



# Optimized stereoelectroencephalography-guided radiofrequency thermocoagulation in the treatment of patients with focal epilepsy

Di Wang<sup>1,2#</sup>, Penghu Wei<sup>3#</sup>, Yongzhi Shan<sup>3#</sup>, Liankun Ren<sup>1,2</sup>, Yuping Wang<sup>1,2</sup>, Guoguang Zhao<sup>3</sup>

<sup>1</sup>Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China; <sup>2</sup>The Beijing Key Laboratory of Neuromodulation, Beijing 100053, China; <sup>3</sup>Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

*Contributions:* (I) Conception and design: L Ren, Y Wang, G Zhao; (II) Administrative support: Y Wang, G Zhao; (III) Provision of study materials or patients: P Wei, Y Shan, G Zhao; (IV) Collection and assembly of data: D Wang, P Wei, Y Shan; (V) Data analysis and interpretation: D Wang, Y Shan, L Ren, G Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

*Correspondence to:* Liankun Ren; Yuping Wang; Guoguang Zhao. Xuanwu Hospital, Capital Medical University, Beijing 100053, China. Email: rlkbrain2000@yahoo.com; wangyuping@xwhosp.org; ggzhao@vip.sina.com.

**Abstract:** Epilepsy is a severe health disorder affecting people of all ages with high prevalence worldwide. The introduction of new antiepileptic drugs has yielded notable effects in recent decades, yet there are still approximately 30% of patients with seizures refractory to medical therapy. Open surgical resection is widely accepted as a highly effective approach for the treatment of drug-resistant focal epilepsy if the epileptogenic zone can be precisely delineated. However, concerns about the impact of open surgery on brain function have driven considerable interest in less invasive techniques. Clinically, stereoelectroencephalography (SEEG) offers a unique means of exploring the pathophysiologic process and accurately mapping the epileptogenic network in presurgical evaluations for patients with epilepsy because of insufficient information from other noninvasive investigations. Moreover, SEEG-guided radiofrequency thermocoagulation (SEEG-guided RF-TC), which ablates lesions directly through the recording electrodes according to electroclinical evidence, has emerged as a promising, minimally invasive modality with notable preservation of neurocognitive functions. This critical review summarizes the technical details of the parameters and the selection of patients for SEEG-guided RF-TC based on the literature as well as our experiences. With respect to the parameters, the power and duration of RF-TC are discussed. In particular, an optimized SEEG-guided RF-TC modality that integrates more contacts from multiple different electrodes to create a confluent lesioning field is proposed for a more curative effect in comparison to the current protocol of palliative treatment in which RF-TC selectively disrupts critical hubs in the epileptic network through contiguous contacts within the range of a single electrode. Currently, SEEG-guided RF-TC is indicated for a variety of small, deeply seeded and well-demarcated epileptogenic foci, such as deep heterotopic nodules and hypothalamic hamartoma. The efficacy of treating patients with focal cortical dysplasias in the eloquent cortex and with mesial temporal lobe epilepsy associated with hippocampal sclerosis needs to be further determined. Given the small number of patients reported, randomized controlled trials are necessary to compare the efficacy of SEEG-guided RF-TC with conventional methods in the future.

**Keywords:** Drug-resistant epilepsy; stereoelectroencephalography (SEEG), radiofrequency thermocoagulation (RF-TC)

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## Introduction

Epilepsy is a severe health disorder affecting people of all ages with high prevalence worldwide. The introduction of new antiepileptic drugs has yielded notable effects in recent decades, yet there are still approximately 30% of patients with drug-resistant epilepsy (1). Currently, epilepsy surgery is widely accepted as a highly effective treatment for drug-resistant epilepsy. The last 20 years have witnessed a remarkable increase in the number of patients who have undergone surgery for drug-resistant epilepsy.

