UNIVERSITÀ DI PARMA

UNIVERSITA' DEGLI STUDI DI PARMA

DOTTORATO DI RICERCA IN NEUROSCIENZE

CICLO XXXVI

Network effects of SEEG-guided Radiofrequency Thermocoagulations

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Anni Accademici 2020/2021 – 2023/2024

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Introduction

"My mom always said life was like a box of chocolates.
You never know what you're gonna get."
Forrest Gump

The human brain, long an object of fascination and mystery, represents one of the most complex challenges for medicine and science. Since the dawn of humanity, scholars and physicians have attempted to decipher the dynamics of this organ, seeking to understand how it generates, regulates, and modifies human behavior and its associated pathologies. My decision to pursue a career in neurosurgery arose from a deep desire to have a direct impact on the treatment of brain diseases, by taking direct action on the organ that most defines our identity.

However, this journey has not been confined to surgical practice. My experience at the "Claudio Munari" Epilepsy Surgery Center of the ASST Grande Ospedale Metropolitano Niguarda in Milan broadened my perspective, revealing the vast possibilities modern science offers in treating complex neurological conditions like epilepsy. It was in this context that I discovered the power of epilepsy surgery, an approach that, in many cases, allows for a definitive cure through the resection of the brain areas responsible for seizures. While the concept may seem simple, it is complicated by the need to precisely identify the epileptogenic zone (EZ), to understand its relationship with normal, functionally relevant brain tissue that is only secondarily involved and to perform resections as safely as possible, minimizing the risk of neurological deficits. Given the indistinct boundaries of the EZ, the diagnostic and therapeutic process demands not only advanced neuroimaging techniques but also high-level neurophysiological diagnostics and precise surgical methodologies.

In this regard, Stereo-electroencephalography (SEEG) has proven to be an essential tool, not only for identifying epileptogenic zones but also for mapping cortical functions. By implanting multicontact intracerebral electrodes, SEEG allows for the direct and precise recording of pathological and physiological neuronal activity, providing an unprecedented window into human neurophysiology.[Rizzolatti et al., 2018; Mercier et al., 2022] Developed at our center, this methodology has not only served as a therapeutic avenue for patients but also

as a foundational research platform, enabling the exploration of the neural bases of complex processes such as the preparation of complex movements,[Caruana et al., 2014a,b] the dynamics underlying the encoding of others' actions via the mirror mechanisms,[Caruana et al., 2017; Del Vecchio et al., 2020] our emotional and motor resonance with others' emotional expressions.[Caruana et al., 2015; Zauli et al., 2022] Not to forget, SEEG contributed to understanding our conscious perception of sensory stimuli,[Avanzini et al., 2018; Del Vecchio et al., 2019; Del Vecchio et al., 2021] a fields that, until a few decades ago, were accessible either through animal studies or in humans with noninvasive recordings with poor spatiotemporal resolutions.

Alongside the growth of my surgical expertise, I had the opportunity to engage in basic neuroscientific research, thanks also to the collaboration with the CNR Institute of Neuroscience in Parma and the Department of Biomedical and Clinical Sciences "L. Sacco" of University of Milan. This pathway led me to a crucial intersection between neurosurgery and fundamental research, opening new perspectives on how brain lesions affect functional, structural, and effective brain connectivity. The classical disconnectionist paradigm, introduced by Norman Geschwind, posited that brain lesions cause disconnection between functionally interconnected brain areas, resulting in specific neurological deficits. However, contemporary research has broadened this framework, demonstrating that, in addition to losing connectivity, the brain can activate compensatory mechanisms that enhance connectivity between intact areas, thus revealing a remarkable capacity for network reorganization in response to injury.[Catani and ffytche, 2005]

This transition from a purely disconnectionist model to a more dynamic understanding of brain plasticity has redefined our conception of how the brain responds to lesions. Despite the loss of connectivity between regions, phenomena such as diaschisis—where functional alterations occur in brain areas not directly affected by structural damage—often manifest as part of the brain's global response to injury.[Carrera and Tononi, 2014] Keeping this notion in mind, the main focus of neuroscientific research has been the mid- to long-term reorganization of the post-lesional brain, largely shaped by the potentiation and suppression modulations intrinsic to neural plasticity. This focus has certainly been driven by the clinical relevance and observability of these processes, but it is also due to the methodological impossibility of obtaining peri-lesional observations that cover both pre- and post-injury periods, as in the case of stroke patients. In other words, since brain lesions occur unpredictably, it has been extremely

difficult to measure the immediate (or short-term) effects of an acute cortical lesion on brain activity and connectivity. Given these premises, our project aims to document this short-term reorganization by examining the effects of an acute cortical lesion induced through SEEG-guided thermocoagulation. These kinds of lesions are obtained by applying radiofrequency selectively between specific pairs of contacts on the SEEG electrode—previously used only for recording—resulting in targeted disruption of the epileptogenic tissue while preserving surrounding areas.

This approach offers a unique opportunity to study, in vivo, how a brain lesion modulates brain connectivity in the short term, without the confound of long-term neuroplastic processes. Thanks to the precision of SEEG, we can accurately document the functional anatomy and neuronal characteristics of the lesioned area and correlate changes in effective connectivity using cortico-cortical evoked potentials (CCEP). These data, collected immediately after lesion induction, provide an exclusive view of how the brain acutely responds to disconnection, challenging the classical Geschwind paradigm and opening new pathways for understanding brain connection and disconnection.

The objective of this work is twofold: on the one hand, to investigate the mechanisms underlying induced cortical disconnection and the related clinical effects in real time; on the other, to document how these same lesions can, in some cases, trigger a compensatory increase in connectivity between brain regions, thus revealing the incredible malleability of the human brain function even up-front injuries. In addition, I believe that new therapeutic perspectives for patients with focal brain lesions can be drawn from these observations, providing a solid foundation for future interventions aimed at modulating brain connectivity.

Chapter one: Stereo-electroencephalography (SEEG): History, Indications, Implantation, Recording, Cortical Stimulation, and Outcomes

Introduction

Stereo-electroencephalography (SEEG) is a methodology that plays a crucial role in the diagnosis and treatment of drug-resistant epilepsy. Developed as a diagnostic tool to localize epileptogenic zones in the brain, SEEG provides unparalleled precision in mapping both the functional and pathological regions of the cerebral cortex. By allowing for the recording of deep brain structures that are otherwise inaccessible via non-invasive techniques, SEEG has become essential in modern epilepsy surgery.

Historical Background

The development of SEEG dates back to the pioneering work of Jean Talairach and Jean Bancaud in the 1950s in France.[Bancaud et al., 1965; Talairach et al., 1974] Talairach's stereotactic method, combined with Bancaud's clinical insights, allowed for the exploration of deep cerebral structures in a minimally invasive manner, offering precise localization of epileptic foci. SEEG was initially developed to study patients with drug-resistant focal epilepsy and has evolved into a gold standard for the identification of epileptogenic networks in cases where non-invasive methods, such as scalp EEG and neuroimaging, fail to provide sufficient localization.[Munari et al., 1994; Cossu et al., 2005] Over the years, SEEG has been refined with advances in imaging technology, electrode design, and computer-based analysis, further enhancing its diagnostic capabilities.[Cardinale et al., 2019]

Indications for SEEG

SEEG is primarily indicated in patients with drug-resistant focal epilepsy who are candidates for epilepsy surgery but have inconclusive results from non-invasive evaluations.[Cossu et al., 2005; Minotti et al., 2018; Cardinale et al., 2019]

It is most commonly used when:

- The epileptogenic zone cannot be clearly identified using scalp EEG, MRI, or functional neuroimaging techniques.
- There is discordance between clinical, imaging, and EEG data regarding the origin of seizures.
- Seizures arise from regions near or within eloquent cortex, making resection risky without precise mapping.
- The epilepsy is multifocal, and there is a need to assess multiple potential epileptogenic regions.

The goal of SEEG is to determine whether a patient is a candidate for surgical resection and, if so, to identify the exact region(s) to target while avoiding areas responsible for critical functions such as language, movement, or sensation.

SEEG Implantation

SEEG requires the implantation of multiple multi-leads electrodes into specific brain regions based on hypotheses derived from clinical data, neuroimaging, and prior EEG studies. The implantation process follows a detailed preoperative planning phase that involves:

1. Hypothesis formulation: Based on clinical data, the epileptogenic zone(s) are hypothesized, typically using scalp EEG, MRI, and other functional imaging modalities.[Kahane et al., 2006]
2. Stereotactic planning: Using high-resolution MRI and computed tomography (CT) scans, a stereotactic frame or a frameless navigation system is employed to determine the exact entry points and trajectories of the electrodes. These paths are carefully selected to avoid vasculature and critical brain structures.[Cardinale et al., 2013; Cardinale et al., 2015]
3. Electrode implantation: Under general anesthesia, intracerebral electrodes are stereotactically implanted through burr holes in the skull. These electrodes penetrate both cortical and subcortical structures, allowing for the recording of both superficial and deep brain activity. The number of electrodes and their precise locations are tailored to the individual patient's epileptogenic hypothesis.[d'Orio et al., 2024a]

4. Post-implantation imaging is typically performed to confirm the accuracy of electrode placement and ensure that no complications, such as hemorrhage, have occurred.
5. In “Claudio Munari” Epilepsy Surgery Centre (Milano), at the end of the surgical procedure, multimodal scenes were constructed with 3D Slicer software package and the position of each recording lead was estimated by means of SEEG-Assistant tool, which is freely available as a 3D Slicer plug-in for running the DEETO software package.[Fedorov et al., 2012; Arnulfo et al., 2015; Narizzano et al., 2017]

SEEG Recording

SEEG recordings are conducted over several days to weeks, with continuous video monitoring to capture spontaneous seizures and interictal activity. Each electrode contains multiple contacts that record electrical activity from different brain regions simultaneously. SEEG offers several advantages over scalp EEG:

- Spatio-temporal resolution: SEEG allows for the recording of electrical activity from deep structures that cannot be detected via surface electrodes, providing a clearer picture of the propagation pathways of seizures.
- Signal clarity: By bypassing the skull and scalp, SEEG avoids the distortion and attenuation of signals that occur with scalp EEG, resulting in higher-quality recordings.

The recording process captures both interictal (between seizures) and ictal (during seizures) events, which are then analyzed to determine the seizure onset zone and the functional connectivity of the epileptogenic network.

Cortical Stimulations

In addition to passive recordings, SEEG electrodes are also used to perform cortical electrical stimulation.[George et al., 2020] This technique fulfills several objectives:

- Functional mapping: Electrical stimulation is applied to specific brain regions to map eloquent cortical areas responsible for essential functions such as language, motor

control, and sensory processing. This ensures that critical regions are preserved during surgical resection.

- Seizure induction: Stimulation can also be used to provoke seizures, helping to identify seizure onset zones when spontaneous seizures are difficult to capture.
- Effective connectivity: It is studied through cortico-cortical evoked potentials (CCEPs) by applying direct electrical stimulation to a cortical area and recording the evoked responses in other connected regions.[Prime et al., 2018]

Cortical stimulation involves delivering brief electrical pulses to the brain through SEEG electrodes while the patient is awake, allowing real-time monitoring of any sensory, motor, or cognitive effects. This functional data is integrated with the electrophysiological recordings to guide surgical planning.

