The impact of radiofrequency thermocoagulation on brain connectivity in drug-resistant epilepsy

Insights from stereo-electroencephalography and cortico-cortical evoked potentials

Gula, Justyna; Van Hoof, Raf H.M.; Krishnan, Balu; Mischi, Massimo; van Kranen-Mastenbroek, Vivianne H.J.M.; Van Straaten, Ilse E.C.W.; Hilkman, Danny; Wagner, Louis; Hunyadi, Borbála; More Authors

DOI
10.1111/epi.18270

Publication date
2025

Document Version
Final published version

Published in
Epilepsia

Received: 20 September 2024 | Revised: 7 January 2025 | Accepted: 7 January 2025

DOI: 10.1111/epi.18270

Epilepsia®

RESEARCH ARTICLE

The impact of radiofrequency thermocoagulation on brain connectivity in drug-resistant epilepsy: Insights from stereo-electroencephalography and cortico-cortical evoked potentials

Justyna Gula[1,2,3] | **Rutger J. Slegers**[2,4] | **Raf H. M. Van Hoof**[2] | **Balu Krishnan**[5] | **Massimo Mischi**[6] | **Vivianne H. J. M. van Kranen-Mastenbroek**[2,3,6] | **Ilse E. C. W. Van Straaten**[2,3,4,6] | **Danny Hilkman**[2,7] | **Louis Wagner**[2,4] | **Albert Colon**[2,8] | **Olaf E. M. G. Schijns**[2,3,4] | **Borbála Hunyadi**[9] | **Jacobus F. A. Jansen**[1,3,6] | **Simon Tousseyn**[2,3,4] | **The ACE Epilepsy Surgery group**

[1]Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

[2]Academic Center for Epileptology (ACE), Kempenhaeghe/Maastricht UMC+, Maastricht & Heeze, Maastricht, The Netherlands

[3]Mental Health and Neuroscience (MHeNS) Research Institute, University Maastricht, Maastricht, The Netherlands

[4]Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands

[5]Epilepsy Center, Neurological Institute, Cleveland Clinic, Cleveland, Ohio, USA

[6]Department of Electrical Engineering, University of Eindhoven, Eindhoven, The Netherlands

[7]Department of Clinical Neurophysiology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

[8]Centre Des Etudes et Traitement de l'Epilepsie (CETE), Centre Hospitalier Universitaire Martinique, Fort-de-France, France

[9]Signal Processing Systems Section, Department of Microelectronics, Delft University of Technology, Delft, The Netherlands

Correspondence
Simon Tousseyn, Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands.
Email: tousseyns@kempenhaeghe.nl

Funding information
EpilepsieNL, Grant/Award Number: 23-08

Abstract

Objective: To investigate whether local lesions created by stereo-electroencephalography (SEEG)–guided radiofrequency thermocoagulation (RFTC) affect distant brain connectivity and excitability in patients with focal, drug-resistant epilepsy (DRE).

Methods: Ten patients with focal DRE underwent SEEG implantation and subsequently 1 Hz bipolar repetitive electrical stimulation (RES) for 30 s before and after RFTC. Root mean square (RMS) of cortico-cortical evoked potentials (CCEPs) was calculated for 15 ms to 300 ms post-stimulation with baseline correction. Contact pairs were categorized as both coagulated, hybrid, or both non-coagulated. The data were divided into nine categories based on the stimulating and recording contact pair combinations. RMS of CCEPs was compared before and after (<12 h) RFTC using a two-sample *t* test (Hochberg corrected, $p < 0.05$)

Justyna Gula and Rutger J. Slegers contributed equally to this work.

for each patient. Boost score, indicating power increase during seizures before RFTC relative to baseline, was analyzed in 4 s windows with 1 s overlap during seizure duration.

Results: RFTC altered connectivity across all categories. Of interest, decreases and increases in RMS were observed in connections between non-coagulated contacts distant from coagulation site (range: 1.09–85 mm, median = 17.7 mm, interquartile range [IQR] 10.1–32.3). Contact pairs involved in significantly altered non-coagulated connections showed a higher boost score correlation in the theta, beta, and gamma bands, as well as a stronger maximum correlation with coagulated sites in the delta band than contacts for which connectivity did not change after RFTC.

Significance: This study highlights how local lesions alter distant brain connectivity, providing insights for future research on epilepsy network changes and seizure outcomes following RFTC.

KEYWORDS

effective connectivity, excitability, RFTC, SEEG

1 | INTRODUCTION

Epilepsy affects ~1% of the population worldwide.[1] Although medication can effectively control the condition for the majority of patients, 30%–40% of adults experience drug-resistant epilepsy (DRE).[2,3] For patients with focal epilepsy, surgery is an evidence-based, potential curative treatment. Before surgery, identification of the highly probable epileptogenic zone (EZ) is crucial.

When non-invasive investigations provide insufficient information regarding the EZ localization, a stereo-electroencephalography (SEEG) evaluation may be suggested. This procedure involves the implantation of multiple intracerebral electrodes, each comprising several contacts. In select patients, SEEG may be transformed into a therapeutic procedure by employing radiofrequency thermocoagulation (RFTC) to induce lesions within the EZ.[4–6]

This procedure's advantage lies in the use of depth electrodes, which are already employed to identify the seizure-onset zone (SOZ). Therapeutic RFTC is also employed for areas that are difficult to reach with open surgery, thereby minimizing invasiveness and risk for patients.[6,7] However, RFTC shows a moderate efficacy with a 23% seizure-freedom rate and a 58% responder rate at 1 year,[8] underscoring the need for further research. Previous studies have shown that etiology impacts RFTC efficacy and that periventricular nodular heterotopia appears to respond best to RFTC.[7,9]

It is increasingly agreed upon that focal epilepsy should be regarded and treated also from a network perspective.

Key points

- Radiofrequency thermocoagulation (RFTC) affects brain connectivity.
- Focal RFTC affects interactions between non-coagulated brain sites.
- The ratio of changed connections seems to be unaffected by the proximity to the coagulated contacts.
- Contact pairs involved in significantly altered connections exhibited similar power increase patterns during seizures in the theta, beta, and gamma frequency bands.
- Stimulation or recording contact pairs involved in significantly altered connections showed higher correlation in boost score with coagulated site in the delta band.

Instead of analyzing local neural activity only, focus should also be directed toward brain connectivity and the detection of important nodes within networks.[10–12] Previous studies have emphasized the importance of insights into patient-specific key network nodes to establish an adequate therapeutic strategy.[13] Disruption of these critical nodes might improve epilepsy treatment. Yet, although the field of scientific interest has now widened somewhat, target selection for RFTC is still commonly based on local features of brain activity on depth electrodes only.

