters might be influential on the amplitude of CCEPs. To examine this hypothesis we categorized our data in two different ways. First, only patients with focal to bilateral tonic-clonic seizures (FBTCS) were compared. The result is depicted in Figure 2A, in which a pattern similar to that noted in Figure 1 can be observed. For those patients with FBTCS, CCEP responses are significantly larger for FCD type I than type II ($p < 10^{-4}$ for near contacts). In addition, we investigated patients with temporal lobe epilepsy separately (this category includes patients with temporo-perisylvian and lateral temporal SEEG hypotheses) because we had a large number of patients in this category. Figure 2B shows that our previous finding holds in this scenario as well: the trimmed mean for RMS of CCEPs is significantly larger for FCD type I than type II ($p < 10^{-4}$ for near contacts). Other epilepsy subtypes were not evaluated due to the smaller number of patients in other categories.

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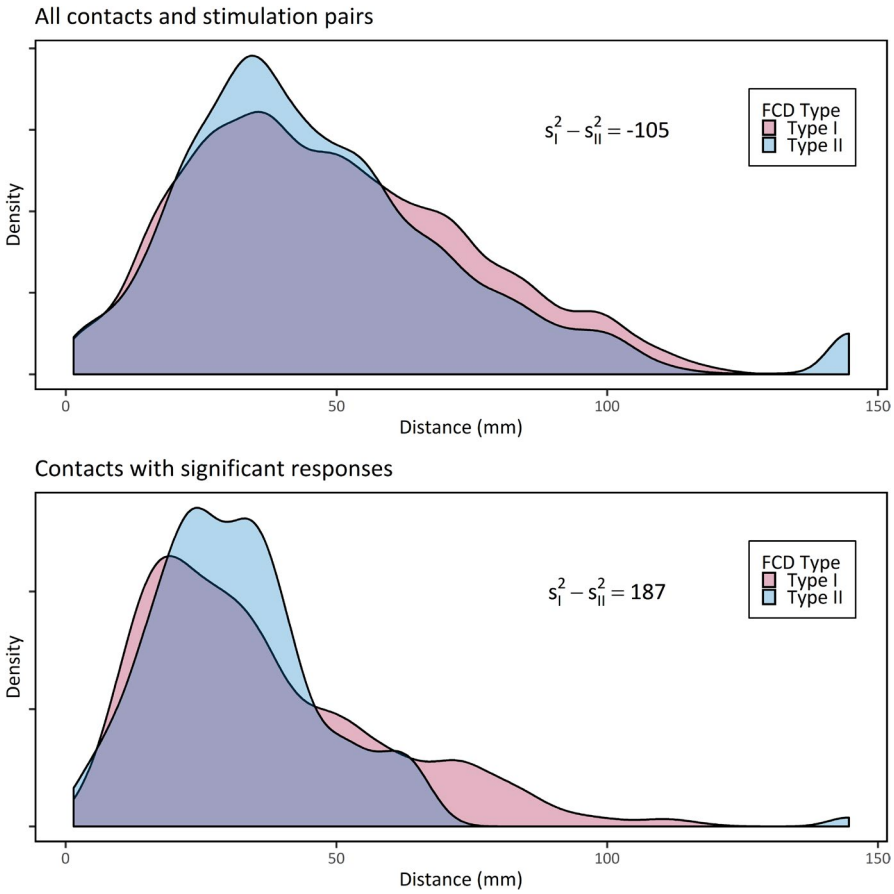


FIGURE 4 Electrode implantation. Probability distribution functions (PDFs) of distances between recording contacts and the stimulation pairs. (A) This plot shows PDFs for type I and type II considering all implanted electrodes and gray matter contacts. (B) This plot is restricted to contacts with significant cortico-cortical evoked potential (CCEP) responses. A between-by-within analysis of variance (ANOVA) based on ranks indicated an interaction among factors (focal cortical dysplasia [FCD] type and significant response) ($p = 5.4 \times 10^{-6}$). In addition, the differences of variances in two cases imply a broader response for FCD type I

3.3 | Latency periods

We divided CCEPs into three latency intervals: early (10–60 ms), middle (60–250 ms), and late (250–600 ms). Figure 3A compares these latency periods between FCD types I and II in patients with FBTCS. Each bar depicts the trimmed mean and confidence interval of the corresponding subgroup.