Outcomes of SEEG

The success of SEEG in identifying epileptogenic zones has greatly enhanced the safety and efficacy of epilepsy surgery. The ability to localize seizures with precision allows for more targeted resections, minimizing the removal of healthy brain tissue while maximizing the chances of seizure freedom. Studies have shown that SEEG-guided resections result in favorable outcomes, with many patients achieving significant reductions in seizure frequency or complete seizure freedom. Additionally, SEEG-guided radiofrequency thermocoagulation (RF-TC) has emerged as a minimally invasive treatment option, where the same SEEG electrodes are used to perform targeted thermocoagulation of epileptogenic tissue, providing a therapeutic alternative to resective surgery for some patients.[Cossu et al., 2015; Cardinale et al., 2019]

However, SEEG is not without limitations. It is an invasive procedure that carries risks, such as hemorrhage, infection, and electrode-related complications, although these risks are generally low with careful planning and execution. Furthermore, the ability to successfully localize seizures depends on the accuracy of the preoperative hypothesis and the placement of electrodes, which requires significant expertise.[Cardinale et al., 2019]

Conclusion

SEEG represents a powerful tool in the management of drug-resistant epilepsy, offering a level of precision in the localization of epileptogenic zones that is unmatched by non-invasive techniques. Through a combination of high-resolution recordings and cortical stimulation, SEEG enables clinicians to tailor surgical interventions, improving outcomes for patients while minimizing risks. As technology advances, SEEG continues to evolve, expanding its applications in both diagnostic and therapeutic realms in epilepsy treatment.

Chapter two: SEEG-Guided Radiofrequency Thermocoagulations (RF-TC)

Introduction

SEEG–guided radiofrequency thermocoagulation (RF-TC) is an innovative and minimally invasive therapeutic approach designed for the treatment of drug-resistant focal epilepsy.[Guenot et al., 2004] This technique, which utilizes SEEG electrodes for both diagnostic mapping and therapeutic intervention, has gained increasing attention in recent years due to its ability to precisely target epileptogenic zones (EZs) while minimizing the risk of damaging surrounding healthy brain tissue. The development of SEEG-guided RF-TC is deeply rooted in advancements in neuroimaging and stereotactic surgical techniques, allowing for accurate localization and treatment of the EZ, even in patients for whom traditional resective surgery may not be feasible.

Historical Background

The concept of using targeted lesions to control epileptic seizures dates back to the mid-20th century.[Leiphart et al., 2014] Mesial temporal lobe structures were the preferred targets for early ablative procedures[Perrent et al., 1999] also in patients who underwent stereotactic amygdalotomy for the treatment of behavioral disorders associated with epilepsy.[Fountas et al., 2007] The outcomes of such interventions, however, were often disappointing, leading to a temporary disillusionment regarding the potential efficacy of these techniques. With the introduction of precision imaging, such as MRI, stereotactic ablative procedures, including RF-TC, entered a new phase of development, proving particularly effective and safe in conditions such as mesial temporal lobe epilepsy and focal cortical dysplasia.

SEEG-Guided RF-TC: Rationale and Technique

The rationale behind SEEG-guided RF-TC is based on the goal of selectively destroying epileptogenic foci or critical nodes within epileptogenic networks, with the hope of controlling seizures without resorting to extensive resective surgery. This approach is

particularly indicated for patients who are not candidates for resective surgery due to the involvement of critical brain regions or other contraindications. RF-TC could also be an alternative for patients with less defined or multifocal EZs, where resection might carry a higher risk of neurological deficits.[Guenot et al., 2004; Cossu et al., 2017]

When the epileptogenic zone has been clearly identified, the electrodes are connected to a radiofrequency generator that delivers energy to create localized thermal lesions. The typical parameters for RF-TC include gradually increasing the power from 1.5 W to 8.32 W over 60 seconds, which raises the temperature of the surrounding tissues to around 78-82°C. This temperature is sufficient to induce thermal necrosis in the targeted tissue, effectively destroying the epileptogenic cells without significantly damaging the surrounding healthy tissue. The number of coagulations varies depending on the specific needs of the patient.[Guenot et al., 2004; Cossu et al., 2015]

A critical aspect of the procedure is the selection of the electrode contacts to be used for thermocoagulation. The selection of contacts is based on criteria such as involvement in the onset of the epileptic discharge, intralesional location, and the ability to induce typical ictal clinical phenomena through electrical stimulation. Contacts that are located too close to vascular structures or near functionally critical areas, such as those involved in movement, language, or vision, are generally excluded from treatment to avoid permanent neurological deficits.

Clinical Outcomes and Applications

SEEG-guided RF-TC has shown considerable promise in the treatment of various forms of focal epilepsy, particularly in patients with gray matter heterotopies, malformations of cortical development (MCDs), and mesial temporal lobe epilepsy (MTLE).[Guenot et al., 2004; Cossu et al., 2014; Cossu et al., 2015; Bourdillon et al., 2017; Cardinale et al., 2019]

Results provided by Bourdillon et al., gathered in a large population over a 10-year period, confirm that SEEG-guided RF-TC is a safe technique, being efficient in many cases. More than two thirds of patients showed a short-term improvement, and 48% of them were responders at 1-year follow-up. At 10 years, 13% of patients maintained this status.[Bourdillon et al., 2017]

However, it is important to note that the overall rate of seizure freedom following RF-TC is generally lower than that achieved with resective surgery. Rates of complete seizure control vary widely, depending on the underlying pathology, the precise localization of the epileptogenic zone, and the extent of the lesions created. These outcomes reflect the complexity of the patient population typically selected for SEEG-guided RF-TC, which often includes individuals with multifocal or poorly localized epileptogenic zones.[Cossu et al., 2017; Bourdillon et al., 2018]

Furthermore, the clinical utility of RF-TC is enhanced by the ability to precisely target epileptogenic foci while sparing adjacent critical brain structures. This precision is particularly important in patients with epileptogenic zones located in or near eloquent cortex, where traditional resective surgery might result in unacceptable functional deficits. By using SEEG to guide the placement of thermal lesions, neurosurgeons can achieve a high degree of accuracy in targeting the epileptogenic zone, thereby minimizing the risk of collateral damage and preserving neurological function.

Limitations and Risks

Despite its advantages, SEEG-guided RF-TC is not without limitations. The main technical limitation is the lack of direct thermal control during the procedure, meaning that it is not possible to monitor in real-time the tissue temperature at the coagulation site. This limitation can lead to variability in the size and efficacy of the lesions created. Moreover, the procedure carries risks of adverse effects, including seizures during coagulation, transient local pain, and, in rare cases, permanent neurological deficits. Another limitation is the relatively low rate of seizure freedom compared to resective surgery. While RF-TC can offer significant seizure reduction, complete seizure control is less common, particularly in patients with complex or multifocal epileptic foci.[Cossu et al., 2017; Bourdillon et al., 2018; Cardinale et al., 2019]

Conclusion

SEEG-guided RF-TC represents a significant advancement in the treatment of focal epilepsy, particularly for patients who are not candidates for resective surgery. While the procedure may not achieve the same level of seizure freedom as traditional surgery, it offers a less invasive alternative with acceptable risks and the potential for significant clinical improvement. As neuroimaging and surgical techniques continue to evolve, SEEG-guided RF-TC may become an increasingly important tool in the management of refractory focal epilepsy.

Chapter three: Effects of SEEG-Guided Radiofrequency Thermocoagulations on Brain Activity and Connectivity

If SEEG has represented the opportunity to have a privileged view for studying the neurophysiology of the human brain,[Mercier et al., 2022] SEEG-guided RF-TCs may represent a paradigm shift for studying the physiology of cortical lesions.

Despite advances in understanding the functional alterations induced by focal cortical lesions, much of the current evidence comes from studies on animal models or non-invasive recordings in patients affected by stroke or traumatic brain injury. However, these approaches present significant limitations. Firstly, the heterogeneous and accidental nature of brain lesions (which can be ischemic, hemorrhagic, or traumatic) introduces intrinsic variability that is difficult to control. Secondly, non-invasive electrophysiological techniques, such as EEG or MEG, suffer from low spatial resolution, limiting the ability to accurately identify local changes in neuronal activity. Finally, one of the major obstacles is the lack of baseline electrophysiological recordings taken before the lesion in the same subject, which could provide an essential reference point for assessing post-lesion alterations. These factors have historically hindered a comprehensive understanding of the electrophysiological changes following lesions and their potential to propagate through large-scale neural networks.

In a recent paper, Russo et al. hypothesized that small, focal cortical lesions induced by SEEG-guided radiofrequency thermocoagulation (RF-TC) could disrupt large-scale brain networks, potentially generating slow wave activity similar to that observed during sleep, even in awake subjects. The study focused on understanding the extent of these disruptions and their propagation across the brain. The researchers conducted the study on 21 patients with drug-resistant epilepsy, using SEEG recordings taken before and after RF-TC. They analyzed both spontaneous brain activity and cortico-cortical evoked potentials (CCEPs) to assess the effects of these lesions on local and network-level brain activity.

The results showed that RF-TC-induced lesions led to the generation of slow waves that propagated from the lesion site to distant brain regions, traveling up to 60 mm along pre-existing connectivity pathways. This propagation was not random but followed the network architecture of the brain, as determined by CCEPs recorded prior to the lesion. The study found that these slow waves resembled those observed during sleep and were particularly pronounced

in regions connected to the lesioned area. This suggests that even small, localized brain lesions can have widespread effects on brain dynamics, affecting both local and distant neural activity. The researchers concluded that the propagation of slow wave activity after RF-TC reflects a form of network-level disruption that extends beyond the site of the lesion. This finding highlights the importance of considering both local and large-scale network effects when studying the impact of cortical lesions on brain function. The study provided new insights into how focal brain injuries can influence brain dynamics on a broader scale, with potential implications for understanding the functional consequences of such injuries in clinical settings.[Russo et al., 2021]

Meanwhile**,** a study of Contento et al. aimed to assess how SEEG-guided radiofrequency thermocoagulation (RF-TC) influences epileptogenic biomarkers, such as spikes, high-frequency oscillations (HFOs), and cross-rate, and their correlation with clinical outcomes. The researchers included 38 patients with drug-resistant epilepsy and analyzed SEEG recordings before and after RF-TC to evaluate the changes in these biomarkers. The study found that in patients who showed clinical improvement, there was a significant reduction in spikes and cross-rate in the epileptogenic zone, and a similar reduction in HFOs in the thermocoagulated zone. In contrast, patients who did not improve clinically showed less pronounced biomarker changes. These findings suggest that the reduction of these biomarkers is a strong predictor of both clinical improvement after RF-TC and successful outcomes following resective surgery. The study concluded that quantified changes in the rate of spikes, HFOs, and cross-rate after RF-TC can be used to predict the effectiveness of the procedure, making them potential clinical tools for decision-making in epilepsy surgery.[Contento et al., 2021]

Subsequently, Simula et al. investigated both local and network-level changes in brain activity after SEEG-guided RF-TC in 33 patients with drug-resistant epilepsy. The aim was to understand how RF-TC affects not only local brain activity but also functional connectivity (FC) across the epileptogenic network, and whether these changes are associated with clinical outcomes. Using power spectral density (PSD) to measure local activity and FC to assess network-level changes, the researchers found that in patients who responded positively to RF-TC, there was a significant reduction in PSD across multiple frequency bands in thermocoagulated channels, while non-responders showed little to no change. At the network level, non-responders exhibited an increase in FC across most frequency bands, suggesting a

disruption of the epileptogenic network, whereas responders displayed a reduction in FC, particularly in the delta and alpha bands, indicating a stabilization of the network. These findings highlight the dual impact of RF-TC on both local and network-level brain activity and suggest that changes in functional connectivity may serve as a predictor of therapeutic success. The study concluded that the neurophysiological differences between responders and non-responders provide insight into the mechanisms of RF-TC and its potential as a treatment for drug-resistant epilepsy.[Simula et al., 2023]

The most recent study investigated the impact of RF-TC on brain connectivity in patients with drug-resistant focal epilepsy, utilizing SEEG and CCEPs to assess functional network alterations before and after the procedure. The findings demonstrated that RF-TC induces significant changes not only in directly coagulated regions but also in remote, non-coagulated areas. Notably, modifications in connectivity between non-coagulated sites were observed at distances exceeding 80 mm from the coagulation site, suggesting a widespread effect on the epileptic network. Furthermore, contact pairs exhibiting significant connectivity changes post-RF-TC showed higher spectral correlation in the theta, beta, and gamma frequency bands during seizures compared to unaffected connections.[Gula et al., 2025]

In conclusion, the evidence suggests that SEEG-guided RF-TC have a multifactorial impact, affecting not only the treated tissue but also brain connectivity and neural network dynamics. This confirms the importance of considering not only the local effects but also the broader network repercussions when evaluating the therapeutic outcomes of thermocoagulation, providing new insights for the development of more effective strategies in the treatment of drug-resistant epilepsy.