SEEG also provides a unique opportunity to better understand brain networks by investigating effective connectivity and excitability. This procedure involves stimulating (repetitive electrical stimulation [RES]) and recording responses in distant contacts (cortico-cortical evoked potentials [CCEPs]).[14–16] CCEP comprises two components: early and late.[17–19] The former is believed to reflect direct structural connectivity, as its amplitude correlates with the number of connected white matter fibers.[20,21] The late component can be recorded in more remote sites; thus it is associated with effective connectivity via a local cortico-cortical or a cortico-subcortico-cortical reverberating circuit.[16,20] Cortical excitability and epileptogenicity were shown to be correlated with the size of the early evoked potentials and its high-frequency activity counterpart at different phases.[16,22–25] Both CCEP amplitude and associated high-frequency oscillations have been used successfully to identify SOZ as one of the approximations of the EZ. A previous study demonstrated CCEP connectivity between the SOZ and remote epileptic network nodes, as determined by subtraction ictal minus interictal single-photon emission computed tomography (SPECT) coregistered to magnetic resonance imaging (MRI) (SISCOM), supporting the network concept.[26]

The epileptogenic network can also be studied by analyzing changes in the spectral properties of brain activity during seizures. The epileptogenicity index (EI) measures epileptogenicity of the brain structures based on spatio-temporal properties of fast oscillations recorded with depth electrodes.[27,28] High-oscillation power and coherence were identified as signal features reflecting epileptogenicity, generalizing both within patients across interictal and ictal states, and between different patients.[28] A previous study showed that some spectral changes during seizure relative to baseline activity are positively correlated with SISCOM perfusion z-scores.[29] During seizures, areas of hyperperfusion show a higher increase in power in the beta to ripple frequency bands when compared to areas of ictal hypoperfusion.

The broader impact of RFTC on distant large-scale brain networks is getting more and more attention; however, it is still largely unexplored. Recent studies have shown the effect of the RFTC on interictal biomarkers.[30–35] This study aims to determine the effect of local RFTC on brain connectivity in patients with DRE, focusing on distant regions not directly involved in the RFTC procedure. Because epilepsy is regarded a network disease, we expect that coagulation of one of the network nodes should lead to alteration in connections between other, non-coagulated nodes. A distinctive advantage of SEEG-guided RFTC is its ability to apply CCEP analysis at exactly the same location with the same stimulation parameters before and immediately after the procedure. We compared effective connectivity before and immediately (<12 h) after the RFTC for each contact and patient. To our knowledge, this is the first study applying and comparing CCEPs before and after RFTC. As our primary focus was the impact of the RFTC on distant brain network connectivity, we then assessed stimulation-recording combinations where both contacts pairs were not coagulated (N–N connections). To address situations in which neither the stimulation nor recording contacts were coagulated, but could be within the lesional range (3–8 mm in diameter[4,5]) produced by the coagulation of another nearby contact, we studied the ratio of changed connections relative to their distance from the nearest coagulated contact. We examined whether the non-coagulated contacts with connectivity affected by RFTC act similarly during pre-RFTC seizures in terms of changes in power spectrum with respect to baseline activity.

2 | METHODS

2.1 | Inclusion criteria

Ten consecutive patients with drug-resistant focal epilepsy were retrospectively examined from the SEEG cohort collected between 2017 and 2020. Inclusion criteria required patients to be adult (≥18 years old), and to have undergone RFTC and pre- and post-RFTC stimulation sessions. These patients were admitted to the Academic Center for Epileptology Kempenhaeghe/Maastricht University Medical Center, location Heeze (ACE) as part of their pre-surgical workup.

2.2 | Study design

All measurements were part of a standard RFTC procedure at ACE.[9] Patients underwent implantation of intracerebral depth electrodes and long-term video-SEEG registration (~2 weeks). During this time, spontaneous and/or stimulated seizures and resting state baseline activity were recorded, after which sessions of stimulation were started. After target selection, RFTC was performed, followed by post-coagulation stimulations. Electrodes were explanted within 24 h after the RFTC procedure. Study workflow is shown in Figure 1A. The study protocol was reviewed and approved by the local independent medical ethical committee and the institutional review board (ACE_2021_01A).

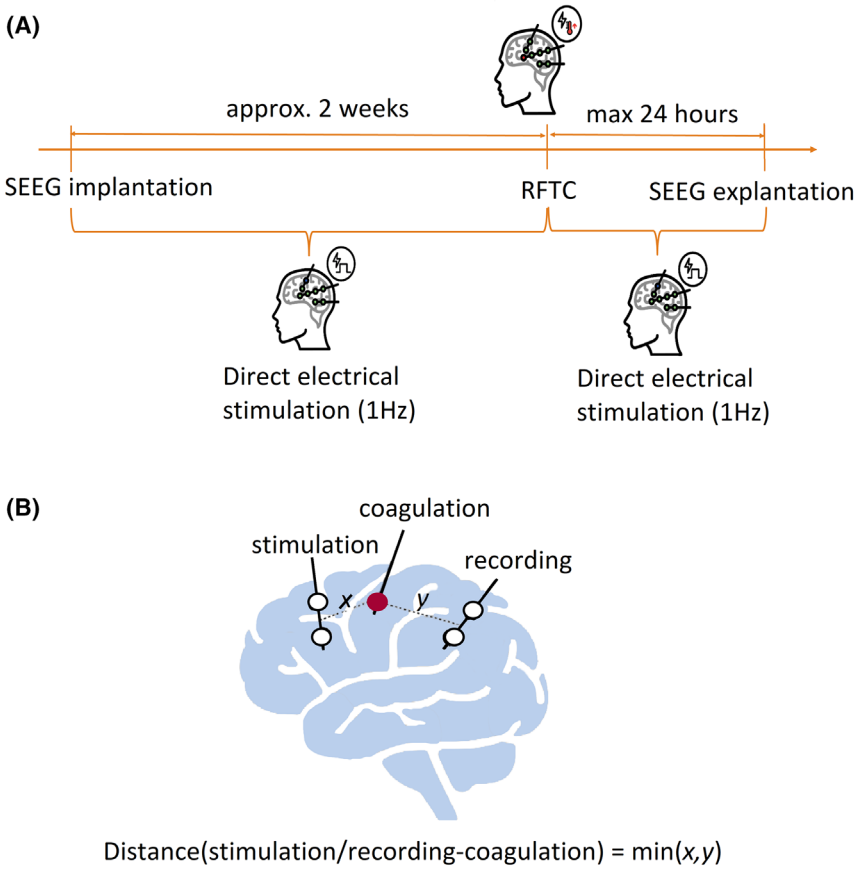

FIGURE 1 (A) Study workflow. (B) Distance calculation.

2.3 | SEEG implantation

Patients were implanted stereotactically (Leksell-frame, Elekta Solutions AB, Stockholm, Sweden) with platinum intracerebral depth electrodes (DIXI Medical, Besancon, France) at ACE. The implantation procedure followed a standard protocol, guided by the results of presurgical non-invasive examinations. The electrode diameter was 0.8 mm, with a contact length of 2 mm and a contact interspace of 1.5 mm. Electrodes were visualized post-implantation with structural MRI and/or computed tomography (CT). Data registration was performed using an audio-video-EEG monitoring system (Micromed, Micromed SpA, Mogliano Veneto, Italy) with a minimum sampling rate of 1024 Hz.

