

## Contralateral insular epileptogenic hub causing seizure relapse after opercular focal cortical dysplasia surgery and response to radiofrequency thermocoagulation: illustrative case

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**BACKGROUND** The reevaluation and management of seizure relapse following resective surgery in magnetic resonance imaging (MRI)-negative pharmaco-resistant epilepsy remains a significant challenge.

**OBSERVATIONS** A 25-year-old right-handed male with medically refractory epilepsy presented with nonlocalizing electroencephalography (EEG) and MRI. Stereo-EEG (SEEG) implantation based on semiology and positron emission tomography imaging revealed a left frontal opercular focus with rapid bilateral insular ictal synchrony. The initial epileptogenic zone was resected and pathologically proven to be type 2A focal cortical dysplasia (FCD). Seizure relapse after 9 months was eventually reinvestigated, and repeat SEEG revealed a secondary epileptogenic focus in the contralateral insula. A novel technique of volumetric stereotactic radiofrequency ablation (vRFA) was utilized for the right insular focus, following which, the patient remains seizure-free for 20 months. He suffered a transient bilateral opercular syndrome following the second intervention that eventually resolved.

**LESSONS** The authors present clinical evidence to suggest epileptogenic nodes distant from the primary focus as a mechanism for seizure relapse following FCD surgery and the importance of bilateral insular SEEG coverage. The authors also describe a novel technique of minimally invasive vRFA that allows ablation of a larger volume of cerebral cortex when compared to conventional bedside SEEG electrode thermocoagulation.

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**KEYWORDS** epilepsy surgery; radiofrequency thermocoagulation; bilateral opercular syndrome; focal cortical dysplasia; insulopercular seizures; seizure relapse

We report a patient with a left frontal opercular type 2 focal cortical dysplasia (FCD) studied initially with bilateral stereoelectroencephalography (SEEG) who developed a seizure relapse in the first year after surgical removal of the FCD. On review of the initial SEEG, there was evidence of bilateral insular epileptogenicity, which was reconfirmed on further extensive SEEG upon relapse. This supports the existence of an independent epileptogenicity distant from a primary focus as a mechanism for seizure relapse after FCD surgery. We describe the use of a novel technique of minimally invasive robotic-assisted stereotactic radiofrequency ablation (RFA) of the contralateral epileptogenic focus responsible for seizure relapse.

### Illustrative Case

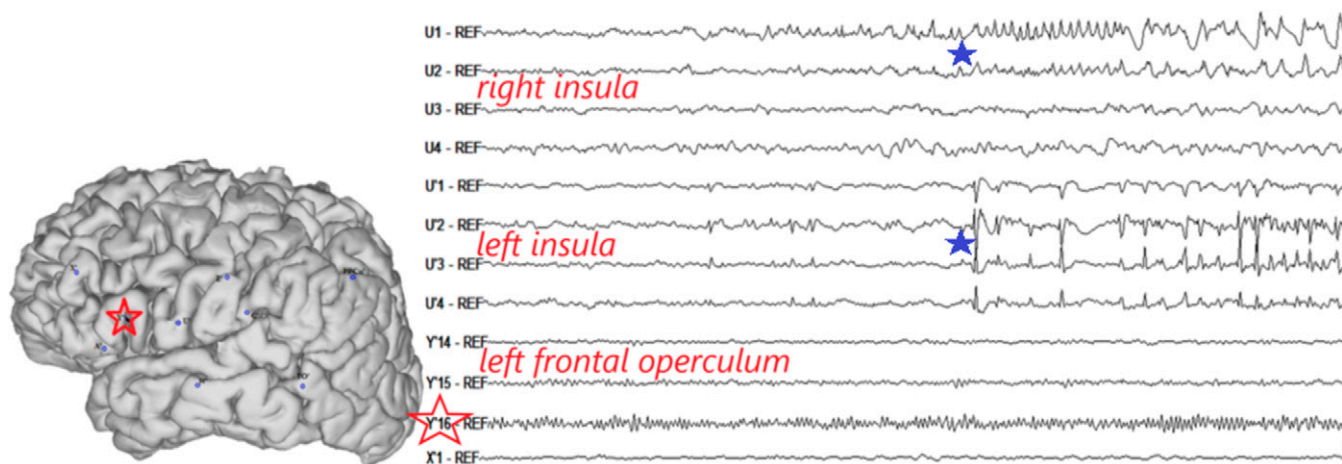
A 25-year-old right-handed male with normal birth and developmental history began experiencing seizures from the age of 19 years. He had one or two events per month characterized by an aura of tinnitus followed by motor manifestations or generalization. He was on three anticonvulsants and neurologically normal. A prolonged scalp electroencephalography (EEG) (56 hours) revealed no interictal discharges, and four electroclinical events were recorded with no convincing lateralization. The semiology included an aura of tinnitus; an unusual form of stereotyped, prolonged inverted ictal pouting; followed by distal limb automatisms; asymmetrical tonic posturing with right upper limb in extension; and finally followed by a postictal

**ABBREVIATIONS** EEG = electroencephalography; FCD = focal cortical dysplasia; FCMS = Foix–Chavany–Marie syndrome; MRI = magnetic resonance imaging; RFA = radiofrequency ablation; SEEG = stereoelectroencephalography; vRFA = volumetric stereotactic radiofrequency ablation.