One of the most important limitations of these studies is that the post-RF-TC recordings were performed after multiple lesions had been applied to the same patient, often in different brain regions. As a result, the observed effects on brain activity and connectivity may not be attributable to the impact of a single lesion but could also be influenced by confounding factors arising from the cumulative effects of the other lesions. This makes it challenging to isolate the precise contribution of each individual thermocoagulation to the overall network changes, and further studies are needed to clarify the specific impact of single-lesion interventions.

In my thesis, I aimed to address this limitation by isolating the effects of individual thermocoagulations, allowing for a more precise evaluation of how a single lesion influences brain activity and connectivity. This approach provides a clearer understanding of the specific impact of RF-TC, which will be explored in the following sections.

Chapter four: Modulation of Effective Connectivity after RF-TC in subacute phase

Introduction

SEEG-guided radiofrequency thermocoagulation (RF-TC) could represent a paradigm shift in the study of the neurophysiology of lesions in human brain. This approach offers unique advantages over traditional lesion models due to several key factors: the size, location, and controlled nature of the lesions, as well as the direct relationship between the lesion and its immediate effects on brain activity.

First, the lesions produced by RF-TC are small, typically confined to cortical areas or limited to U-fibers, thereby minimizing the risk of extensive damage to adjacent brain structures. Second, these lesions are highly controlled: the exact location of the lesion is known because it is delivered through the SEEG electrodes implanted according to a pre-determined, stereotactic plan. This controlled process enables the direct comparison of brain activity before and after the lesion. By using the pre-lesion recordings as a baseline, one can accurately document the functional changes induced by the lesion, establishing a clear cause-effect relationship.

Another significant advantage of SEEG-guided RF-TC is the ability to record and analyze the brain's immediate response to the lesion, shortly after it is made. This proximity in time minimizes the influence of neuroplastic processes, which could otherwise obscure the direct effects of the lesion. As a result, SEEG-guided RF-TC offers an unprecedented opportunity to isolate the impact of focal cortical lesions on brain connectivity, without the confounding effects of long-term reorganization.

Moreover, SEEG electrodes not only allow the recording of resting cortical activity but also provide the ability to study cortico-cortical evoked potentials (CCEPs) between different electrode contacts.[Enatsu et al., 2015; Dionisio et al., 2019; Lemaréchel et al., 2022] This enables the investigation of effective connectivity - the causal interactions between brain regions - both before and after the lesion. RF-TC can thus be used as a controlled traumatic

event within the brain, providing insights into how the brain responds to injury and how effective connectivity is modulated in response to such an insult.

Cortico-cortical evoked potentials (CCEPs) are a valuable tool for studying effective connectivity.[Kunieda et al., 2015; Matsumoto et al., 2017; Keller et al., 2014; Lemaréchal et al., 2022] They are obtained by applying electrical stimuli to one cortical region and recording the evoked responses in other functionally connected areas. This method allows for the mapping of direct communication pathways between different cortical areas. CCEPs have been widely used to explore functional brain networks in both healthy and pathological states.

However, to date, there is a notable gap in the literature regarding the use of CCEPs to study the effects of brain lesions, particularly those induced by RF-TC. No studies have systematically recorded CCEPs after a controlled cortical lesion, making this research a novel contribution to the understanding of brain connectivity dynamics following focal injury.

Methods

This study aimed to investigate the modulation of effective connectivity following SEEG- RF-TC, focusing on regions of the brain with high connectivity as determined by CCEPs. The study was conducted in a cohort of 67 patients with drug-resistant focal epilepsy who underwent SEEG monitoring and subsequent RF-TC as part of their presurgical evaluation between 2021 and 2023.

Out of a total of 145 patients who underwent SEEG monitoring at our center during the same period, 67 were included in this study based on the following selection criteria:

- Neuroimaging findings: Only patients with a negative MRI or a well-defined focal lesion were considered. Patients with complex or extensive cortical malformations were excluded.
- Surgical candidacy: Patients who, at the end of the SEEG evaluation, were deemed unsuitable for epilepsy surgery and therefore did not undergo RF-TC were not included in the study.
- Post hoc selection: To maintain consistency with the clinical workflow of our center, patients were selected prospectively based on the presence of regions with strong epileptogenic activity and high effective connectivity, as determined by CCEP analysis.

Furthermore, priority was given to cases in which at least one of the coagulation targets, selected for clinical purposes, was located in a region of particular neurophysiological interest.

SEEG Implantation

Patients included in the study had drug-resistant focal epilepsy and were undergoing SEEG monitoring for presurgical evaluation. SEEG electrodes were stereotactically implanted, and their placement was tailored to each patient based on clinical, imaging, and neurophysiological findings. The number of electrodes varied between patients, but all SEEG arrays were designed to capture the epileptogenic zone as well as surrounding regions involved in the seizure network. Each electrode had multiple contacts to ensure comprehensive sampling of cortical regions.

CCEP Mapping and Region Selection for Thermocoagulation

In the initial days following SEEG electrode implantation, single-pulse electrical stimulation (SPES) was performed across all electrode contacts in an "all against all" fashion to map cortico-cortical connectivity. SPES was delivered through a pair of adjacent contacts, using biphasic rectangular stimuli of alternating polarity with a frequency of 1 Hz, pulse width of 0.5 ms, duration of 15 seconds (thus cumulating 15 repetitions for a given site stimulation), and a current intensity of 5 mA. This protocol allowed us to assess the CCEPs generated by each stimulation and identify regions of high connectivity within the cortical network. These early stimulation sessions were critical for identifying the regions of interest for subsequent thermocoagulation.

A typical cortico-cortical evoked potential (CCEP) consists of two main components:[Matsumoto et al., 2017]

- The N1 component, which is an initial negative deflection, typically occurring in the first 50 ms after the stimulus. This is thought to represent the direct activation of axonal pathways between the stimulated and recorded regions.

- The N2 component, a subsequent deflection occurring 50-200 ms post-stimulus, is believed to reflect post-synaptic responses and may involve more complex network interactions, including feedback from distant cortical regions.

Unlike structural and functional connectivity analyses, CCEPs provide critical information on the directionality of connectivity between two points in the brain. Specifically, they allow us to determine whether the connection is unidirectional, from point A to point B, or bidirectional, indicating reciprocal communication between the two regions. This directional insight is crucial for understanding the flow of information within cortical networks, as well as for identifying potential hubs of communication within the brain.

Thermocoagulation Protocol

At the end of SEEG monitoring, and once all the necessary data for defining the epileptogenic zone have been collected, the epileptologists compile a detailed list of all the contacts and brain regions that need to be thermocoagulated for sole clinical purpose. This list is based on SEEG recordings, responses to stimulations, and clinical information gathered during the monitoring process.

Given our interest in evaluating the effects of a single RF-TC, among the proposed lesion sites, we selected those targeting a single specific cortical region. This selection was based on the richness of prior CCEP investigations. Before proceeding with the full set of thermocoagulations planned for clinical purposes, we focused our attention on this specific site.

Hence, following the analysis of CCEP data, we identified the region exhibiting the highest number of connections, as determined by CCEP responses, for thermocoagulation. This region was chosen based on both its high connectivity and its relevance within the broader epileptogenic network, ensuring that it aligned with our research objectives while also holding significant potential for future studies on clinical impact. Importantly, the selection process balanced both clinical and research considerations, addressing the need to treat epilepsy while simultaneously enabling the study of connectivity changes induced by RF-TC.

Once the region of interest for RF-TC was selected based on the CCEP results, the following protocol was applied:

- Pre-lesion baseline recording: Prior to the thermocoagulation, we recorded 10 minutes of resting-state SEEG to establish a stable baseline of cortical activity.

- Targeted thermocoagulation: RF-TC was performed in the selected region using the SEEG electrodes. The lesion was created between two contiguous contacts of the electrode implanted in the highly connected region. To perform the thermocoagulation, we apply a ramp-up from 1.5W to 8.32W over approximately 60 seconds, in order to create an oval-shaped lesion with a volume of about 1 cubic centimeter.

- Post-lesion recording: Immediately after the post-lesion stimulation, another 10 minutes of resting-state SEEG was recorded to monitor any changes in spontaneous brain activity following the thermocoagulation.

- Post-lesion stimulations: Following the thermocoagulation, we stimulated at least 10 sites that had previously shown strong connectivity with the thermocoagulated region, as determined by the initial CCEP mapping. In addition, one stimulation was performed in a control region outside the main network, to serve as a reference point. This allowed us to assess how the lesion impacted effective connectivity both within the connected network and in areas that were not directly connected.

- Completion of other suggested thermocoagulation: After completing the experimental phase, the remaining RF-TC lesions suggested by the clinical team were performed to address the patient's epileptogenic zone.

- Final rest recording and electrode removal: Following the completion of all thermocoagulations, an additional 10 minutes of resting-state SEEG was recorded to capture the brain's activity post-thermocoagulation. Finally, the SEEG electrodes were removed, marking the end of the study protocol.

Comparison of Pre- and Post-lesion CCEPs

A crucial aspect of our study was the comparison of CCEPs before and after the thermocoagulation in the selected region. The same stimulation protocol used prior to the lesion was applied post-lesion, allowing us to directly compare the CCEP responses between the two conditions. In this context, the thermocoagulation itself was considered purely as a stressor, while effective connectivity was measured across all other contacts, rather than at the lesion site. This approach provided a clear measure of how the thermocoagulation altered effective connectivity between the lesion site and the rest of the network. The connectivity changes were quantified by studying the amplitude, latency, and overall morphology of CCEPs in both conditions. All CCEPs were inspected by aligning 15 trials, plotting each individual trial, and subsequently computing and plotting the average response (figures 1, 2, 3, and 4).