2.4 | SEEG stimulation

Stimulation was based on the institutional protocol and performed at 1 Hz with a pulse width of 1025 μs and duration of 30 s, ramping up the current from 1 mA in three varying steps initially up to a maximum of 10 mA, more recently up to a maximum of 7 mA. On each single electrode, only contiguous contact points were stimulated in order to localize eloquent areas to be spared during RFTC and reproduce (parts of) habitual seizures, respectively. Each 1 Hz stimulation session consisted of 30 repeated stimulations for a given amplitude and contact pair for each patient (pre-RFTC signal). During stimulation, patients were awake with eyes open. Stimulations were performed outside the period of antiseizure medication (ASM) withdrawal. Stimulation amplitude was not increased if clinical signs were evoked or if the stimulation was perceived as painful. Moreover, the clinical neurologist could omit stimulation if deemed irrelevant to the diagnostic investigation or repeat stimulation with the same amplitude to confirm observations. Immediately after the RFTC procedure, stimulations with the highest amplitude were repeated (<12 h).

2.5 | RFTC treatment

Target selection for RFTC was based on a combination of ictal and interictal SEEG, stimulation data, and non-invasive pre-implantation imaging. After obtaining patient informed consent, RFTC was performed without anesthesia, using a radiofrequency generator system (RFG-1B Radiofrequency Generator, COSMAN Medical, Burlington, MA, USA) set to an output of 50 V for 30 s between two contiguous electrode contact points. The coagulation site is expected to reach a temperature of 70–80°C and forms an ovoid lesion of 3–8 mm in

diameter.[4,5] Based on the presence of residual interictal epileptiform discharges (IEDs) at the lesioned site following the first RFTC session, a second or third session of thermocoagulation was applied in selected patients after a new informed consent within 1–2 h after the first session. Electrodes were explanted at ACE, location Maastricht University Medical Center (MUMC+), within 24 h after RFTC.

2.6 | Data analysis: CCEPs

Effective connectivity was assessed using CCEPs before and after RFTC. A bipolar montage was applied. Contact pairs were classified into three categories: both coagulated (C), hybrid (H; one coagulated, one non-coagulated), or both non-coagulated (N). The data set was then organized into nine categories based on combinations of stimulation and recording contact pairs (e.g., C–C, C–H, C–N, H–C, and so on).

Artifact detection was performed visually with BrainQuick software (Micromed SpA, Mogliano Veneto, Italy). Faulty contacts were excluded from the subsequent analysis. In case of duplicated stimulations during a stimulation session (e.g., before or after RFTC), the final was analyzed.

Signal analysis was performed using Matlab (MathWorks Inc., Natick, Massachusetts, USA). Root mean square (RMS) of the signal following 1 Hz stimulation was computed within the 15–300 ms interval post-stimulation to avoid stimulation artifact. The pre-stimulus period from −200 to −15 ms relative to stimulation was used for baseline correction. A signal was classified as CCEP if it exhibited significant deviation from the pre-stimulus baseline before and/or after RFTC (RMS significantly higher than pre-stimulus period, t test, $p < 0.05$).

RFTC could influence not only connectivity, but also baseline SEEG activity.[32] Consequently, differences in reported CCEPs may arise due to alterations in baseline activity rather than changes in connectivity. To mitigate the impact of changes in baseline activity following RFTC, the amplitude of post-RFTC signal was normalized with respect to the amplitude of pre-RFTC signal using the following equations[1,2]:

$$\sigma_{rel} = \frac{\sigma_{post}}{\sigma_{pre}} \quad (1)$$

$$s_{post\_corr} = \frac{s_{post}}{\sigma_{rel}} + \left(\sigma_{rel} - 1\right) \bullet \frac{\bar{s}_{post}}{\sigma_{rel}} \quad (2)$$

where σ_{post}—standard deviation (SD) of post-RFTC signal, σ_{pre}—SD of pre-RFTC signal, s_{post_corr}—corrected post-RFTC signal, s_{post}—post-RFTC signal, and $\bar{s}_{post}$—mean post-RFTC signal after stimulation.

2.7 | Data analysis: Distances from coagulation site

We were interested if the observed connectivity changes following RFTC depend on the distance to coagulated site. For connections between non-coagulated contact pairs (N–N connections), the ratio of significantly changed CCEPs relative to their proximity to the nearest coagulation site was analyzed. The actual positions of electrodes were obtained from post-implantation CT or MRI. The Euclidean distance was calculated from the midpoint between neighboring contacts in a bipolar montage to the closest coagulated contact for both stimulation and recording. The smaller of the two values was selected as the distance for a specific stimulation-recording pair. The distance calculation method is illustrated in Figure 1B. We then examined the impact of proximity to the nearest coagulation site. Observing a greater total number of CCEPs near the coagulation site, we analyzed the percentage of significantly altered CCEPs in relation to the overall number of CCEPs. We also compared the number of increased and decreased RMS with regard to the distance to the closest coagulation site.

Average Euclidean distance between stimulation and recording site for both significantly changed and non-changed N–N connections per subject was calculated. Similarly, average distance to the closest RFTC was compared between significantly changed and non-changed N–N connections.

2.8 | Data analysis: Correlation of boost score

We aimed to determine whether contacts involved in altered connections exhibit similar patterns of activity during seizures. To investigate this, we analyzed the correlation of boost scores between contacts. Detailed methodology of boost score is described in a previous study.[29] Boost and suppression scores quantify the increase and decrease in the power spectrum within a specific frequency band relative to the baseline. A positive boost score indicates an increase in power, whereas a positive suppression score indicates a decrease in power within the frequency band during a seizure relative to the baseline.

Nine patients had spontaneous seizure recordings. Spectral decomposition was performed using 4 s window with 1 sec overlap for the whole spontaneous seizure and

baseline (2 min) recordings. The average power spectral density was thus estimated in seven frequency bands: delta (0.1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–49 Hz), high gamma (51–100 Hz), and ripple band (100–150 Hz) for each signal. For each time point, scores are calculated as the integral of the difference between power during seizure and baseline, normalized with respect to seizure duration.

Before analyzing the boost correlation, we accounted for the fact that patients experienced multiple seizures, which could vary in duration and spread. We clustered the seizures based on correlations of boost and suppression scores between seizures for each patient. Because the number of potential seizure clusters is not known, we used Louvain community detection algorithm implemented in Brain Connectivity Toolbox,[36] which determines the best non-overlapping division of network nodes to maximize within-group edges while minimizing between-group edges. In subsequent analyses, the seizure clusters involving the highest number of contacts were selected for each patient. The largest cluster was analyzed to identify contacts potentially involved in seizure propagation, with involvement defined by a non-zero boost score.

After seizure cluster selection, the boost score was averaged across seizures within selected cluster for each contact. Finally, correlation of the boost scores time series between contacts for each N–N pair and maximal correlation between either stimulation or recording and coagulated contacts were calculated.

2.9 | Statistical analysis

The RMS of the CCEPs following each stimulation within a stimulation session were compared before and after RFTC for stimulation with the same amplitude (two-sample t test, Hochberg correction, $p < 0.05$) for each contact pair and participant. For each participant, the percentage of significantly changed CCEP following RFTC, relative to all CCEPs, was calculated. The average percentage of significantly different RMS within each category was then computed across all participants. Subsequently, for significantly altered connections, the average percentage of decreased RMS was computed per category.

The increased and decreased RMS values were compared across each 5 mm distance interval from the nearest coagulation site using a paired t test.