Consistent with our previous findings, the main-effects analysis of the between-by-within test indicated a larger RMS response for FCD type I than type II ($p < 10^{-4}$). In the post hoc analysis, middle and late latency periods of the CCEPs exhibited the same pattern ($p < 10^{-4}$ for both); however, results revealed a slightly greater response in the early latency period (10–60 ms) for type II ($p = .0283$ in Figure 3A for patients with FBTCS). Furthermore, we compared different latency periods for each level of FCD type. Type I presented a substantial increase from early to middle and late latency intervals ($p < 10^{-4}$ for both comparisons among patients with FBTCS). In type II, when comparing early to other latency periods, we observed a decrease in amplitude of RMS responses ($p < 10^{-4}$ for early-middle and $p < 10^{-2}$ early-late). In addition, our statistical analysis indicated an interaction between FCD types and latencies ($p < 10^{-4}$ for early-middle). Finally, FCD type II showed a steeper falloff in significant electrodes, denoted as *NP* in Figure 3A, by the end of the response, indicating its temporal restriction.

A similar analysis was conducted when considering patients with temporal lobe epilepsy (Figure 3B). Results are largely similar to the previous plot. FCD type I represents a larger response than type II in the middle and late latency periods ($p = .004$ and $p < 10^{-4}$, respectively). FCD type II shows diminishing RMS values from the middle to late latency periods ($p = .017$). We also find a decline for type I when comparing early and middle latency periods to late ($p = .005$ for early-late and $p = .0002$ for middle-late).

3.4 | Electrode implantation

One question that may arise is whether observed differences between the two types of FCD are due to the electrode implantations. In clinical practice, planning of the SEEG implantation incorporates the results of multiple non-invasive tests. Although the presence of a lesion on MRI may affect the position of one or two electrodes, suspicion of FCD type I over type II or vice versa does not alter the overall implantation targets. To demonstrate, we computed empirical probability distribution functions (PDFs) of distances between contacts from the stimulation

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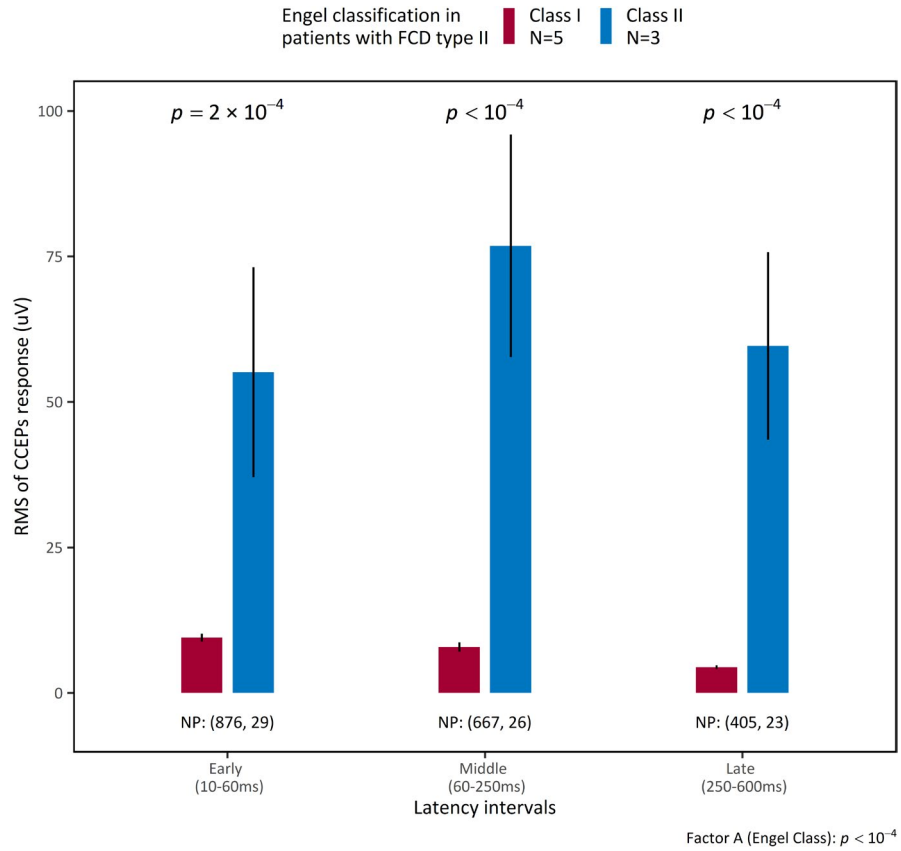