We must point out that while a possible analysis approach would have been to statistically compare the two pools of responses across conditions (before and after RF-TC), we soon realized that normative and reference procedures are lacking in the literature. Indeed, CCEPs are typically analyzed in isolation (for instance, by evaluating whether N1 or N2 components significantly deviate from the baseline) and are rarely compared across conditions, especially following a perturbative approach that may alter the bioelectrical properties of current conductivity and the signal-to-noise ratio of CCEPs. Furthermore, topographical factors - such as the site of RF-TC, the site of stimulation, and the recorded site - play a crucial role in shaping CCEP responses.

Given these premises, the preliminary analysis on the entire sample remained observational, aiming to classify the major and prevalent patterns of CCEP changes following RF-TC. From this foundation, and by further restricting the analysis to RF-TC administered in a specific region, in the next chapter, we devised a tentative statistical approach to quantify this CCEP modulation.

Results

As expected, no changes in CCEPs are detected in most stimulations (figure 1, panel A) but our preliminary observational phase has revealed several distinct changes in effective connectivity following SEEG-guided RF-TC.

First, we observed that certain connections, present before the thermocoagulation, were no longer detectable afterwards, indicating a complete loss of connectivity (figure 1, panel B). Furthermore, we also documented reductions in CCEP amplitude in a number of previously connected regions.

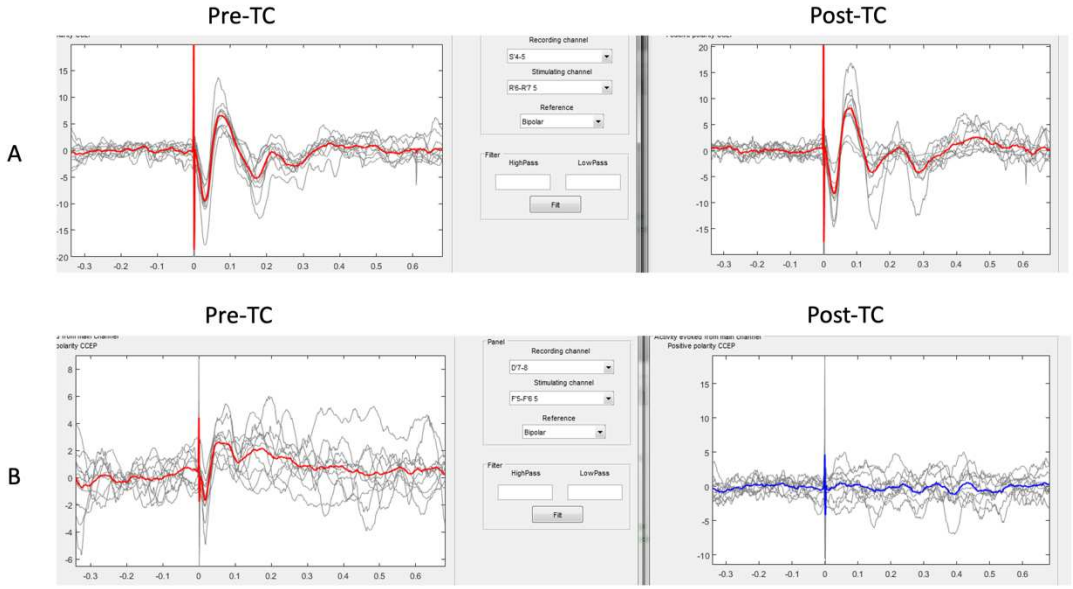

Figure 1

Middle-posterior portion of collateral sulcus SEEG-guided RF-TC. Panel A: SPES delivered to the motor subcentral operculum, CCEP recorded in sensory subcentral operculum. Panel B: SPES delivered to the posterior portion of hippocampus, CCEP recorded in the anterior portion of lateral temporo-occipital sulcus

The most novel finding, however, was the emergence of increased CCEP amplitude in certain connections (figure 2), suggesting a paradoxical strengthening of connectivity in response to the lesion.

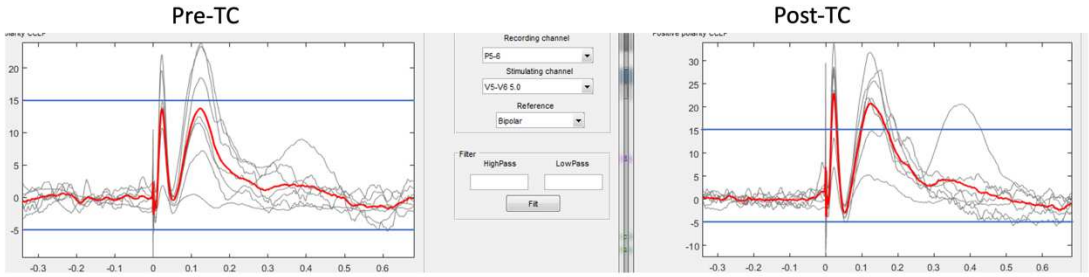

Figure 2

Posterior portion of fusiform gyrus SEEG-guided RF-TC. SPES delivered to the occipital pole, CCEP recorded into the intra-parietal sulcus.

In a few cases, we also observed the appearance of new CCEPs responses that were not present before the thermocoagulation but became evident afterwards (figure 3). This could suggest the formation of new functional connections or the unmasking of latent pathways following the focal cortical insult.

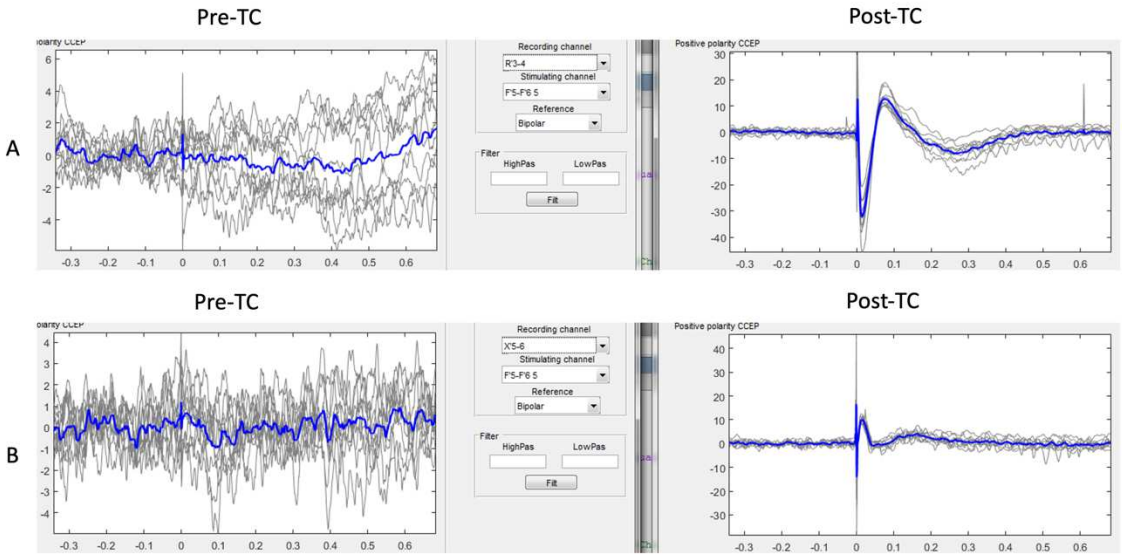

Figure 3

Middle-posterior portion of collateral sulcus SEEG-guided RF-TC. Panel A: SPES delivered to the posterior portion of hippocampus, CCEP recorded in motor subcentral operculum. Panel B: Same SPES of panel A, CCEP recorded in the "pars triangularis" of inferior frontal gyrus.

Another noteworthy observation involved morphological changes in CCEPs (figure 4). In some cases, one or both components of the evoked potential displayed a widening in duration, along with alterations in waveform shape, both in the positive and negative directions.

These changes in morphology may reflect complex underlying mechanisms, potentially involving the reorganization of cortical circuits or compensatory processes triggered by the focal lesion.

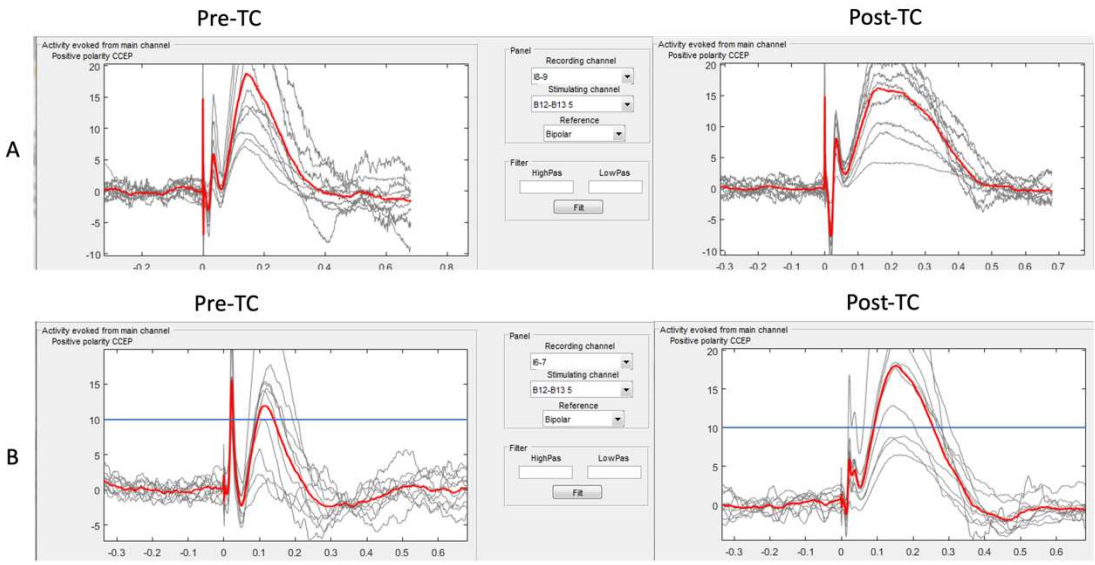

Figure 4

Middle-posterior para-hippocampal gyrus SEEG-guided RF-TC. Panel A: SPES delivered to the middle portion of middle temporal gyrus, CCEP recorded in the polar portion of middle temporal gyrus. Panel B: Same SPES of panel A, CCEP recorded in the polar portion of inferior temporal sulcus.

Speculatively, these findings suggest that thermocoagulation is not only able to disrupt existing connections but also triggers adaptive or compensatory changes within the network. The emergence of new connections and increases in amplitude might indicate a form of network reserve, where the brain attempts to re-establish communication pathways that have been disrupted. Alternatively, these changes could reflect the unmasking of previously inhibited circuits, now free to express themselves after the lesion has altered the balance of excitatory and inhibitory influences within the network. This complex interplay of disruption and reorganization highlights the dynamic nature of brain connectivity and its ability to adapt to local injuries in ways that may both hinder and enhance communication between cortical regions, even in this subacute phase.

Chapter five: Modulation of direct effective connectivity after RF-TC in central operculo-insular cortex

Premise

In this chapter, we delve deeper into the experimental phase of our study, building on the observational findings presented previously. We narrowed our focus to a subset of patients who underwent their first RF-TC in the central operculo-insular region. This specific focus allows us to explore direct effective connectivity in more detail both within and outside this critical region.