Classically, open surgical resection of the epileptogenic zone is the preferred procedure, with high rates of seizure-free outcomes. However, concerns about the impact of open surgery on brain function have driven considerable interest in less invasive techniques as an alternative to open surgery. Less-invasive treatment strategies, including laser interstitial thermotherapy, stereotactic radiosurgery, and high-intensity focal ultrasound, have been investigated over the years in an effort to reduce the risk of neurological and neuropsychological impairment by sparing functional tissue (2,3). These minimally invasive interventions also lead to less suffering, shorter hospitalization, better preservation of cerebral function, and reduced surgical complications (4,5).

Clinically, invasive EEG is indicated for approximately 30% of patients suffering from drug-resistant focal seizures in presurgical evaluation because of insufficient information from noninvasive investigation. Stereoelectroencephalography (SEEG), which was conceived by Bancaud and Talairach in the 1960s, offers a unique means of exploring the pathophysiologic process and accurately mapping the epileptogenic network through the analysis of the anatomo-electroclinical correlations. SEEG-guided radiofrequency thermocoagulation (SEEG-guided RF-TC) has been reported since a 2004 feasibility study, initially intended to alleviate seizures (6). This technique allows ablation of the epileptogenic foci directly through the recording electrodes with electroclinical evidence. Due to its ability to achieve relatively well-circumscribed lesions and perform stimulation and recording at the same time as well as real-time monitoring of the impedance, the number of studies reporting SEEG-guided RF-TC for drug-resistant focal epilepsy has considerably increased in recent years (7-16). Overall, the basic principle of SEEG-guided RF-TC involves selectively destroying epileptogenic foci or critical nodes in epileptogenic networks, which can be considered a palliative approach. In addition, the curative effect of this procedure has been proposed in patients

with epilepsy related to gray matter nodular heterotopy (9,12,17). Currently, the seizure outcome varies widely across studies, and the factors associated with efficacy remain elusive. Herein, we attempt to address the technical details and the selection of patients for this procedure based on the literature as well as our experiences to shed light on optimized SEEG-guided RF-TC in the treatment of patients with focal epilepsy.

## Optimization of SEEG-guided RF-TC parameters to ablate seizure onset zone

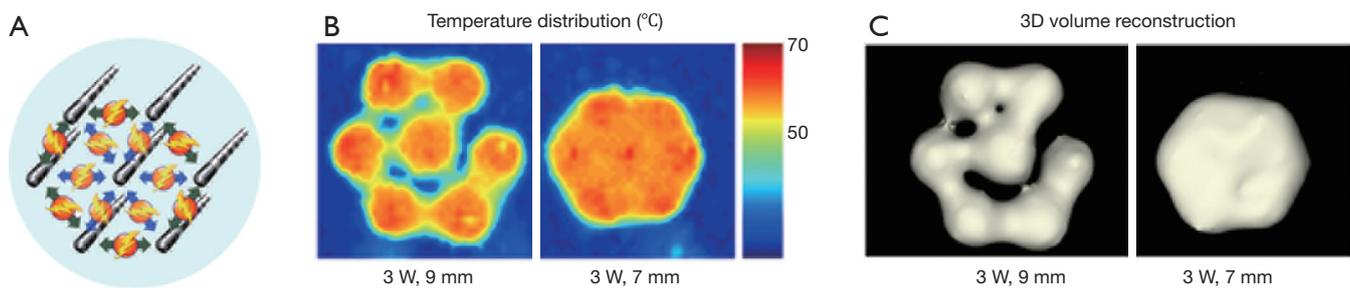
The primary purpose of SEEG-guided RF-TC is to disrupt the epileptogenic network based on the SEEG findings, thereby reducing the seizure burden or achieving seizure-free status. The identification of seizure-onset and early propagation areas are fundamental to the treatment. Importantly, various protocols and RF-TC parameters have been tested across epilepsy centers to date.