Correlation coefficients of boost score were averaged within significantly changed and non-changed N–N connection groups within subject, Fisher z-transformed, and compared with paired t tests.

We additionally analyzed resting-state connectivity (see Data S1) using the full-frequency Directed Transfer Function (ffDTF). To compare the overlap between significantly changed CCEPs and ffDTF values, we calculated the Dice score.

2.10 | CCEP reproducibility

To ensure that the observed changes in connectivity were induced by the RFTC, we analyzed CCEP reproducibility. Three ACE patients, who were not part of the main analysis, received pairs of identical stimulations during their pre-RFTC registration. The subsequent analysis followed the same steps described in Sections 2.6 and 2.9.

3 | RESULTS

3.1 | Study population

Ten patients (six female; average age ± SD, 33.2 ± 13.8 years) were included in the study, with on average 19.7 (SD = 9.3) years of epilepsy. Two patients were non-lesional (MRI-negative), one had a post-traumatic cyst, six had periventricular nodular heterotopia (including one patient with also malformation of cortical development and one with hippocampal sclerosis), and one patient had malformation of cortical development only. (See Table 1).

3.2 | Stimulation

On average, 9 electrodes (range 4–16, SD = 4) were implanted per patient, with an average of 113 contacts (range 54–191, SD = 5). Prior to RFTC, each patient underwent an average of 109 1 Hz stimulation sessions (range 38–195, SD = 61), with a mean amplitude of 5 mA (SD = 2). Following RFTC, there were an average of 38 stimulations (range 11–87, SD = 24), with a mean amplitude of 7 mA (SD = 2). After detecting artifacts and removing repeated stimulations within the same session, per patient an average of 31 stimulations (range 8–54, SD = 17) were analyzed with a mean amplitude of 7 mA (SD = 2). On average, 2933 connections (range 552–5670, SD = 2088) were analyzed, of which 2351 (80%, range 218–4770, SD = 1709) were identified as CCEPs. On average, 11 contacts (range 3–33, SD = 10) were coagulated.

3.3 | CCEP changes following RFTC

Our study revealed changes in connectivity following RFTC across all categories of contact pairs, as shown in Table 2A. The mean ratio of significantly altered connections

TABLE 1 Study population.

Participant no.	Gender	Age at epilepsy onset (y)	Age at RFTC (y)	MRI findings	No. of electrodes	No. of contacts	Side of implantation	SOZ localization	Coagulation localization	No. of coagulated contacts	ILAE outcome[38] at 1 year
1	F	12	46	PVNH occipital R	7	108	R	PVNH occipital R	PVNH occipital right	9	5
2	F	4	20	Non-lesional	11	109	B	Precuneus R	Precuneus right	13	3
3	M	18	44	PVNH occipital B	16	191	B	PVNH occipital R, neocortex R	PVNH occipital bilateral	24	5
4	F	3	22	PVNH occipital L	5	57	L	N/A (no spontaneous seizures recorded)	PVNH occipital left	3	1
5	M	39	59	Post-surgical and post-traumatic cyst temporal R	9	113	R	Temporal operculum R	Temporaal operculum R	3	5
6	M	12	40	MCD insula B	12	171	B	Posterior insula-operculum R and L	Posterior insula R, temporal operculum R	4	3
7	F	6	23	PVNH occipitotemporal R, MCD parietal R, HS right	10	136	R	PVNH occipital R	PVNH occipital R	33	4
8	F	19	24	PVNH occipital B, small hippocampus R	6	68	B	PVNH occipital R, +/− occipital neocortex R, hippocampus R	PVNH occipital R	7	1
9	F	12	18	PVNH parietal R	4	54	R	PVNH parietal R, neocortex R, hippocampus R	PVNH parietal R	6	5
10	M	10	36	Non-lesional	13	124	R	Precuneus R	Precuneus R	6	4

Abbreviations: B, bilateral; F, female; HS, hippocampal sclerosis; L, left; M, male; MCD, malformation of cortical development; N/A, not applicable; PVNH, periventricular nodular heterotopia; R, right; SOZ, seizure-onset zone; y, years.

TABLE 2 Percentage of (A) significantly changed CCEPs following RFTC and (B) decreased CCEPs after RFTC relative to significantly changed CCEPs.

(A)			
Stimulation: Recording:	**Coagulated**	**Hybrid**	**Non-coagulated**
Coagulated	69.1 ± 33.2	45.1 ± 35.7	28.9 ± 15.8
Hybrid	73.6 ± 18.8	43.2 ± 36.9	37.6 ± 30
Non-coagulated	26.8 ± 16.8	23.4 ± 17.9	22.2 ± 14.3
(B)			
Stimulation: Recording:	**Coagulated**	**Hybrid**	**Non-coagulated**
Coagulated	91.3 ± 14.4	85.1 ± 37.5	43.7 ± 29
Hybrid	98.2 ± 4.3	88.2 ± 18.7	36 ± 35.2
Non-coagulated	72 ± 28.6	70.3 ± 30.1	44.6 ± 20.8

Data are mean ± SD.