The central operculo-insular cortex was selected for several reasons. First, this region closely resembles the lesions typically seen in stroke patients,[Bonkhoff et al., 2024] a condition whose neurophysiological consequences have been studied with various methodologies.[Carrera and Tononi, 2014] By targeting this area, we aim to build on existing knowledge while exploring new dimensions of effective connectivity. Second, the perisylvian region is among the most frequently studied areas in SEEG, particularly due to its complex involvement in epilepsy networks and its relevance in drug-resistant epilepsy.[Mălîia et al., 2018; Dionisio et al., 2019; Ryvlin et al., 2021] In addition, in our center, exploration pattern of these patients is quite similar with the most of electrodes targeting all perisylvian cortex, the insular lobe, pre-motor, motor and parietal cortices and cingulate gyrus. Also, the electrodes nomenclature is usually standardized for these regions. Third, operculo-insular cortex is particularly critical in our clinical practice because its higher surgical risks and morbidity after resective surgery.[d'Orio et al., 2024b]

In addition, the central operculo-insular cortex has been extensively studied thanks to the collaboration between the "Claudio Munari" Epilepsy Surgery Centre (Milan) and the Institute of Neuroscience of CNR (Parma) in SEEG-guided research. Several key studies have mapped the neurophysiology of this area, providing a solid foundation for our investigation.[Avanzini et al., 2016; Del Vecchio et al., 2019; Del Vecchio et al., 2020; Del Vecchio et al., 2021]

This chapter, then, focuses on the modulation of direct effective connectivity following RF-TC in the central operculo-insular cortex. The analysis was specifically targeted to N1 component of CCEPs, observed within the first 50 milliseconds after stimulation. This early response window provides a precise measure of the immediate, direct effects of cortical stimulation.[Lemerèchel et al., 2022] By applying SEEG-guided RF-TC to this highly connected region and examining the N1 component, we aim to capture the direct changes in connectivity between brain regions following a controlled lesion in the operculo-insular cortex. This approach allows us to explore how direct pathways are modulated in response to a focal cortical stressor, offering insights into the dynamics of cortical networks after RF-TC.

Methods

As previously affirmed, during the presurgical evaluation and before the RF-TC procedure, an extensive effective connectivity assessment was performed on each patient using Single Pulse Electrical Stimulation (SPES) and Cortico-Cortical Evoked Potentials (CCEPs)

Initial CCEP responsiveness definition

The CCEPs, both pre- and post-RF-TC, were pre-processed using an automatic pipeline. First, the electrical stimulation artefact was removed by applying a Tukey-windowed median filter. The signals were then filtered with a 0.5 Hz high-pass 3rd order Butterworth filter, and the individual trials were split based on the inter-stimulus interval (−330 ms, +666 ms). Baseline correction was performed for each trial, using the window from −300 ms to −20 ms before stimulation to avoid any residual stimulation artefact.

SPES, delivered with alternate monophasic pulses, was separated into positive and negative components and analyzed independently. Automatic rejection of trials with epileptiform abnormalities or electrical artefacts was performed as follows:

1- For each time sample and single trial, the average of all trials was subtracted from each individual trial.
2- To define pre-stimulus activity, a null distribution was created by merging the baselines (−300 ms to −20 ms) of all trials.[Usami et al., 2015]

3- Trials exceeding the null distribution were identified using Chebyshev's inequality.
4- If the maximum voltage value across trials exceeded 7σ of the null distribution (corresponding to $\alpha = 0.05$), the trial was rejected.
5- This process was performed iteratively, with rejected trials excluded from both the dataset and the null distribution, until no trial exceeded the Chebyshev threshold.[Le Van Quyen et al., 2001]

After the automatic rejection of artifact-ridden trials, we quantified the power of the significant CCEPs elicited by SPES from the RF-TC contacts. Finally, CCEPs were z-scored with respect to the baseline interval pre-stimulation pulse. The responsiveness was initially set if its peak value reached the threshold of $z > 5$[Lemerèchel et al., 2022] during the first 50ms post-stimulation pulse for 10 consecutive time-bins of duration in order to limit the analysis to the N1 component.

CCEP's parameter definition and analysis

Due to the variability in waveform responses and the need to minimize false-negative results, the initial phase of our study involved a thorough visual inspection of all pre-RF-TC CCEPs to assess the performance of the automatic responsiveness pipeline. Specifically, we evaluated both the presence of responsiveness (yes/no) and the accuracy of peak detection (yes/no).

A total of 10303 CCEPs from eight patients (5 males, median age 26.5 years old, median electrodes implanted of 18, median stimulations after RF-TC of 10, median CCEPs evaluated of 1377) were analyzed. The median z-score of the responsive channels was 9, while the median z-score for non-responsive channels was 2. Focusing exclusively on the responsive channels, we examined the temporal distribution of CCEP peaks, finding that most of them of them occurred between 11 and 35 ms post-stimulation. The initial 10 ms were excluded to avoid confounding due to the stimulation artifact. A comparison between the automatic pipeline and the visual inspection showed that a z-score threshold of 4.5 provided an accuracy of 80%.

Based on these findings, we applied a refined pipeline to all patients included in the study, defining a responsive channel as one with an evoked potential peaking between 11 and 35 ms, exceeding 4.5 z-scores above baseline for at least 10 consecutive time bins.

Results

Descriptive Statistics of CCEPs Before and After Thermocoagulation

A total of 18,948 CCEPs were analyzed before and after RF-TC. Descriptive statistics of the main parameters, including amplitude (Z-score), latency, and duration, are summarized in Table 1.

	Zpre	LatenzaPre	SignPre	DurataPre	Zpost	LatenzaPost	SignPost	DurataPost	DeltaZ	DeltaLat	DeltaDur
mean	4,1	23,9	0,2	14,4	3,9	23,9	0,2	14,0	0,2	0,1	0,3
median	1,8	24,0	0,0	15,0	1,8	24,0	0,0	14,0	0,1	0,0	0,0
std	7,7	9,1	0,4	7,4	7,3	9,1	0,4	7,5	5,9	11,7	7,4
min	-2,4	11,0	0,0	1,0	-2,0	11,0	0,0	1,0	-99,8	-25,0	-26,0
25%	0,6	15,0	0,0	8,0	0,6	15,0	0,0	8,0	-1,5	-6,0	0,0
50%	1,8	24,0	0,0	15,0	1,8	24,0	0,0	14,0	0,1	0,0	0,0
75%	4,5	33,0	0,0	21,0	4,3	33,0	0,0	20,0	1,7	6,0	0,0
max	179,9	36,0	1,0	26,0	177,7	36,0	1,0	26,0	99,3	25,0	26,0

Table 1. Descriptive statistics of CCEP parameters before and after RFTC.

Changes in CCEP Significance Due to RF-TC

The majority of CCEPs remained stable following RF-TC, with 2.452 (12.94%) maintaining their significance both before and after the intervention. This indicates that a notable proportion of cortico-cortical connections are resilient to thermocoagulation, preserving their functional integrity despite the procedure. Conversely, 1.563 (8.25%) CCEPs that were initially significant lost their response, suggesting that RF-TC effectively disrupts certain pathways. Meanwhile, 1.292 (6.82%) previously non-significant CCEPs became active, highlighting the potential for compensatory mechanisms or the unmasking of latent connections. The remaining responses exhibited no significant activity before or after the procedure, indicating a subset of connections that remain unresponsive to stimulation, regardless of RF-TC.

Distribution of Amplitude Changes After RF-TC

Figure 1 presents the distribution of changes in CCEP amplitude (DeltaZ) following RF-TC. The histogram illustrates the variability in CCEP strength modifications, highlighting a broad range of responses with a central tendency around null values, reflecting no amplitude modulations upon RF-TC.

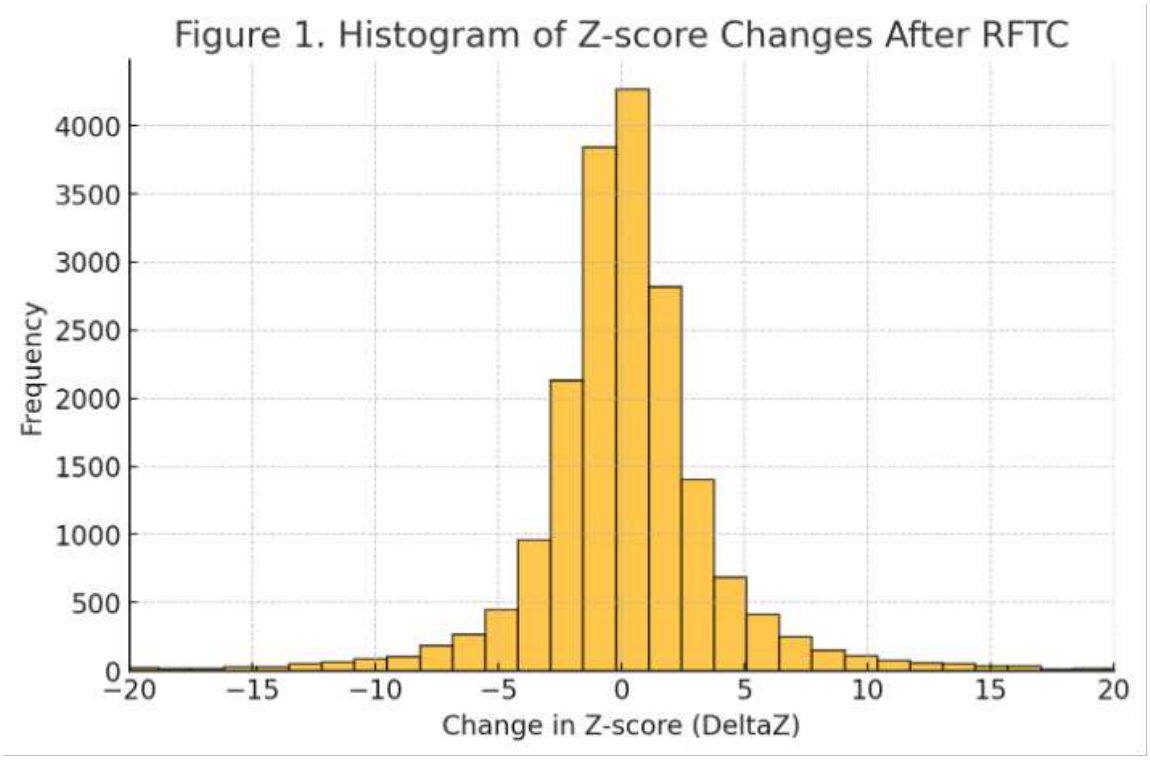

Figure 1. Histogram of Z-score changes after RFTC.

Relationship Between Pre- and Post-RF-TC CCEP Amplitude

A scatter plot illustrating the relationship between pre- and post-RF-TC Z-scores is shown in Figure 2. Data points are color-coded according to their significance categories, providing a visual representation of the impact of RF-TC. Blue points correspond to CCEPs that remained significant before and after RF-TC, demonstrating stability in connectivity. Red points indicate CCEPs that were significant before but lost their response following the procedure, emphasizing the disruptive effect of thermocoagulation. In contrast, Green points represent CCEPs that became significant only after RF-TC, suggesting possible network plasticity or recruitment of alternative pathways. Lastly, Gray points depict CCEPs that were not significant before or after the procedure, reinforcing the existence of non-responsive connections that remain unaffected by RF-TC.