High power levels of 6–8.32 W have been typically adopted in European epilepsy centers. With these power levels that could result in impedance collapse, it was believed that the range of RF-TC could be largest at maximum power, and the resulting lesions were reported to be 5–7 mm in diameter (6). In addition to power, attention was paid to lengthening the total duration of coagulation in the report by Bourdillon *et al.*, in which increasing the voltage of the delivered current until these parameters spontaneously collapsed provided larger lesions than using fixed parameters (11). Regarding the constitution of the dipole field, coagulation should be performed via a pair of consecutive contacts within a single electrode according to French guidelines (18). Of note, Staudt *et al.* attempted to use different power levels in egg albumen and found that when 3 W was delivered, the lesioning size could be increased by increasing the effective duration of the power delivery. They also showed that the lesioning field obviously increased through a pair of contacts from different electrodes in a parallel arrangement (19).

Among these observations, earlier protocols from European centers have been widely adopted in clinical usage. The seizure outcomes of reported clinical cases are summarized as follows.

### *Lyon's protocol*

In 2004, SEEG-guided RF-TC was first reported in 20



**Figure 1** Optimization of parameters for extended thermocoagulative lesion in polyacrylamide gel. (A) Schematic map of the electrodes array. (B) It showed the thermocoagulative effect of the inter-contacts distances at 7 and 9 mm respectively by temperature distribution. Of note, the dispersed lesioning fields at 9 mm are growing into a single confluent piece at 7 mm. (C) Thermocoagulative lesions of different distances were reconstructed in 3D space.

patients with focal epilepsy in a study by Guenot *et al.* (6). in Lyon's group. In their preliminary study, coagulations were created between two contiguous contacts by delivering 6 W within 40–50 s and thereby acquiring an estimated temperature of 78–82 °C. With these parameters, lesions of 5 to 7 mm in diameter could be reliably produced. No permanent neurologic or cognitive impairment was observed in their series, and 15% of the patients were seizure-free, while 40% experienced a seizure frequency reduction of at least 80%. Seven years later, with the same parameters and technical details, Guenot *et al.* reported their experiences among 41 patients, showing 48.7% of them with at least 50% seizure frequency reduction (8). Up to 162 patients were enrolled over ten years after the initiation of their protocol, and 7% of patients were seizure-free (14). Of note, the same technical protocol was employed in 14 patients with malformation of cortical development (MCD) at another center, and 64% of the patients obtained more than 50% seizure reduction, of whom 43% patients were seizure-free at an average follow-up of 41.7 months (10).

### *Milano's protocol*

In a study focused on the SEEG-guided RF-TC of gray-matter nodular heterotopy by Cossu *et al.* in Milano's group, 8.32 W was delivered within 40–50 s to reach an estimated tissue temperature of 78–82 °C. In this study, five patients were enrolled, 4 of whom were seizure-free at an average follow-up of 33.5 months (9). In another series presented by Cossu *et al.*, 89 patients with epileptogenic zones were treated with the same parameters. Among them, 16 patients were seizure-free (16). For patients with periventricular nodular heterotopia (PNH), the same protocol was proven

to be efficacious in 76% of the patients (12).

### *The early experiences of RF-TC in Xuanwu Hospital*

Selective disruption of the epileptogenic network is effective if the network can be delineated based on the analysis of anatomico-electroclinical correlations. However, incomplete mapping of the circuit is inevitable. Alternatively, ablation of small, deeply seeded or well-demarcated epileptogenic foci can be speculated. Based on the experiences from the above epilepsy centers, we further examined ways to produce extended thermocoagulative lesions. Therefore, a targeted multielectrode RF-TC procedure was addressed experimentally in our center, which can be defined as optimized cross-bonding RF-TC (15,20).