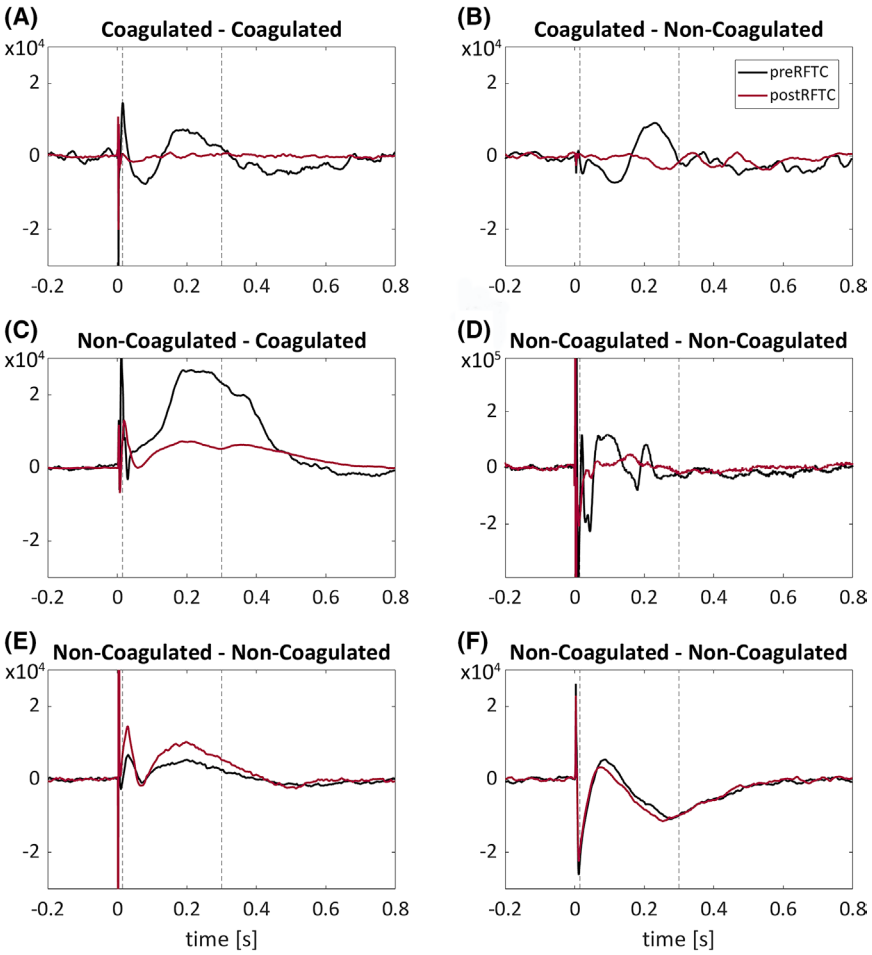

FIGURE 2 Exemplary CCEP responses before (blue) and after (red) RFTC for Coagulated—Coagulated connections (A), Coagulated—Non-Coagulated connections (B), Non-Coagulated—Coagulated (C), and Non-Coagulated—Non-Coagulated connections (D–F). Decreased (A–D), increased (E), and non-changed (F) responses were observed following RFTC. Abbreviations: CCEP, cortico-cortical evoked potentials; RFTC, radiofrequency thermocoagulation.

exhibited a decreasing trend from coagulated to hybrid to non-coagulated contacts, spanning from 73.6% to 22.2%. The mean ratio of altered connections in all categories was higher than the variability of CCEPs observed in pre-RFTC data in reproducibility analysis (3.7). The majority of connections involving coagulated or hybrid contacts demonstrated a reduction in RMS values after the RFTC. Conversely, connections between non-coagulated contacts showed a similar number of increased and decreased RMS values. The majority of coagulated—non-coagulated connections decreased following RFTC, whereas reverse connections (non-coagulated—coagulated) increased (Table 2B). The exemplary CCEP responses are shown in Figure 2. The overview of all results is presented in Table 3.

TABLE 3 Overview of results.

	Range/significance	Explanation
CCEP analysis		
Changes in all contact categories	22.2–73.6 [%]	Changes in connectivity/excitibility including contacts not directly affected by RFTC; indication of network changes following RFTC
Increased connections	36–91.3 [%] of changed connections	Abolition of an inhibitory influence of the coagulated brain site on stimulation and/or recording sites; sleep-like slow waves are described following RFTC in areas connected to the RFTC lesion which could increase CCEP size
Decreased connections	8.7–64 [%] of changed connections	For coagulated contacts: indication of successful RFTC. For other contacts: abolition of an excitatory influence of the coagulated brain site on stimulation and/or recording site; disruption of pathways between stimulation and recording sites by the lesion
Distance analysis		Significantly changed connections observed outside lesion radius; indication of network changes following RFTC
Difference in number of increased and decreased connections in 5 mm distance interval	NS	
NN changed vs NN non-changed connections		
Distance to the closest coagulated site	NS	
Correlation of a boost score between recording and stimulation contact	Theta, beta, and gamma bands: $p < 0.05$, *uncorr*	Similar activity pattern during seizure suggesting involvement in the same network
Maximal correlation of a boost score between coagulated contact and either recording and stimulation contact	Delta band: $p < 0.05$, *uncorr*	Similar activity pattern during seizure suggesting involvement in the same network for coagulated and either recording or stimulating site

Abbreviations: CCEP, cortico-cortical evoked potentials;RFTC, radiofrequency thermocoagulation; NS, not significant ($p > 0.05$); uncorr, not corrected result.

We observed widespread changes in resting-state connectivity (see Table S1); however, clusters of significantly altered CCEP and ffDTF values did not completely overlap (see Table S2).

3.4 | Distances from coagulation site

Although more significantly changed connections are observed close to coagulation (Figure 3A,B), the ratio of changed connections relative to the total number of connections seems to remain stable (Figure 3C). The maximum number of significantly altered non-coagulated—non-coagulated connections were observed 5–15 mm from the closest coagulation site. However, we observed significant changes in connections among non-coagulated contacts, even at considerable distances from induced lesions (range: 1.09–85 mm, median = 17.7 mm, interquartile range [IQR] 10.1–32.3), well outside of the lesion size described in the literature (3–8 mm in diameter[4,5]). We did not observe a difference in average distance from the closest coagulated contact between contact pairs involved in significantly changed and non-changed connections. However, in these pairs, stimulation and recording sites were significantly closer to each other than in non-changed connections. We did not observe significant differences between number of increased and decreased connections (Figure 3B).

3.5 | Correlation of boost score between recording and stimulation site

Contact pairs involved in significantly changed connections following RFTC showed higher correlation than non-changed connections in their boost scores during seizure in theta, beta, and gamma bands (Figure 4A). In addition, we observed a trend toward significance in the alpha band ($p = 0.06$).

3.6 | Correlation of boost score between recording or stimulation and coagulation site

Contact pairs involved in significantly changed connections following RFTC showed higher maximal correlation between either stimulation or recording boost score and coagulation site in the delta band (Figure 4B).

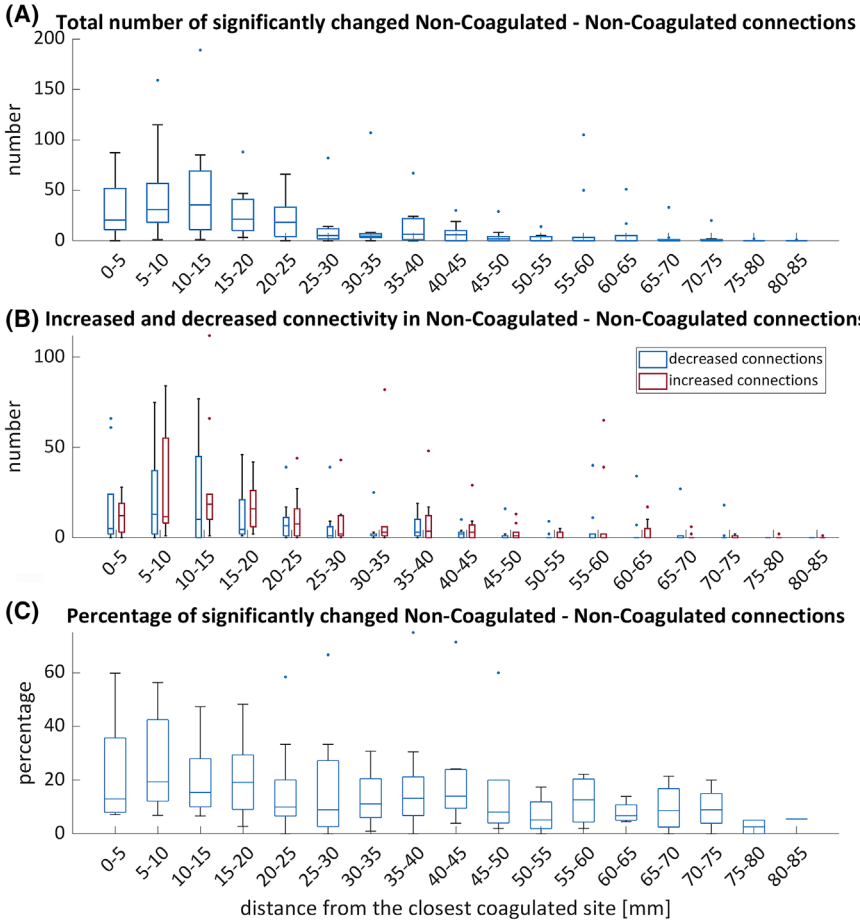

FIGURE 3 Significantly changed non-coagulated—non-coagulated connections relative to distance to the closest coagulated site. (A) Total number of significantly altered connections. (B) Number of increased and decreased connections. No significant differences were observed. (C) Percentage of significantly changed CCEPs outside coagulated contact pairs concerning distance from the closest coagulated site.