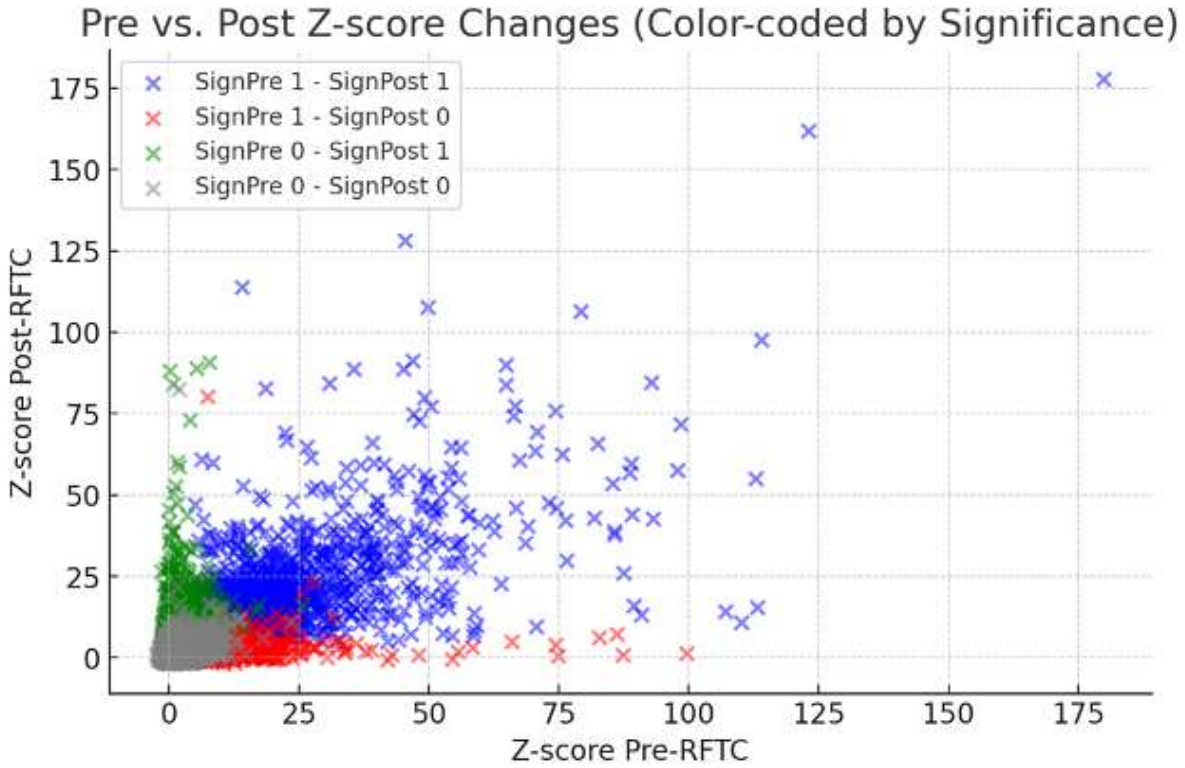

Figure 2. Pre- vs. Post-RFTC Z-scores categorized by CCEP significance.

This visualization highlights the differential effects of RF-TC on CCEP strength across different response categories, with distinct clusters reflecting varying degrees of amplitude modification. Such modulation (Zpre-Zpost) was also computed explicitly and is reported in corresponding color code in Figure 3, where it is possible to appreciate that CCEPs losing significance upon RF-TC present a decay of amplitude, while those gaining significance exhibit the opposite trend. The remaining, stable classes present on the contrary distributions centered on a zero modulation of amplitude.

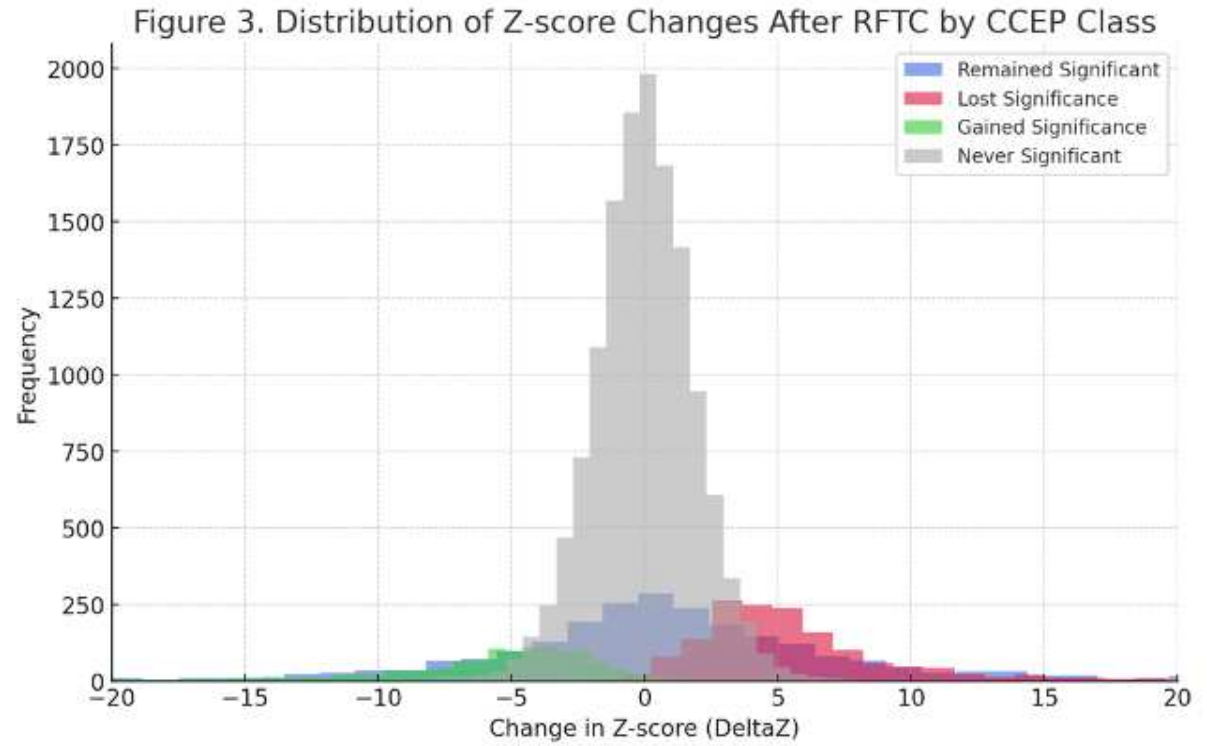

Figure 3. Distribution of Z-score Changes After RFTC by CCEP Class.

Analysis of CCEP Classes Based on Significance Before and After RF-TC

In the following sections, we will analyze separately the four classes of CCEPs based on their significance before and after RF-TC, providing a detailed examination of the distribution of amplitude and latency changes.

CCEPs That Remained Significant

The 2,452 CCEPs that remained significant before and after RF-TC exhibited a relatively stable distribution of amplitude, latency, and duration changes. The mean change in Z-score (DeltaZ) was 1.12, with a median of 0.64 and a standard deviation of 11.05, indicating variability across the sample. The latency change (DeltaLat) showed a mean shift of -0.13 ms, with a median of 0.0 ms, suggesting minimal systematic alterations in conduction timing. Similarly, the duration of CCEPs (DeltaDur) demonstrated an average increase of 0.29 ms, with a median of 0.0 ms, reinforcing the general stability of these responses despite RF-TC. The mean change in Z-score (DeltaZ) was 1.12, with a median of 0.64 and a standard deviation

of 11.05, indicating variability across the sample. The latency change (DeltaLat) showed a mean shift of -0.13 ms, with a median of 0.0 ms, suggesting minimal systematic alterations in conduction timing.

CCEPs That Lost Significance

Among the 1,563 CCEPs that lost significance after RF-TC, there was a notable increase in amplitude before the procedure, followed by a strong reduction post-RF-TC. The mean DeltaZ was 6.24, with a median of 4.85 and a standard deviation of 7.49, indicating a substantial drop in excitability. The latency distribution showed a mean DeltaLat of 0.15 ms, with a standard deviation of 10.22 ms, reflecting increased variability in conduction time post-RF-TC. Additionally, the duration of CCEP responses (DeltaDur) increased significantly, with a mean change of 14.83 ms, a median of 15.0 ms, and a standard deviation of 6.74 ms, suggesting that prior to RF-TC, these responses were longer-lasting but subsequently suppressed.

CCEPs That Gained Significance

The 1,292 CCEPs that became significant only after RF-TC displayed an opposite pattern to those that lost significance. The mean DeltaZ was -7.05, with a median of -5.03 and a standard deviation of 8.11, suggesting that these connections had low pre-RF-TC excitability that became more pronounced after the intervention. The latency shift showed a mean DeltaLat of -0.46 ms, with a median of 0.0 ms, indicating a slight trend toward reduced latency but no major systematic shift. Interestingly, the duration of these newly emerged responses decreased significantly, with a mean DeltaDur of -15.03 ms, a median of -15.0 ms, and a standard deviation of 6.91 ms, suggesting that the newly recruited responses had shorter durations than pre-existing ones.

CCEPs That Were Never Significant

The CCEPs that were non-significant both before and after RF-TC exhibited the smallest amplitude, latency, and duration fluctuations. The mean DeltaZ was -0.02, with a median of -0.01 and a standard deviation of 2.07, reinforcing the stability of these connections. The mean DeltaLat was 0.14 ms, with a standard deviation of 12.71 ms, suggesting that these

responses were largely unaffected by the intervention. Similarly, the duration of these responses remained mostly unchanged, with a mean DeltaDur of 0.05 ms, a median of 0.0 ms, and a standard deviation of 4.08 ms, indicating that these connections remained functionally dormant throughout the experiment.

Predicting CCEP Class Based on Pre- and Post-RF-TC Amplitude

To assess whether the pre- and post-RF-TC amplitude (Zpre and Zpost) could predict the classification of CCEPs following RF-TC, we trained separate Random Forest classifiers using Zpre and Zpost as independent predictors.

The model using Zpre as the sole predictor achieved an overall accuracy of 76.5%, suggesting that pre-RF-TC amplitude alone provides a reasonable, though incomplete, basis for distinguishing between CCEP response classes. The model performed well in identifying CCEPs that remained non-significant, with a precision of 0.89 and recall of 0.89, indicating that lower pre-RF-TC amplitudes strongly predict non-responsiveness. It also showed moderate performance in classifying CCEPs that remained significant, with a precision of 0.65 and recall of 0.63, suggesting that higher Zpre values contribute to maintaining significant responses. However, the classification of CCEPs that lost or gained significance was less reliable, with lower precision and recall scores, indicating that additional factors influence these transitions.

When using Zpost as the predictor, the model achieved a slightly lower overall accuracy of 74.7%. The classification of CCEPs that remained significant was similar to the Zpre-based model (precision: 0.62, recall: 0.65), and CCEPs that remained non-significant were still identified with high accuracy (precision: 0.89, recall: 0.88). Interestingly, the classification of CCEPs that gained significance improved (precision: 0.33, recall: 0.33), suggesting that post-RF-TC amplitude is a stronger indicator of newly emerging significant responses. However, the model still struggled to classify CCEPs that lost significance (precision: 0.10, recall: 0.10), highlighting the complexity of changes induced by RF-TC.