*In vitro* experiments performed on egg albumen helped to confirm the feasibility of our optimized cross-bonding RF-TC. We also noticed that the volume and shape of cross-bonding RF-TC in egg albumen were not very stable or repeatable. Considering that the brain tissue is solid rather than liquid, experiments in a solid phantom were considered to be more appropriate for imitating the cerebral environment. Therefore, using a more uniform solid phantom of polyacrylamide gel and a more quantitative approach, we observed that an extended confluent volume of coagulation could be created and a temperature between 60–78 °C could be achieved by integrating more contacts from multiple different electrodes together and delivering 3 W for 150 s. Moreover, the effective distance between contacts was found to be approximately 7 mm (Figure 1). Of note, the working parameters of clinical RF-TC cannot be decided based on *In vitro* experiments because the brain is not isotropic and is composed of different tissues, such

as gray matter, white matter, vessels, CSF and lesions. It appeared that the suggested RF-TC power used in the human brain still should be reduced somehow compared with the polyacrylamide gel, or the impedance would be much more likely to collapse.

Regarding the protocol, stimulation of the suspected target to determine whether a habitual seizure could be provoked is also crucial for improving the seizure outcome, in line with the French guidelines (18). Additionally, we evaluated the function of all possible targets by bipolar electrical stimulation during a video-SEEG recording session before the ablation procedure, and a lesioning process without anesthesia was required if possible. We commonly heated the target to 42–43 °C by using a power of 2 W delivered for 30 s to observe whether neurological deficits would occur prior to the irreversible ablation. It is recommended to monitor SEEG activity after the coagulation process.

### Refinement in patient selection for SEEG-guided RF-TC

According to the French guidelines, SEEG-guided RF-TC has been suggested to be a therapeutic alternative when there is contraindication to surgical resection. In particular, deep heterotopic nodules and hypothalamic hamartoma (HH) are recommended to avoid the high risk of open surgery (17,21).

Moreover, SEEG-guided RF-TC might be optional for patients with other types of epilepsy, such as focal epilepsy due to focal cortical dysplasias in the eloquent cortex or mesial temporal lobe epilepsy.

#### *Deeply seeded epileptic lesions: hamartomas and NH*

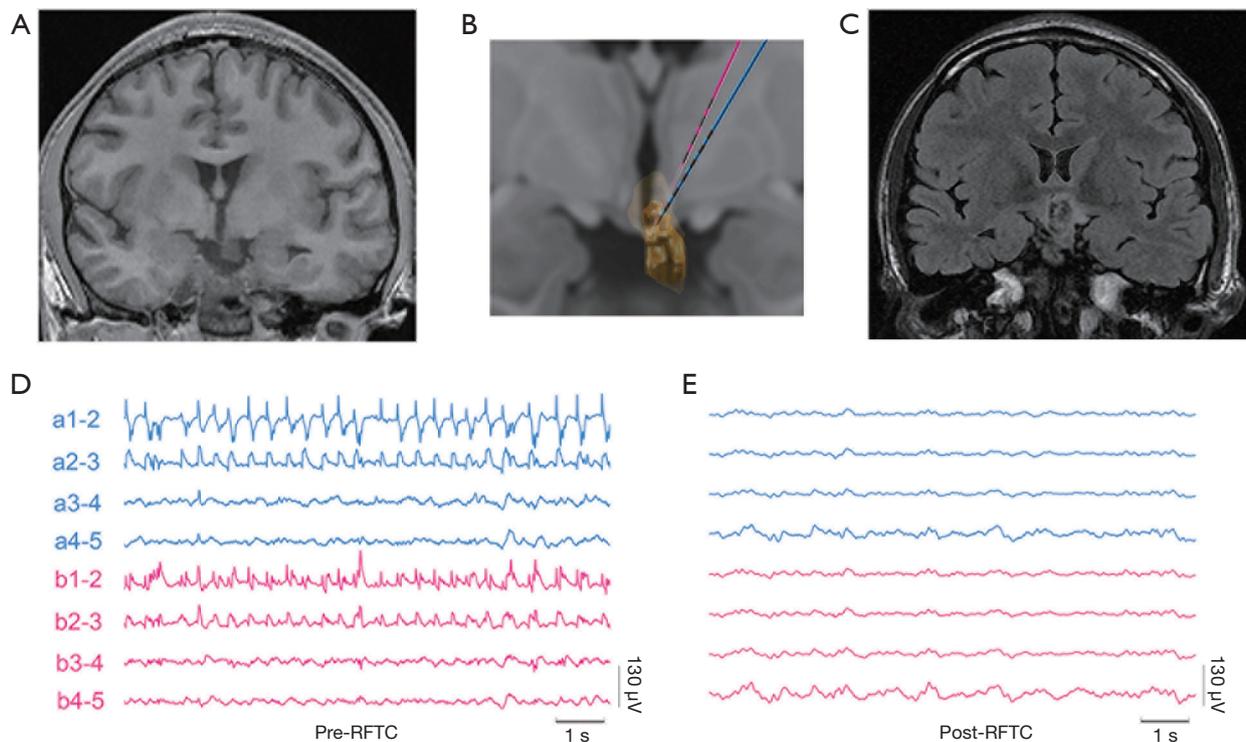
HH is a peculiar clinico-radiological syndrome with an incidence ranging from 1 in 100,000 to 1 in 1,000,000 (22). HH is a congenital, ectopic mass lesion typically arising from the tuber cinereum, which can be small, large, pedunculated, or sessile (23). HH is associated with a range of neurological symptoms, neuropsychiatric comorbidities, and endocrine disorders, which are mainly influenced by neuroanatomical features of the lesion (24–27). In particular, epilepsy has been recognized as the hallmark clinical picture of HH characteristically presenting with quite stereotyped gelastic and dacrytic seizures as well as with combinations of other types of seizures (28–30). Epilepsy related to HH