3.7 | CCEP reproducibility

The mean percentage of significantly different connections between identical stimulation sessions was 10.26% (8.41%–13.26%). The mean time between compared stimulations was equal to 45 h (13 h–76 h).

4 | DISCUSSION

Our findings show that RFTC affects brain connectivity in patients with DRE. Particularly, we observed CCEP changes between non-coagulated regions (N–N) after RFTC. Notably, connectivity changes after the procedure seem to be unaffected by the proximity to the coagulation site, as the ratio of significantly altered CCEPs relative to total number of CCEPs appears to remain stable across distances from the nearest coagulated site.

Recent studies have highlighted the effects of RFTC on interictal biomarkers.[33–35] Previous studies have reported the suppression of interictal epileptiform discharges including non-coagulated sites[30–32] and increased ripple rates outside epileptogenic network[30] following RFTC. In line with these studies, our study shows altered connectivity between not only coagulated regions, but also between areas outside the predicted lesion (3 to 8 mm in diameter[4,5]).

Significant changes in CCEPs were observed in all categories of contact pairs. The observed modifications in CCEPs following RFTC at coagulated sites are expected confirmation of the procedure's influence on the coagulated area's capacity to interact with its surroundings in terms of sending and/or receiving signals. However, results show that not all connections involving coagulated contacts changed following the RFTC, which might be an indication of unsuccessful coagulation, similar to the findings in a recent study.[37] Another possible explanation could be the influence of volume conduction or the impact of stimulating a brain volume larger than the lesion created by RFTC.

Both decreased and increased RMS following RFTC was observed. The majority of connections with coagulated stimulation contacts show decreased RMS (Table 2B). Contact pairs with non-coagulated stimulation contacts showed a more equal proportion of increased and decreased RMS. A possible explanation for the decrease in CCEP RMS is abolition of an excitatory influence of the coagulated brain site toward these sites or disruption of pathways between stimulation and recording sites by the lesion. An alternative explanation is the presence of

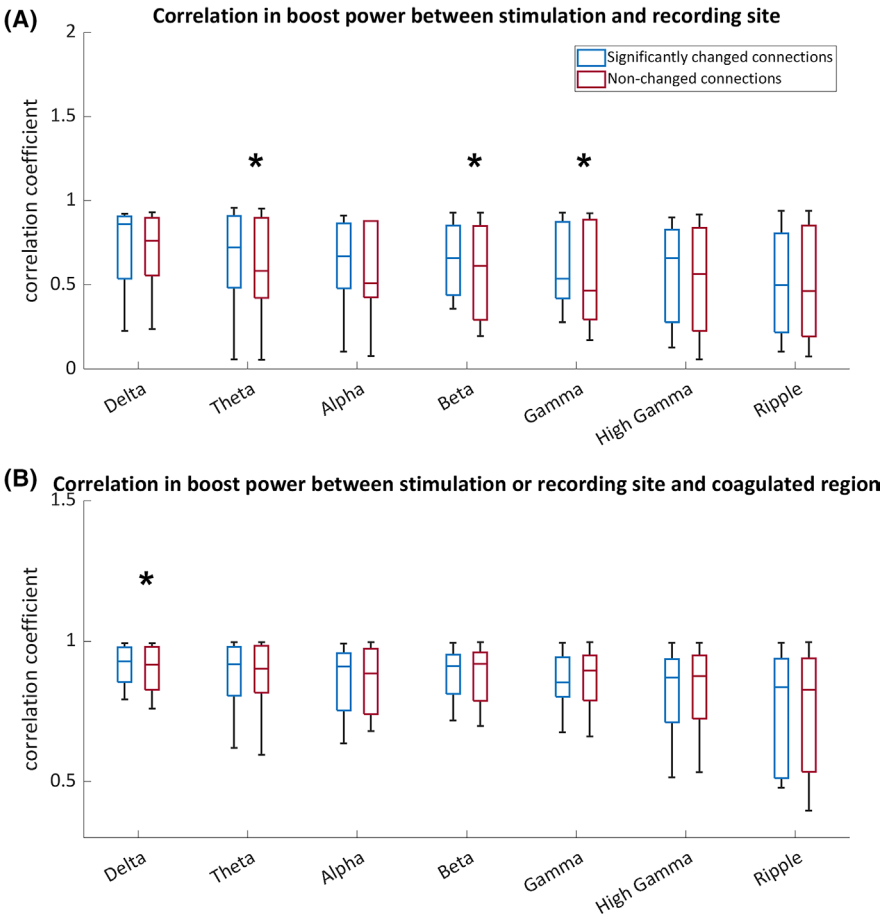

FIGURE 4 Correlation coefficient of boost score between (A) recording and stimulation sites and (B) coagulation and either recording or stimulation sites in significantly altered (blue) and unchanged (red) N–N connections following RFTC. Asterisks mark significant ($p < 0.05$) differences between groups.

edema surrounding the coagulated lesion when stimulation or recording contacts are close to coagulated contact points. However, decreased RMS was observed in areas beyond those expected to be structurally altered.[4,5]

An increase in CCEP RMS may be due to RFTC affecting an area that previously had an inhibitory influence on stimulation and/or recording sites. This effect may induce an increase in effective connectivity or excitability after treatment. Alternatively, sleep-like slow waves are described following RFTC[32] in areas connected to the RFTC lesion. Such "sleep" activity could increase CCEP size.[22] Regardless of the direction of connectivity change, these observations demonstrate that very focal changes in the brain can have far-reaching effects on distant connections, even on those not directly involved in the RFTC procedure. This strongly supports a network-based approach to understanding epilepsy.

We found that the correlation of the boost score during seizure (across theta, beta, and gamma bands) between stimulation and recording contact pairs was higher in significantly altered N–N connections compared to unchanged ones. This indicates that contacts involved in altered connections following RFTC show similar spectral changes in these frequency bands during seizures relative to baseline, suggesting their involvement in the same network.

In addition, significantly altered N–N connections exhibited a higher maximal correlation of the boost score with coagulated contacts in the delta band. This implies that at least one site in the stimulation-recording pair shares similar ictal spectral changes with one or more of the coagulated contacts.

4.1 | Limitations

Despite the significance of our findings, several limitations warrant consideration. The relatively sparse spatial sampling of SEEG electrodes may have limited the detection of some significant connectivity changes, yet this constraint is inherent to the method itself. The number of electrodes cannot be increased freely because of added risks to patients. To mitigate this limitation, electrode implantation was guided strategically by detailed non-invasive investigations, targeting regions suspected to be involved in the EZ for further exploration. Despite its sparse spatial resolution, SEEG-guided RFTC offers a unique advantage: it enables the examination of immediate changes following the procedure in precisely the same localizations as before. In addition, it allows the examination of more deeply located areas.