These results suggest that Zpre is more effective at predicting stable and non-responsive CCEPs, whereas Zpost provides additional insights into newly emerging responses. However, both models demonstrate the need for additional parameters, such as latency and duration, to

improve classification performance and better capture the full spectrum of CCEP modifications following RF-TC.

Class	Precision	Recall	F1-score	Support
Remained Significant	0.65	0.63	0.64	490
Lost Significance	0.38	0.4	0.39	313
Gained Significance	0.11	0.11	0.11	258
Never Significant	0.89	0.89	0.89	2729
Overall Accuracy	0.765	-	-	3790

Class	Precision	Recall	F1-score	Support
Remained Significant	0.62	0.65	0.64	490
Lost Significance	0.1	0.1	0.1	313
Gained Significance	0.33	0.33	0.33	258
Never Significant	0.89	0.88	0.88	2729
Overall Accuracy	0.747	-	-	3790

Table 2. Classification performance of a Random Forest model using Zpre (left) and Zpost (right) as the sole predictors.

Localization of the most prominent effects of RF-TC on CCEPs

The only missing part of this large within-subject comparison of CCEP parameters before and after RF-TC remains the localization of the connections mostly impacted by the thermocoagulation. The issue is particularly challenging, given that we have to deal with three different spatial localizations: the RF-TC site, the stimulated electrode and the recording one. Adding to the picture the sparsity of the implantation typical of the SEEG patients, the composition of a typical 3D neuroimaging set requires very large samples.

To mitigate this critical point, here we narrowed the analysis to the patients receiving the first RF-TC in the central operculo-insular region, typically explored by electrodes R and S, and computed the matrix reporting the number of occurrences between stimulated and recorded electrodes in the Lost (Table 3) and Gained (Table 4) Significance classes.

Stimulted Electrde	Recording Electrode																									
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	W	X	Y	Z	Tot
A	3	2	1	0	0	0	1	1	0	0	1	3	1	3	0	0	0	3	2	0	1	1	1	0	3	27
C	0	0	0	0	0	0	0	0	0	2	5	0	0	0	4	0	0	0	0	0	0	0	1	0	3	15
D	0	0	0	1	2	0	2	0	0	0	0	2	1	2	0	0	8	2	1	0	3	3	3	6	3	39
E	0	1	5	7	3	0	2	5	2	3	1	18	4	0	2	3	4	8	8	1	4	7	25	4	5	122
F	0	1	0	0	0	2	1	4	2	1	0	3	3	0	0	1	2	3	0	0	1	0	2	0	0	26
G	0	0	2	1	2	0	0	0	0	0	0	0	0	0	1	0	0	1	0	2	0	1	2	0	0	12
H	3	0	0	0	0	1	6	3	0	2	6	1	3	1	8	4	1	3	2	1	4	0	8	0	6	63
I	1	1	2	0	0	1	0	1	7	10	0	0	0	9	1	7	0	1	3	0	6	0	9	9	2	70
J	0	0	4	0	0	0	2	0	0	2	4	0	0	1	6	0	0	2	0	0	0	0	7	0	1	29
K	0	0	1	0	0	0	5	1	0	2	6	0	0	1	3	0	2	2	1	0	0	0	5	0	4	33
L	0	1	2	0	3	1	3	5	2	0	0	0	5	1	3	0	4	2	5	2	2	2	8	4	3	58
M	5	3	4	0	0	5	3	1	0	9	5	1	5	4	1	0	0	4	1	0	0	1	4	2	3	61
N	0	1	5	0	2	0	2	5	0	6	5	2	2	12	2	2	0	8	5	1	0	3	8	4	2	77
O	1	4	0	1	0	0	3	2	5	1	2	0	2	1	7	0	0	3	5	1	3	0	15	3	2	61
P	3	1	1	0	2	6	0	3	5	1	2	3	4	7	2	6	1	3	1	0	2	3	5	4	0	65
Q	1	2	1	5	2	2	3	6	0	5	1	5	7	2	4	3	2	6	10	6	1	15	12	0	10	111
R	1	6	1	0	6	0	5	12	2	11	6	9	11	23	6	5	4	4	14	10	13	11	35	6	16	217
S	4	2	2	0	7	2	2	6	1	1	5	6	2	9	0	1	6	12	6	5	7	6	21	7	9	129
T	0	1	0	0	1	1	1	2	3	1	0	1	1	6	2	1	0	4	4	0	8	3	0	2	3	45
U	1	3	0	0	0	0	0	1	1	0	0	1	1	8	0	0	1	2	2	4	6	8	6	1	0	46
W	1	0	0	0	0	1	4	1	0	2	0	4	4	2	2	1	5	6	8	1	5	6	6	0	4	63
X	0	2	0	0	1	4	3	2	4	1	1	1	2	2	4	2	4	10	2	8	9	6	1	2	5	76
Y	2	3	2	1	2	8	9	7	2	1	1	4	3	11	5	2	3	10	4	1	2	1	8	7	5	104
Z	0	0	2	0	0	0	1	1	0	3	0	1	0	1	1	0	0	0	1	0	0	0	0	0	3	14
Tot	26	34	35	16	33	34	58	69	36	64	51	65	61	106	64	38	47	99	85	43	77	77	192	61	92	1563

Table 3. Matrix of occurrences of Lost Significance CCEPs between stimulated (rows) and recording (columns) electrodes. Red numbers refer to the stimulations of electrodes exploring centro-parietal operculum. Green scale coloring reflects the richness of the occurrences counts, with darker green cells indicating the most frequent coupling.

It is not surprising that many Lost Significance connections (346, i.e. >20%) are found in CCEPs driven by the stimulation close to the coagulated territory. However, it can be noted that also the connectivity from electrodes E, Q, and Y is considerably disrupted, each contributing with more than 100 CCEPs losing significance upon RF-TC.

Stimulted Electrde \ Recording Electrode	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	W	X	Y	Z	Tot
A	0	0	1	0	0	0	2	1	0	0	1	2	0	2	1	0	0	1	0	0	1	0	2	0	1	15
C	0	0	1	0	0	0	0	0	0	3	1	0	0	1	1	1	0	0	0	0	0	0	3	0	1	12
D	7	1	3	0	2	2	0	2	7	6	1	0	3	3	0	2	0	0	0	0	3	2	0	0	0	44
E	0	2	2	1	4	2	5	0	2	1	0	3	0	2	2	0	0	4	1	2	2	0	8	4	6	53
F	0	0	0	2	0	0	0	1	3	0	4	0	4	8	0	0	3	1	2	1	0	0	2	3	1	35
G	1	0	2	2	1	3	1	0	1	0	1	1	0	0	2	0	2	0	1	3	0	0	3	3	0	27
H	2	3	2	0	0	3	7	3	0	4	1	6	4	3	9	4	0	5	3	2	0	2	4	3	8	78
I	2	10	4	1	2	0	4	1	1	4	0	9	4	8	1	1	2	3	2	2	6	12	3	0	3	85
J	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0	3	0	1	8
K	1	0	4	0	0	0	1	1	0	6	3	0	0	0	0	2	0	2	0	0	0	0	5	0	2	27
L	0	2	0	0	3	2	1	2	1	3	0	3	3	1	5	2	2	3	3	3	1	6	2	1	4	53
M	0	0	0	0	0	4	1	0	0	3	2	0	2	1	2	0	0	2	7	1	1	2	3	0	5	36
N	0	0	4	1	0	0	2	2	0	4	5	0	1	3	3	1	0	5	2	3	3	4	7	3	0	53
O	1	2	0	0	2	2	1	0	0	2	1	1	0	1	5	0	0	2	2	4	2	1	5	1	0	35
P	2	3	3	3	0	4	14	10	2	0	0	10	2	7	13	2	1	7	4	5	6	6	8	2	15	129
Q	0	1	3	0	3	0	1	3	1	2	1	1	2	4	0	2	2	3	5	2	4	6	7	3	3	59
R	7	7	0	0	5	2	7	8	3	5	5	8	1	11	3	2	2	8	6	10	9	4	18	4	12	147
S	2	1	0	0	0	1	0	3	4	6	1	5	3	5	0	5	3	5	4	4	11	6	17	1	9	96
T	0	0	0	0	0	1	0	1	0	0	0	0	0	5	1	2	2	8	8	2	2	0	1	0	0	33
U	0	1	0	2	1	0	0	0	4	0	0	3	0	9	0	2	2	2	4	4	0	7	4	1	1	47
W	2	4	6	0	0	1	0	6	0	3	0	2	1	0	2	0	1	1	5	0	1	0	1	3	0	39
X	0	4	0	0	3	4	2	4	4	6	1	0	0	3	2	0	3	6	1	2	3	1	6	1	5	61
Y	3	1	1	3	1	2	5	6	5	7	4	3	3	8	2	0	2	3	8	3	12	9	14	1	8	114
Z	0	0	1	0	0	0	1	0	0	0	1	2	0	0	1	0	0	0	0	0	0	0	0	0	0	6
Tot	30	42	38	15	27	33	55	54	38	65	34	59	33	85	57	28	27	71	68	53	67	68	126	34	85	1292

Table 4. Matrix of occurrences of Gained Significance CCEPs between stimulated (rows) and recording (columns) electrodes. Red numbers refer to the stimulations of electrodes exploring centro-parietal operculum. Green scale coloring reflects the richness of the occurrences counts, with darker green cells indicating the most frequent coupling.

Examining the matrix relative to the Gained Significance, it immediately emerges that R and S electrodes also generate, when stimulated, gained significance CCEPs. While this finding might seem counterintuitive, it can be easily evinced that the disruption of part of the centro-parietal operculum enhances the capacity of surrounding territories (still covered by the same electrodes) to recruit connections towards other centers.

At the same time, it is extremely intriguing that electrodes like P and Y, typically entering the inferior parietal cortices and the reaching mesial parietal regions, increase their connectivity towards other areas like the anterior cingulate and prefrontal regions (electrodes G and H). In summary, the comparison of the electrodes involved in Lost and Gained Significance CCEPs shows some overlap mainly attributable to the bioelectrical effects of the RF-TC, and also some divergencies capable of revealing the modulatory role that the

coagulated site (in this case the centro-parietal operculum) plays on the connectivity between distant regions.

Discussion

Our study documents significant changes in effective connectivity following SEEG-guided thermocoagulation, recorded in the subacute phase. Importantly, these changes were observed before the onset of long-term neural plasticity, which typically requires more time to develop.[Sophie SU et al., 2016] This allows us to exclude potential confounding effects related to plasticity and focus on the immediate impacts of the procedure. The innovative nature of this work lies in its examination of effective connectivity following thermocoagulation in a single cortical region, specifically the central-opercular region and/or the insula. To our knowledge, this is the first study to assess effective, rather than functional, connectivity changes in such a targeted manner.

Our study, while focusing on a single cortical region, yielded results that are comparable to those of Simula et al., who examined the effects of multiple thermocoagulations.[Simula et al., 2023] While their work explored changes in functional connectivity, it lacked insights into the directionality of network interactions and had a more clinical focus, aiming to explain why some patients respond better to thermocoagulation than others. The observed reductions also in epileptogenic markers, such as high-frequency oscillations (HFOs) and spikes, further support the therapeutic efficacy of SEEG-guided thermocoagulation.[Contento et al., 2021]

In contrast, our approach provides a more detailed understanding of direct and directional influences within cortical networks, offering novel insights into how cortical networks are altered by focal thermocoagulation.