is often drug-resistant, and studies defining the intrinsic epileptogenicity of HH in the 1990s confirmed the rationale of surgical treatment (30,31). Open surgery of HH could result in seizure-free status in approximately 50% of cases, yet some patients suffered from short-term memory disturbances and deep-seated ischemic injuries after the craniotomy (32–34). Apart from these complications, this surgical intervention has been typically associated with incomplete hamartoma resection (32–34). Given the risks, less invasive lesioning techniques for HH, including RF-TC, radiosurgery, and deep brain stimulation, have been proposed (15,35,36).

In the epilepsy center of our hospital, optimized cross-bonding RF-TC was performed on HH-associated drug-resistant epilepsy with high effectiveness and low complication rates (15). In brief, SEEG electrodes were implanted into the HH. The numbers of electrodes targeting the hamartoma ranging from 1 to 4 depending on the anatomic location and size of the HH. *Figure 2* illustrates an example patient with HH who underwent SEEG-guided RF-TC at our hospital. This 19-year-old man had daily drug-resistant gelastic seizures, sometimes followed by tonic-clonic seizures. MRI revealed a sessile HH. The SEEG study showed continuous interictal epileptiform discharges in the hamartoma before RF-TC. Spiking activity following the application of RF-TC to the HH contacts completely disappeared. Currently, the patient is seizure-free 16 months after the procedure.

NH is a congenital disorder of neuronal migration characterized by ectopic nodules of neurons frequently located along the walls of the lateral ventricles (PNH) or masses of gray matter within the deep white matter (subcortical heterotopia) (37). Seizures related to NH are usually drug-resistant, and it is difficult for surgery to achieve a radical effect due to the unclear role of the heterotopic lesion in the epileptogenic network (38–40). According to the experiences reported by Cossu *et al.*, SEEG-guided RF-TC is a curative first-line therapy in patients with epilepsy related to NH. Two-thirds of such patients achieved sustained seizure freedom after SEEG-guided RF-TC based on this report, so the implantation schedule of SEEG in this kind of case is now aimed at an intensive sampling of the epileptogenic network for effective thermocoagulation (17).