FIGURE 5 Cortico-cortical evoked potential (CCEP) responses for different surgery outcomes. Variations of CCEP responses in different latency intervals for two Engel classes of surgery outcomes in patients with focal cortical dysplasia (FCD) type II. Root mean square (RMS) values of CCEPs are computed in early, middle, and late latencies. The plot shows the trimmed mean (20% trimming on each side) with 95% confidence interval based on the trimmed mean. A robust between-by-within analysis presented a significant difference in factor A (Engel class). Numerical *p*-values illustrate the distinction between two Engel classes for each latency. *N* denotes the number of patients in each category. The variable NP represents the number of contacts that passed the permutation test for each latency. All *p*-values are corrected

areas for type I and type II in two scenarios. In the first scenario we considered all pairs of contacts and stimulation sites. In the second we considered only pairs with significant responses in recording contacts based on the permutation test (see Section 2). These distributions are depicted in Figure 4. Visually, the PDFs are similar when considering all electrodes (Figure 4A). However, when considering electrodes that were deemed significant, the corresponding PDF for type II exhibits a more rapid falloff (Figure 4B). This restrictive spatial response in type II can be verified by two analyses. First, by comparing the differences between the variances of each distribution in Figure 4A,B, which changes from −105 to 187 when subtracting the variance of type II from type I. Second, the interaction term of a between-by-within analysis of variance (ANOVA) test based on ranks[26] can contrast the effect of sign permutation test on distance distributions for two FCD types. We found that this interaction is statistically significant ($p = 5.4 \times 10^{-6}$), suggesting that FCD type II has a more restricted distribution of highly connected contacts with the ictal-onset zone than type I. These investigations indicate that our findings were not impacted by initial electrode implantation.

3.5 | Surgery outcomes

In this study, the surgery outcomes of all but one of the patients with FCD type I were classified as Engel I, that is, seizure-free. For type II, we had a wider range of outcomes: five patients with Engel class I vs three patients with Engel class II. This observation might seem contradictory to our assumption that, in general, FCD type II would have a higher chance of seizure freedom. However, it is important to note that the surgery outcomes in our data are the result of the study design and the resective surgery, since the size of the resection was larger in patients with FCD type I (see Section 2 and Supporting Information). We analyzed FCD type II patients who required SEEG, which suggests a less clear surgical hypothesis from just

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the non-invasive data (such as non-lesional MRI). FCD type I patients, on the other hand, were matched to FCD type II, and the FCD type I cases with best surgical outcomes were chosen to ensure adequate matching of epilepsy localization.

We compared the RMS of the CCEP responses between two Engel classes in FCD type II patients. Figure 5 illustrates these differences. We observe that patients with a better surgery outcome (class I) have smaller and more restricted CCEP responses than class II. A 2-by-3 between-by-within test (percentile bootstrap on trimmed means) was conducted in which Engel class and latency were Factors A and B, respectively. The main-effects analysis of this test indicated a larger RMS response for class II than class I ($p < 10^{-4}$ for Factor A). Post hoc analysis for the three latency intervals also revealed a similar pattern ($p = 2 \times 10^{-4}$ for early and $p < 10^{-4}$ for middle and late periods).

4 | DISCUSSION

We used CCEPs, a measure of effective connectivity, to demonstrate that FCD type II shows a more restricted pattern of connectivity compared to type I. We examined CCEP responses that were close to the ictal-onset zone (distances within 50 mm) for two reasons: (1) this distance has been shown previously to be significantly modulated by CCEPs,[27] and (2) our analysis showed that significant responses in FCD type II were seen predominantly within 50 mm. In this study, we showed increased hyperexcitability at the ictal-onset zone in FCD type I compared to type II (Figure 1C,D). We also observed a greater extent of hyperexcitability in FCD type I compared with type II. In other words, FCD type I induces a higher degree of distal connectivity than type II (Figures 1C and 4B). These observations lend support to the notion of the formation of a local epileptogenic network in FCD type II and a more extended epileptogenic network in type I. This difference could explain the results of a previous study showing better seizure-free outcomes following epilepsy surgery in patients with FCD type II.[28] Effective connectivity based on clinical seizure types in FCD was also assessed in our study. We found the same difference in the pattern of connectivity between FCD types I and II when considering the presence of FBTCS (Figure 3A). Focal epilepsy with FBTCS has been noted to have a larger propagation network than in focal epilepsy without FBTCS.[29,30] Therefore, the question could be raised of whether the increase in RMS CCEPs both near and distant from the ictal-onset zone in FCD type I could be attributable to a greater percentage of patients having FBTCS. Our analysis shows that this is not the case in this study. When patients with FBTCS were analyzed separately, the difference between types I and II was more clearly seen in the middle and late periods of the CCEP response than in the early period (Figure 3A). In FCD type I, the middle and late components of CCEPs significantly increased compared to the early component. The middle and late components of CCEPs have been attributed to the activation of cortico-thalamo-cortical networks in epilepsy, whereas the early latency component is believed to result from cortico-cortical activation.[19,31] The thalamus has been implicated as one of the hubs that modulates propagation of FBTCS in focal epilepsy.[32] The findings of the later components of CCEPs being accentuated in FBTCS in FCD type I could represent activation of these cortico-thalamo-cortical pathways. In patients with FBTCS and FCD type II, the early component was larger than the earlier component in type I yet still retained the same pattern of a dramatic fall-off in RMS values in middle and late components, suggesting a restricted region of hyperexcitability. In FCD type II with FBTCS, the larger RMS values in early latency may suggest that the mechanism of propagation relies on the cortico-cortical pathways as opposed to the cortico-thalamo-cortical pathways as noted in FCD type I. Aberrant functional connectivity profiles have been reported within and beyond FCD type II lesions as determined by seed-based functional MRI combined with geodesic distance maps both within and beyond the MRI visible lesion.[28]