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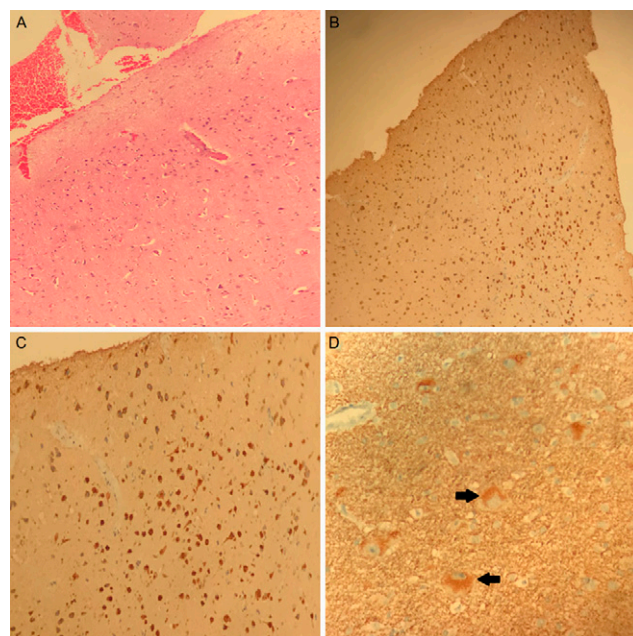
**FIG. 1.** Low-voltage fast activity in the left frontal opercular electrode (red stars) with immediate synchronization of both ipsilateral and contralateral posterior insula (blue stars).

aphasia of several minutes. A high-resolution 3T-magnetic resonance imaging (MRI) scan of the brain was apparently normal, and an 18F-fluorodeoxyglucose positron emission tomography scan showed left frontal opercular hypometabolism. A language functional MRI showed blood oxygen level-dependent activation predominantly in Brodmann area 6, with minimal language task activation in the opercular region. Magnetoencephalography revealed scattered left temporal and right parietal dipoles. Robotic-assisted (Rosa, Zimmer Biomet) guided SEEG electrode implantation was done, and 11 stereotypical electroclinical events were recorded. Electrical onset was first noted as a low-voltage fast activity in the left frontal opercular electrode with immediate synchronization of both ipsilateral and contralateral posterior insula (Fig. 1). Habitual seizures were reproduced on stimulation of the left frontal opercular electrode, matching the electrical onset location. Extraoperative mapping showed no language function in the gyrus of seizure onset, and an awake craniotomy with language cortex mapping confirmed the absence of language function in the immediate environs of the electrical onset. An electrocorticography-guided resection of the left frontal opercular epileptic focus was completed. Histopathology of the resected specimen was type 2A FCD (Fig. 2). There were no fresh neurological deficits, and he remained seizure-free for 9 months, followed by relapse with auras gradually increasing in frequency. The frequency and intensity of events continued to increase, occasionally with secondary generalization. When events were recorded in EEG telemetry, careful review of the semiology revealed the following noteworthy changes: 1) initial aura of tinnitus present but subjectively different from his preoperative stereotyped experience; 2) no ictal pouting, which was prominent and prolonged before; 3) distal automatisms continued as before; 4) asymmetrical tonic posturing phase now showed a reversal with the left side in tonic extension; and 5) no postictal aphasia. Coregistration of volumetric postresection MRI with initial SEEG electrode positions showed the SEEG electrode contacts representing the ictal onset to be well within resection cavity. Prolonged scalp EEG still had no interictal discharges. After discussion of the option of repeat SEEG to localize and characterize residual or new epileptogenic tissue either adjacent or distant to the previous resection, the patient opted for a repeat exploration and consideration of revision epilepsy surgery. A SEEG exploration with circumferential coverage of the previous resection margins and the opposite insuloopercular region was undertaken. One electroclinical

event was recorded after drug tapering in 95 hours of monitoring. Electrical onset preceded the clinical event by 18 sec with onset from the right insular electrodes (Fig. 3). Habitual seizures were reproduced on seizure stimulation mapping from the right insular electrodes. There was no evidence of residual epileptogenicity in the electrodes surrounding the previous resection cavity.