*Figure 3* illustrates an example patient with PNH in our hospital. To define the roles of the heterotopic and normotopic cortexes in the epileptogenic network in this



**Figure 2** Pre-RFTC, post-RFTC coronal MRI, and SEEG study in an example patient with HH. (A) Pre-RFTC T1-weighted MRI showing a pedunculated HH. (B) The color-coded reconstruction of depth electrodes into HH consistent with the colors of SEEG traces shown in *Figure 2D,E*. (C) post-RFTC coronal MRI obtained 4 days after RF-TC treatment. (D) Pre-RFTC SEEG activity showing continuous periodic interictal epileptiform discharges inside HH. (E) Post-RFTC SEEG activity showing no discharges.

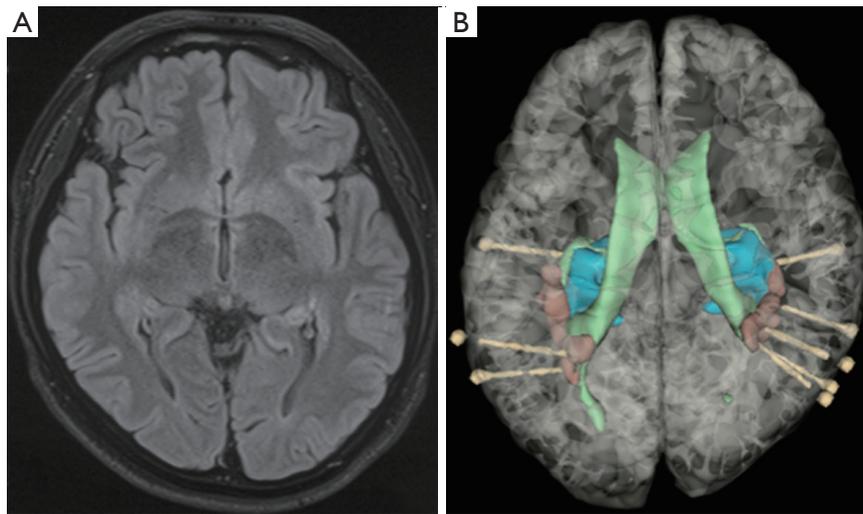
23-year-old man, implantation of depth electrodes was scheduled. Bilateral heterotopic lesions and right mesial temporal structures were involved in the epileptogenic network, which was confirmed by SEEG recordings. The patient was seizure-free 2 years after multitargeting thermocoagulation of the bilateral periventricular lesions and right mesial temporal structures.

#### *MTLE with unilateral hippocampal sclerosis*

MTLE with hippocampal sclerosis has been drawing considerable interest due to its high prevalence and being the most common indication for surgery in adults with drug-resistant epilepsy. Anterior-mesial temporal lobectomy by open resection or selective amygdalohippocampectomy is an effective treatment for drug-resistant MTLE-HS patients (41-43). Prospective, randomized trials demonstrate that seizure-free rates are significantly higher in surgically treated patients compared to those given the best medical therapy. Surgical resection,

however, entails risks for injury of normal brain tissue and accompanying neuropsychological deficits, especially cognitive impairments (44,45). A postoperative decline in episodic memory performance following ATL surgery has been observed in 25–50% of these patients (46). Thus, in recent years, various minimally invasive approaches have been explored for MTLE by maximizing seizure control and minimizing cognitive impairments. Among them, laser interstitial thermal therapy (LiTT) has been investigated with a relatively satisfactory outcome (2,5). However, LiTT is not universally available, and its indications, safety, and efficacy need further evaluation. SEEG-guided RF-TC for the treatment of MTLE with hippocampal sclerosis is attractive. Nevertheless, Lyon's group found that SEEG-guided RF-TC was not as effective as anterior temporal lobectomy (ATL) since none of the patients was seizure-free in the RF-TC group, in contrast to the seizure-free rate of 75.5% among the ALT group (13).