Our study does not address the stability of connectivity changes following RFTC, as electrodes were explanted within 24 h after the procedure for safety concerns. Instead, we focused on the immediate effects of RFTC on connectivity. Although we were not able to study the stability of observed changes over time and we were limited by the spatial resolution of the method, we observed interesting changes in connectivity, distant from coagulated brain regions. We hypothesize that these connectivity changes might have predictive value for the success of epilepsy surgery. In our current, limited sample, we cannot test this hypothesis in a robust way as it requires more study in a larger group of patients.

In conclusion, our study provides valuable insights into the immediate connectivity and excitability changes in the brain following RFTC in patients with epilepsy, highlighting the broader network-level impact of focal interventions on neural dynamics. Future study will examine the relationship between observed connectivity changes and the seizure outcome in a larger cohort. A robust analysis of the correlation between reported changes and clinical outcomes will enable the use of widespread network changes as a marker of successful RFTC. The post-RFTC network changes could then indicate the need for a stepwise increase in the target size of RFTC. In addition, as the Euclidean distance and actual distance through connecting fibers may differ, we plan to study the alteration of CCEPs together with non-invasive modalities like diffusion tensor imaging (DTI).

AUTHOR CONTRIBUTIONS

Gula J: formal analysis, writing—original draft preparation, writing—review and editing. **Slegers RJ**: formal analysis, writing—review. **Van Hoof RHM:** data curation, software, writing—review. **Krishnan B:** formal analysis: suggested method for clustering analysis of seizures, writing—review. **Mischi M:** writing—review. **van Kranen-Mastenbroek VHJM:** writing—review. **Van Straaten ECW:** writing—review. **Hilkman D:** writing—review. **Wagner L:** writing—review. **Colon A:** writing—review. **Schijns OEMG:** writing—review. **Hunyadi B:** writing—review. **Jansen JFA:** supervision, writing—review. **Tousseyn S:** conceptualization, funding acquisition, supervision, writing—review.

ACKNOWLEDGMENTS

The authors would like to acknowledge that this research was supported by EpilepsieNL grant 23-08.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

We 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.

ORCID

Rutger J. Slegers https://orcid.org/0000-0003-2537-428X
Balu Krishnan https://orcid.org/0000-0002-1897-3359
Jacobus F. A. Jansen https://orcid.org/0000-0002-5271-8060
Simon Tousseyn https://orcid.org/0000-0003-4139-0909

REFERENCES

1. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy-a review. Epilepsy Res. 2009;85(1):31–45.
2. Xue-Ping W, Hai-Jiao W, Li-Na Z, Xu D, Ling L. Risk factors for drug-resistant epilepsy. Medicine. 2019;98(30):e16402.
3. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia. 2010;51(6):1069–77.
4. Catenoix H, Mauguière F, Montavont A, Ryvlin P, Guénot M, Isnard J. Seizures outcome after Stereoelectroencephalography-guided Thermocoagulations in malformations of cortical development poorly accessible to surgical resection. Neurosurgery. 2015;77(1):9–15.
5. Guénot M, Isnard J, Ryvlin P, Fischer C, Mauguière F, Sindou M. SEEG-guided RF Thermocoagulation of epileptic foci: feasibility, safety, and preliminary results. Epilepsia. 2004;45(11):1368–74.
6. Bourdillon P, Isnard J, Catenoix H, Montavont A, Rheims S, Ryvlin P, et al. Stereo electroencephalography–guided radiofrequency thermocoagulation (SEEG-guided RF-TC) in drug-resistant focal epilepsy: results from a 10-year experience. Epilepsia. 2017;58(1):85–93.
7. Bourdillon P, Cucherat M, Isnard J, Ostrowsky-Coste K, Catenoix H, Guénot M, et al. Stereo-electroencephalography-guided radiofrequency thermocoagulation in patients with focal epilepsy: a systematic review and meta-analysis. Epilepsia. 2018;59(12):2296–304.
8. Bourdillon P, Rheims S, Catenoix H, Montavont A, Ostrowsky-Coste K, Isnard J, et al. Surgical techniques: Stereoelectroencephalography-guided radiofrequency-thermocoagulation (SEEG-guided RF-TC). Seizure. 2020;77:64–8.
9. Slegers R, Wagner L, van Kuijk S, Hilkman D, Hofman P, van Hoof R, et al. Stereo-electroencephalography-guided radiofrequency thermocoagulation restricted to periventricular