A more comprehensive neurophysiological understanding of the impact of SEEG-guided RF-TC on effective connectivity in the subacute phase could be achieved by analyzing it through the framework of disconnection syndromes. Disconnection syndromes, as conceptualized by Geschwind and earlier pioneers such as Wernicke, emphasize how lesions in white matter tracts disrupt communication between different brain regions, leading to

functional impairments that extend beyond the localized site of injury. Thermocoagulation, by creating focal lesions in specific cortical areas, mirrors the mechanism underlying disconnection syndromes. Catani and ffytche's review discuss how modern neuroimaging techniques, such as diffusion tensor imaging (DTI), have revitalized the study of disconnection syndromes by allowing the direct observation of white matter tract disruption in vivo.[Catani and ffytche, 2005] This approach supports the idea that tract disconnection can lead to both hypo- and hyperconnectivity within brain networks, phenomena that could be analogously applied to our findings. Increases in effective connectivity observed post-thermocoagulation may reflect a form of compensatory hyperconnectivity, where the brain attempts to restore functionality by enhancing connections in undamaged regions, thereby re-establishing network coherence.

Furthermore, the distinction between topological and hodological mechanisms of dysfunction provides a more nuanced interpretation of our results:

- Topological dysfunction refers to abnormalities in cortical areas themselves, which can be caused by lesions directly affecting cortical regions (as in thermocoagulation) or by cortical hyperactivity (such as in seizure activity). In topological dysfunction, the cortex is the primary site of pathology, leading to changes in local network activity. This can result in either deficits (due to the loss of function in specialized cortical regions) or hyperfunction (such as increased excitability in seizure-prone areas). For example, lesions from thermocoagulation may reduce local excitability in epileptogenic zones, disrupting their ability to generate seizures but also potentially reducing their contribution to broader network activity.

- Hodological dysfunction, on the other hand, refers to disruptions in the white matter tracts that connect different cortical regions. When these pathways are damaged or disconnected, as can occur after focal lesions like those created by thermocoagulation, the communication between distant cortical areas is impaired. This leads to what is termed disconnection syndrome, where even though the cortical areas themselves may be intact, their ability to interact effectively with other regions is compromised. Hodological dysfunction can lead to functional deficits that extend beyond the immediate area of the lesion, causing network-wide disturbances in brain function. Additionally, hodological dysfunction is not limited to disconnections but can also

manifest as hyperconnectivity if certain pathways become overly active due to compensatory mechanisms.

In our study, the cortical lesions induced by SEEG-guided thermocoagulation primarily result in hodological disruptions, meaning that they disrupt the white matter connections between cortical areas. These disruptions, however, have widespread consequences, influencing both topological and hodological pathways. The cortical areas directly affected by thermocoagulation exhibit reduced activity (a form of topological dysfunction), while distant regions may show altered connectivity (due to hodological disconnections) or compensatory increases in activity, possibly reflecting attempts by the brain to reorganize its networks to maintain functional integrity.

This distinction is crucial for understanding the mixed patterns of disconnection and reorganization observed in our results. While thermocoagulation creates focal disconnections, the brain's compensatory mechanisms may lead to increased effective connectivity in undamaged regions, as the brain seeks to re-establish functional network interactions through alternative pathways.

Applying the classical and modern disconnection frameworks to our study allows us to better contextualize the functional and effective connectivity alterations following SEEG-guided thermocoagulation. It supports the hypothesis that network disconnection is a driving factor behind the observed changes in connectivity, including both reduced effective connectivity in some areas and increased compensatory connectivity in others, thus offering a deeper understanding also of the therapeutic mechanisms at play.

Although still under more in-depth analysis, the initial results from the anatomical localization of response changes reveal that stimulations in the peri-lesional cerebral cortex (especially from electrodes R and S) exhibit the most pronounced modifications, both in positive (gained significance) and negative (lost significance) directions. This observation provides further support for the previously described hypothesis regarding the network-wide impact of focal cortical lesions. Even more intriguingly, certain compensatory changes—potentially indicative of adaptive mechanisms—were observed in cortical regions not directly or functionally associated with the damaged area (for instance, from electrodes P and Y, exploring parietal lobe, projecting toward anterior cingulate and prefrontal regions). These

findings suggest that the effects of RF-TC extend beyond local disruptions, influencing broader network dynamics and reinforcing the notion of a complex interplay between local lesions and large-scale reorganization of connectivity.

Over a longer time-span, our results could also enhance the understanding of the physiological mechanisms of diaschisis[Russo et al., 2021] in humans by providing insights into how remote regions may exhibit changes in excitability or connectivity following the induction of a local lesion.

One key aspect of diaschisis that could be relevant to our findings is the connectional diaschisis, which refers to changes in the strength and directionality of distant connections within a defined network. This aligns with our observation of disrupted and reorganized effective connectivity following thermocoagulation, particularly when considering new cortico-cortical evoked potentials (CCEPs) that may arise as a result of altered network dynamics.

Moreover, the concept of connectomal diaschisis—where lesions induce widespread alterations in brain network organization—might explain some of the compensatory connectivity increases observed in our study. These changes are indicative of the brain's attempt to re-establish network functionality through alternative pathways or reorganized subgraphs. This phenomenon may also provide a mechanistic explanation for the variability in patient outcomes, as individual differences in network reorganization could influence therapeutic efficacy.

Conclusion

In conclusion, our findings provide novel insights into the immediate impacts of SEEG-guided thermocoagulation on effective connectivity, highlighting both the focal and network-wide consequences of the procedure. The application of disconnection and diaschisis frameworks has allowed us to better understand the intricate dynamics of cortical and subcortical reorganization following focal interventions. Our work also underscores the importance of studying not only the localized effects of thermocoagulation but also the broader network responses that may contribute to understanding of clinical response. Future studies

should further explore the temporal evolution of these connectivity changes to better understand the relationship between early network reconfiguration and long-term seizure outcomes.

Chapter six: Conclusions and Future Directions

The thesis reported here could represent an important step in the exploration of how focal cortical lesions, such as those induced by SEEG-guided RF-TC, might modulate brain connectivity. By systematically analyzing cortico-cortical evoked potentials (CCEPs) - and eventually also the responses evoked by peripheral simulations - before and after RF-TC, this work offers new insights into how effective and functional connectivity in the human brain can be altered by targeted cortical disruptions. Although the focus has been primarily on the operculo-insular region, the implications of this research could extend far beyond this single area, influencing various fields within neuroscience and clinical practice.

Preliminary Insights into Brain Connectivity Dynamics

The results from this study suggest that localized cortical disruptions could have a dynamic impact on effective connectivity, both locally and across broader networks. By focusing on the N1 component of CCEPs, which reflects the direct axonal pathways between regions, this research has provided a precise window into how the brain's immediate response to focal lesions unfolds. The changes observed, including both decreases and unexpected increases in connectivity, suggest the possibility of a connectivity reserve—latent pathways that could be activated or unmasked when primary connections are disrupted.

This finding, while preliminary, opens up new avenues for exploring the brain's intrinsic capacity for adaptation and reorganization, challenging the traditional view of lesion-induced connectivity loss. The strengthening of connections observed in some cases might indicate that the brain actively reorganizes its networks in response to localized damage, which could have far-reaching implications for understanding plasticity mechanisms.

Expanding the Potential Scope of RF-TC Applications

Although this study has focused on the operculo-insular cortex, it is essential to recognize that the methodology developed here is highly adaptable. SEEG-guided RF-TC could be applied to virtually any cortical region, offering a versatile platform for studying effective connectivity across the brain. Exploring how different cortical regions respond to

focal disruptions could provide a more comprehensive understanding of network dynamics in both healthy and diseased brains. This approach could also help elucidate the functional roles of less-studied areas of the brain, potentially uncovering new therapeutic targets for patients with drug-resistant focal epilepsy.

The Untapped Complexity of N2 component and Beyond

Thus far, the analysis has centered on the N1 component, which reflects early, direct connectivity. However, the N2 component, which involves later network interactions, represents an even more complex and intriguing dimension of connectivity. As future studies begin to investigate the N2 component, the full scope of how brain networks adapt to focal cortical disruptions will likely become clearer. This may provide deeper insights into the long-range effects of RF-TC and how these changes influence both local and distant networks over time.

Implications for Epilepsy Surgery and Stroke Rehabilitation

The clinical applications of this work are particularly promising in the field of epilepsy surgery. Understanding how RF-TC affects connectivity in real-time could inform surgical decision-making, allowing clinicians to predict the effects of disrupting specific networks more accurately. This could lead to more refined and targeted interventions for patients with drug-resistant epilepsy, potentially improving surgical outcomes by preserving critical networks while effectively treating the epileptogenic zone.

Additionally, these insights could have profound implications for stroke rehabilitation. The regions studied in this project, such as the operculo-insular cortex, are often affected by stroke. Understanding how the brain reorganizes after RF-TC could offer clues into how to stimulate plasticity and enhance recovery after stroke. The concept of a connectivity reserve suggests that, with the right interventions, the brain might activate alternative pathways to compensate for lost functions, leading to more effective rehabilitation strategies.

Technological and Methodological Contributions

The methods developed in this study represent an important contribution to neuroscience research methodology. By combining SEEG-guided RF-TC with real-time evoked potential analysis, this work has pioneered a novel approach for studying effective connectivity. The ability to introduce controlled, focal lesions and observe their immediate effects on network dynamics in human subjects could provide a powerful tool for both clinical applications and experimental models in basic neuroscience.

This technique could be adapted for studying other neurological conditions where network disruptions play a key role, such as neurodegenerative diseases or psychiatric disorders. Moreover, the ability to monitor network changes in real-time opens the door to personalized interventions, where surgical or therapeutic strategies are tailored to the patient's specific brain connectivity profile, potentially improving outcomes in a variety of clinical contexts.

Future Directions: A Broader Revolution in Neuroscience

While the findings of this study are preliminary, they lay the groundwork for future research that could transform the way we understand and treat neurological disorders. Extending the investigation to other cortical regions and larger networks could reveal how disrupting a single connection influences the broader brain. This is particularly relevant in the context of neuropsychiatric disorders, where network disconnections are thought to underlie complex symptoms. Understanding these dynamics could provide new avenues for therapeutic intervention, both surgically and pharmacologically.

Moreover, as the analysis of the N2 component progresses, future research could unlock a deeper understanding of how the brain's networks reorganize over time, offering new insights into long-term plasticity and functional recovery. This knowledge might also prove valuable in predictive modeling, helping clinicians anticipate which patients will benefit most from specific treatments, and facilitating more personalized medicine in both neurology and neurosurgery.

In conclusion, while this thesis has focused on a specific region and a preliminary analysis of the N1 component, its broader implications suggest that brain connectivity is far

more dynamic and adaptable than previously thought. This work not only advances our understanding of how focal cortical lesions affect effective connectivity but also opens the door to a new era of personalized neuroscience, where interventions are tailored to the unique connectivity profiles of individual patients. The insights gained here could help shape future research, leading to more effective treatments for epilepsy, stroke, and other neurological disorders, while deepening our understanding of the brain's remarkable capacity for adaptation and recovery.

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