To optimize SEEG-guided RF-TC as a potential minimally invasive treatment option for MTLE, we



**Figure 3** Pre-RFTC axial MRI, and three-dimensional (3D) reconstructions of depth electrodes in an example patient with PNH. (A) Pre-RFTC T1-weighted MRI showing bilateral PNH; (B) reconstruction of electrodes are superimposed on bilateral PNH and hippocampus. Lateral ventricles, hippocampus, and PNH were indicated by green, blue, and brown color, respectively.

recently conducted SEEG-guided RF-TC with 3D cross-bonded electrode contacts to maximize RF-TC efficacy in patients with MTLE-HS. In brief, SEEG electrode implantation was designed to form a focal stereotaxic array to sample mesial temporal structures widely and guide the subsequent RF-TC. Instead of delivering RF-TC to a predetermined location in the sclerotic hippocampus via one electrode, a targeted multielectrode RF-TC procedure was conducted based on the identification of the ictal onset zone or zones by SEEG. Thus, the modified approach produced extended thermocoagulative lesions similar to a selective amygdalohippocampectomy involving the amygdalohippocampal complex, subiculum, and part of the entorhinal cortex (*Figure 4*). Our preliminary observations demonstrated a relatively favorable seizure outcome and no surgical complications in patients with unilateral HS (20).

#### *Focal cortical dysplasias in eloquent cortex*

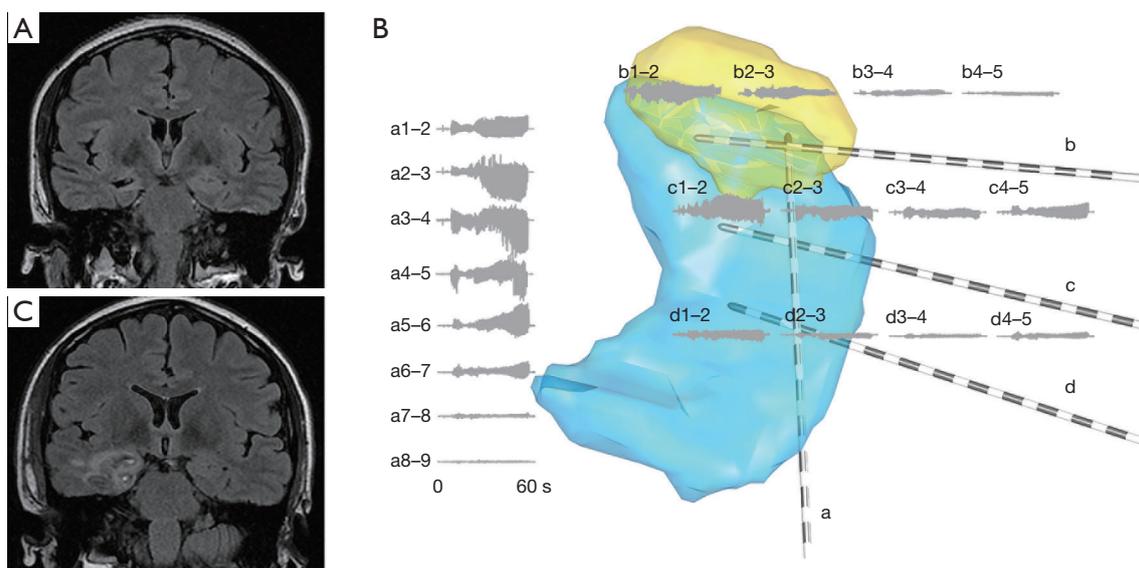
Patients with seizures originating primarily from the eloquent cortex pose a challenge because the removal of such epileptic tissue carries a high risk of specific and irreversible neurological functional deficits. In particular, permanent neurological deficits can occur following resection of primary functional areas, including the primary motor, sensory, visual cortex, Broca's area, and Wernicke's

area (47,48). Therefore, the exploration of alternative therapeutic methods for drug-resistant epilepsy patients with epileptogenic zones involving the eloquent cortex continues to be a topic of intensive study.