In connectivity analysis of FCD, the degree and extent of abnormal synchronization may also vary according to the pathology and location of the focus. We looked at whether the difference in the pattern of synchronization between FCD types I and II would hold when controlling for the location of epilepsy. In our cohort, we had an adequate number of patients with temporal lobe epilepsy to perform this analysis. A similar difference of a more restricted area of hyperexcitability and synchronization was seen in FCD type II compared to type I in this localization (Figure 3B). Therefore our findings held up when controlling for a specific epilepsy localization.

In FCD type II we also found that patients with Engel class I outcome had an even more restricted region of hyperexcitability than those with Engel class II (Figure 5). The more restricted epileptogenicity may explain the reason for the improved postoperative seizure outcome. In general, surgical management of FCD focuses on the assessment of epileptogenicity in relation to an MRI lesion, if present.[33] For instance, the correlation of frequent rhythmic epileptogenic discharges measured by electrocorticography in relation to the lesion can be used as a guide to assess the required extent of surgical resection.[33] However, the margins of resection in cases of nonlesional epilepsy are more difficult to assess, as indicated by the lower postoperative seizure-freedom rates.[34] Our results

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suggest that CCEPs in patients with FCD type II and MRI-negative epilepsy who undergo SEEG may help predict postoperative seizure outcomes.

Our finding of more widespread excitability in FCD type I compared to type II may be related to the following mechanisms: tangential migration of γ-aminobutyric acid (GABA) ergic inhibitory interneurons, which may be impaired in patients with FCD type I[35,36]; more extensive hyperexcitable network as supported by nuclear imaging studies showing diffuse GABA type A receptors[37]; and large-scale brain connectivity difference as noted in the subtypes of FCD type IIA vs type IIB.[38] Although different patterns of connectivity could exist for the various subtypes of FCD type II, we did not have sufficient numbers in our cohort to analyze any potential difference in CCEP connectivity.

In conclusion, FCD type I has a greater degree of excitability in cortices both near ictal zone regions and regions of the brain distant from the ictal zone. Our finding of widespread hyperexcitability and functional connectivity noted in FCD type I, a common pathological substrate of nonlesional epilepsy, is supported by the observation of poor surgical outcomes after a focal resection in this group.[39,40] FCD type II with Engel class I outcomes had the most restricted region of hyperexcitability. These differences in connectivity between types I and II were maintained when controlling for epilepsy localization and seizure type. Some important limitations of this study include the following: first, this is a single-center study with a relatively small number of FCD type II patients, and second, CCEP methodology requires intracranial EEG analysis and this is a retrospective study.

A larger prospective clinical trial is needed to confirm our findings. There is the question of whether brain connectivity can distinguish FCD type II regardless of the presence or extent of MRI findings. In addition, our analysis demonstrated that the extent of surgical resection in type I is larger than type II. Further studies will be required to determine whether differences in connectivity patterns or identification of key nodes in the epileptic network can inform the volume and margins of resection.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We (authors) confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

D.N. contributed to the conception and design of the study; all authors contributed to the acquisition and analysis of data; H.S., K.T., J.B., R.L., and D.N. contributed to drafting the text and preparing the figures.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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