nodular heterotopias in patients with drug-resistant epilepsy: a single center experience. Seizure. 2024;121:105–13.
10. Krishnan B, Tousseyn S, Nayak CS, Aung T. Dynamical connectivity within ictal perfusion evaluated using stereo-EEG. In American Epilepsy Society (AES) Annual Meeting. New Orleans, LA. 2018.
11. Tousseyn S, Dupont P, Robben D, Goffin K, Sunaert S, Van Paesschen W. A reliable and time-saving semiautomatic spike-template–based analysis of interictal EEG –f MRI. Epilepsia. 2014;55(12):2048–58.
12. Tousseyn S, Dupont P, Goffin K, Sunaert S, Van Paesschen W. Correspondence between large-scale ictal and interictal epileptic networks revealed by single photon emission computed tomography (SPECT) and electroencephalography (EEG)–functional magnetic resonance imaging (fMRI). Epilepsia. 2015;56(3):382–92.
13. Pittau F, Mégevand P, Sheybani L, Abela E, Grouiller F, Spinelli L, et al. Mapping epileptic activity: sources or networks for the clinicians? Front Neurol. 2014;5:218.
14. Valentin A. Responses to single pulse electrical stimulation identify epileptogenesis in the human brain in vivo. Brain. 2002;125(8):1709–18.
15. Lega B, Dionisio S, Flanigan P, Bingaman W, Najm I, Nair D, et al. Cortico-cortical evoked potentials for sites of early versus late seizure spread in stereoelectroencephalography. Epilepsy Res. 2015;115:17–29.
16. Matsumoto R, Kunieda T, Nair D. Single pulse electrical stimulation to probe functional and pathological connectivity in epilepsy. Seizure. 2017;44:27–36.
17. Enatsu R, Gonzalez-Martinez J, Bulacio J, Mosher JC, Burgess RC, Najm I, et al. Connectivity of the frontal and anterior insular network: a cortico-cortical evoked potential study. J Neurosurg. 2016;125(1):90–101.
18. Kubota Y, Enatsu R, Gonzalez-Martinez J, Bulacio J, Mosher J, Burgess RC, et al. In vivo human hippocampal cingulate connectivity: a corticocortical evoked potentials (CCEPs) study. Clin Neurophysiol. 2013;124(8):1547–56.
19. Enatsu R, Gonzalez-Martinez J, Bulacio J, Kubota Y, Mosher J, Burgess RC, et al. Connections of the limbic network: a cortico-cortical evoked potentials study. Cortex. 2015;62:20–33.
20. Jo H, Kim D, Song J, Seo DW. New approach of using cortico-cortical evoked potential for functional brain evaluation. Ann Clin Neurophysiol. 2021;23(2):69–81.
21. Conner CR, Ellmore TM, DiSano MA, Pieters TA, Potter AW, Tandon N. Anatomic and electro-physiologic connectivity of the language system: a combined DTI-CCEP study. Comput Biol Med. 2011;41(12):1100–9.
22. Usami K, Matsumoto R, Kobayashi K, Hitomi T, Shimotake A, Kikuchi T, et al. Sleep modulates cortical connectivity and excitability in humans: direct evidence from neural activity induced by single-pulse electrical stimulation. Hum Brain Mapp. 2015;36(11):4714–29.
23. Iwasaki M, Enatsu R, Matsumoto R, Novak E, Thankappen B, Piao Z, et al. Accentuated cortico-cortical evoked potentials in neocortical epilepsy in areas of ictal onset. Epileptic Disord. 2010;12(4):292–302.
24. Matsumoto R, Kinoshita M, Taki J, Hitomi T, Mikuni N, Shibasaki H, et al. In vivo Epileptogenicity of focal cortical dysplasia: a direct cortical paired stimulation study. Epilepsia. 2005;46(11):1744–9.
25. Kobayashi K, Matsumoto R, Matsuhashi M, Usami K, Shimotake A, Kunieda T, et al. High frequency activity overriding cortico-cortical evoked potentials reflects altered excitability in the human epileptic focus. Clin Neurophysiol. 2017;128(9):1673–81.
26. Tousseyn S, Krishnan B, Wang ZI, Wongwiangjunt S, Nayak CS, Mosher JC, et al. Connectivity in ictal single photon emission computed tomography perfusion: a cortico-cortical evoked potential study. Brain. 2017;140(7):1872–84.
27. Bartolomei F, Chauvel P, Wendling F. Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral EEG. Brain. 2008;131(7):1818–30.
28. Karimi-Rouzbahani H, McGonigal A. Generalisability of epileptiform patterns across time and patients. Sci Rep. 2024;14(1):6293.
29. Krishnan B, Tousseyn S, Nayak CS, Aung T, Kheder A, Wang ZI, et al. Neurovascular networks in epilepsy: correlating ictal blood perfusion with intracranial electrophysiology. NeuroImage. 2021;231:117838.
30. Bruder JC, Kahane P, Lachner D, Bernibeau L, Olivier D. Successful radiofrequency Thermocoagulation for seizures reduces the generation of IES and ripples but enhances fast ripple production. In American Epilepsy Society (AES) 74th Annual Meeting. Virtual Meeting. 2020
31. Dimova P, de Palma L, Job-Chapron A, Minotti L, Hoffmann D, Kahane P. Radiofrequency thermocoagulation of the seizure-onset zone during stereoelectroencephalography. Epilepsia. 2017;58(3):381–92.
32. Russo S, Pigorini A, Mikulan E, Sarasso S, Rubino A, Zauli FM, et al. Focal lesions induce large-scale percolation of sleep-like intracerebral activity in awake humans. NeuroImage. 2021;234:117964.
33. Scholly J, Pizzo F, Timofeev A, Valenti-Hirsch MP, Ollivier I, Proust F, et al. High-frequency oscillations and spikes running down after SEEG-guided thermocoagulations in the epileptogenic network of periventricular nodular heterotopia. Epilepsy Res. 2019;150:27–31.
34. Contento M, Pizzo F, López-Madrona VJ, Lagarde S, Makhalova J, Trébuchon A, et al. Changes in epileptogenicity biomarkers after stereotactic thermocoagulation. Epilepsia. 2021;62(9):2048–59.
35. Simula S, Garnier E, Contento M, Pizzo F, Makhalova J, Lagarde S, et al. Changes in local and network brain activity after stereotactic thermocoagulation in patients with drug-resistant epilepsy. Epilepsia. 2023;64(6):1582–93.
36. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. NeuroImage. 2010;52(3):1059–69.
37. Azeem A, Abdallah C, von Ellenrieder N, El Kosseifi C, Frauscher B, Gotman J. Explaining slow seizure propagation with white matter tractography. Brain. 2024;147:3458–70.
38. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gula J, Slegers RJ, Van Hoof RHM, Krishnan B, Mischi M, van Kranen-Mastenbroek VHJM, et al. The impact of radiofrequency thermocoagulation on brain connectivity in drug-resistant epilepsy: Insights from stereo-electroencephalography and cortico-cortical evoked potentials. Epilepsia. 2025;00:1–14. https://doi.org/10.1111/epi.18270

APPENDIX A1

ACE Epilepsy Surgery group.

Gwendolyn de Bruyn, MD, child neurologist, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Albert Colon, MD, PhD, neurologist/clinical neurophysiologist, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Jim Dings, MD, PhD, neurosurgeon, Department of Neurosurgery, MUMC+, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Marc Hendriks, PhD, clinical neuropsychologist, Academic Center for Epileptology, Kempenhaeghe/MUMC+ & Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen.

Danny Hilkman, MD, neurologist, Department of Clinical Neurophysiology MUMC+, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Christianne Hoeberigs, MD, radiologist, Department of Medical Imaging, MUMC+, Academic Center for Epileptology, Kempenhaeghe.

Jochem van der Pol, MD, nuclear medicine physician, Department of Medical Imaging, MUMC+.

Lotte de Jong, MSc, Physician assistant Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Kim Rijkers, MD, PhD, neurosurgeon, Department of Neurosurgery MUMC+, School for Mental Health & Neuroscience Maastricht University, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Sylvia Klinkenberg, MD, PhD, child neurologist, Department of Neurology MUMC+, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Vivianne van Kranen—Mastenbroek, MD, PhD, neurologist/clinical neurophysiologist, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Jeske Nelissen, MSc, nurse practitioner AZG, Departments of Neurology & Neurosurgery MUMC+, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Pieter Kubben, MD, PhD, neurosurgeon, Department of Neurosurgery MUMC+, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Walter M. Palm, MD, PhD, neuroradiologist, Department of Medical Imaging MUMC+, Academic Center for Epileptology, Kempenhaeghe.

Rob P.W. Rouhl, MD, PhD, Department of Neurology MUMC+, School for Mental Health & Neuroscience Maastricht University, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Olaf Schijns, MD, PhD, neurosurgeon, Department of Neurosurgery MUMC+, School for Mental Health & Neuroscience Maastricht University, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Ilse van Straaten, MD, PhD, neurologist/clinical neurophysiologist, Academic Center for Epileptology, Kempenhaeghe/MUMC+ and Department of Electrical Engineering, Eindhoven University of Technology.

Simon Tousseyn, MD, PhD, neurologist, Academic Center for Epileptology, Kempenhaeghe/ MUMC+, School for Mental Health & Neuroscience Maastricht University.

Marielle Vlooswijk, MD, PhD, neurologist, Department of Neurology MUMC+, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Louis Wagner, MD, neurologist, Academic Center for Epileptology, Kempenhaeghe/MUMC+.

Dorien Weckhuysen, MD, neurologist, Academic Center for Epileptology, Kempenhaeghe/MUMC+.