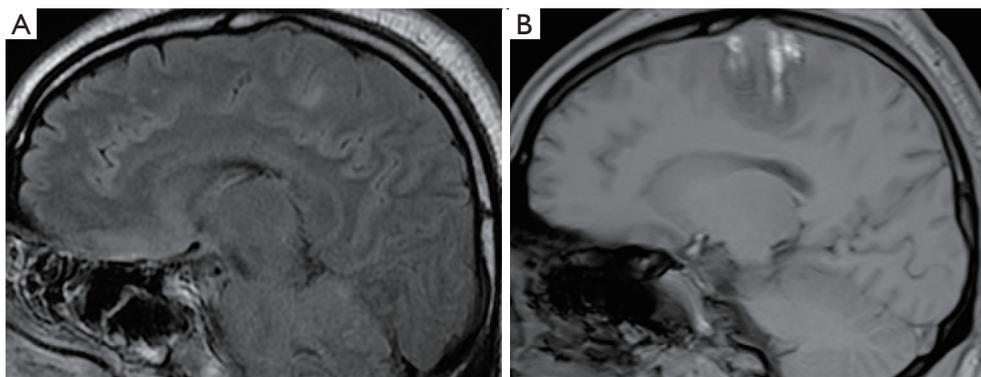
Confronted with this challenge, we performed SEEG-guided RF-TC in refractory focal epilepsy patients with clinically well-demarcated epileptic foci in the eloquent cortex. *Figure 5* illustrates one representative patient with a lesion located in the right paracentral lobule who was treated with SEEG-guided RF-TC. This 26-year-old man had daily refractory seizures manifesting as ictal tonic posturing of the left leg. A transient weakness of the left foot completely disappeared within a few weeks. The patient was seizure-free 2 years after the procedure.

#### **Conclusions**

Currently, SEEG-guided RF-TC is increasingly recognized as a treatment option for patients with focal drug-resistant seizures. Optimization of SEEG-guided RF-TC parameters and refinements in patient selection for SEEG-guided RF-TC are essential to attain favorable efficacy. Although accumulating evidence has shown that SEEG-guided RF-TC is a promising option for patients with refractory seizures, the indications for SEEG-guided RF-TC are still being investigated. More caution should be taken in the selection of patients who can benefit significantly from such



**Figure 4** Optimized SEEG-guided RF-TC for MTLE-HS. (A) Pre-RFTC coronal MRI showing hippocampal sclerosis on the right side. (B) Schematic protocol of the 3D cross-bonding electrodes and spatially distributed ictal discharges of one representative clinical seizure indicated by grey color. Reconstruction of the trajectories of the electrodes were superimposed on the amygdalohippocampal complex. Electrode an implanted was along the long axis of the amygdalohippocampal complex, reaching the amygdala. Three orthogonal electrodes b, c and d targeted amygdala, ventral head and anterior body of hippocampus respectively. (C) One-day post-RFTC coronal MRI showing the thermocoagulative lesion induced by RF-TC.



**Figure 5** Pre-RFTC and post-RFTC sagittal MRI in a representative patient with SOZ arising from eloquent cortex. (A) Sites of restricted lesion located in right paracentral lobule; (B) T1-weighted MRI obtained 1 day following RF-TC treatment.

a novel intervention. In particular, the application of SEEG-guided RF-TC in patients with uncertain epileptogenic foci is unreasonable.

Future investigations of SEEG-guided RF-TC are needed in some aspects. Since parameters and protocols among epilepsy centers worldwide vary, consensus is necessary to guide SEEG-guided RF-TC in clinical

practice. Technically, developing new devices for RF-TC that provide intraoperative control over lesion temperature and real-time lesion visualization would help produce ablated volumes as expected with better outcomes. Importantly, randomized controlled trials with long-term follow-up are needed to compare the efficacy of SEEG-guided RF-TC with conventional methods in the future.

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## Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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