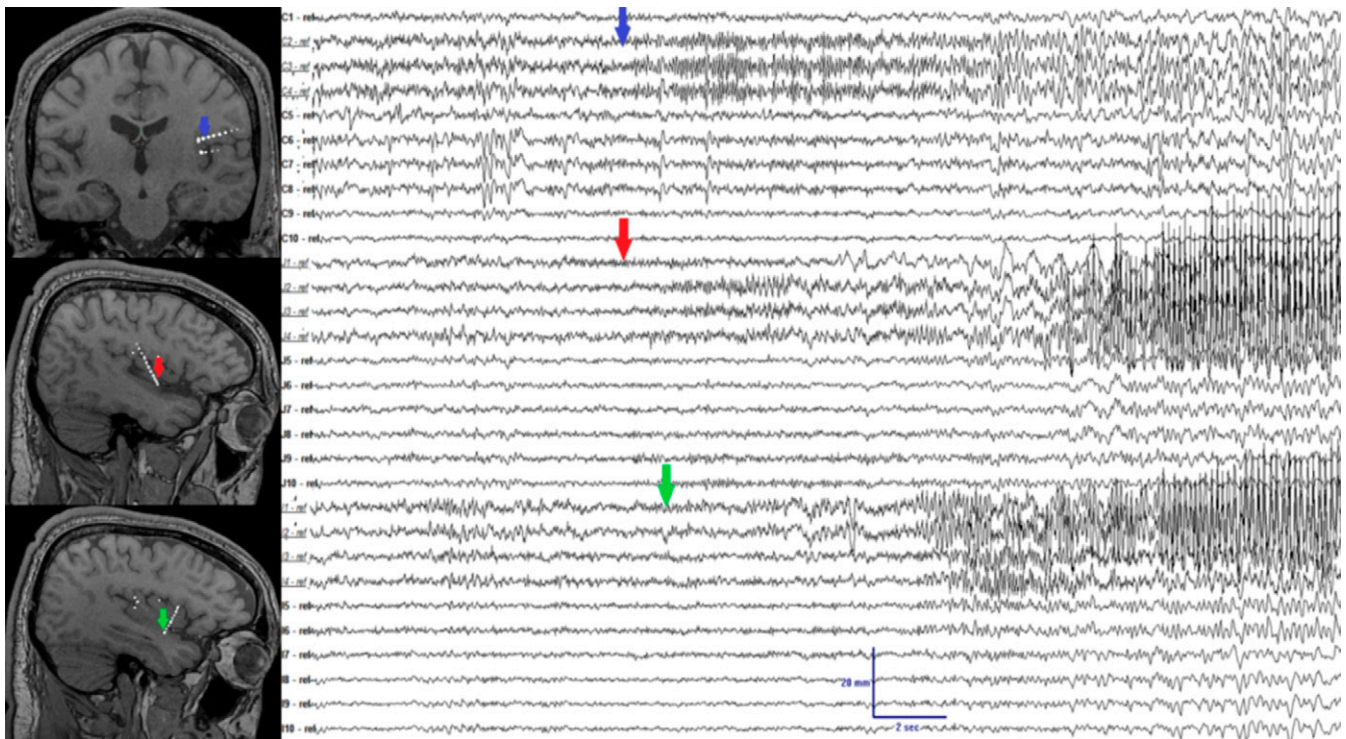
### Surgical Technique

We formulated a novel technique of robotic stereotaxy-guided RFA, hereafter referred to as volumetric stereotactic RFA (vRFA), using an



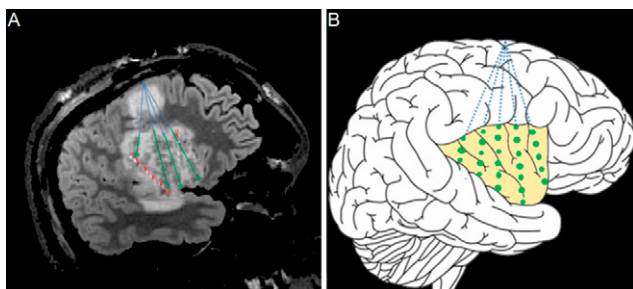
**FIG. 2.** Dyslamination of neuronal arrangement in hematoxylin and eosin stain (original magnification  $\times 100$ ) (A), Neu-N stain (original magnification  $\times 100$ ) (B), and Neu-N stain (original magnification  $\times 200$ ) (C). D: Dysmorphic neurons (black arrows) in neurofilament stain (original magnification  $\times 400$ ).





**FIG. 3.** Electrical onsets (colored arrows) in the right insular SEEG electrode contacts (white dots) in the second SEEG study.

LG2 Lesion generator (Inomed Medizintechnik) with robotic stereotactic guidance. Multiple trajectories were designed to ablate the involved insular cortex fanning out from a single burr hole as the common entry point in the sagittal axis (Fig. 4). In this patient, six trajectories were planned with a total of twenty-six targets of ablation. RF thermoablation was done using a bipolar tip RF electrode, heated to 80°C for 1 min in duplicate at spacing intervals of 5–8 mm between each target along the desired length of each trajectory. A volumetric cone was virtually created to cover the insular cortex, perceived as the epileptogenic zone from the insular SEEG electrodes. The epileptogenic focus was included in the schema of the “ablative cone.” The epileptogenic network disruption in this case was primarily by ablation of the right insular epileptogenic cortex that we identified on SEEG.



**FIG. 4. A:** Post-vRFA MRI (sagittal) on POD1 superimposed on post-implant CT image of electrode contacts (red and white dots) with post-ablation changes; whole length of multiple trajectories (blue-green arrows) fanning out from a common entry with ablated targets (exclusively along the green line). **B:** Schematic representation of the trajectories with targets of ablation (green dots).

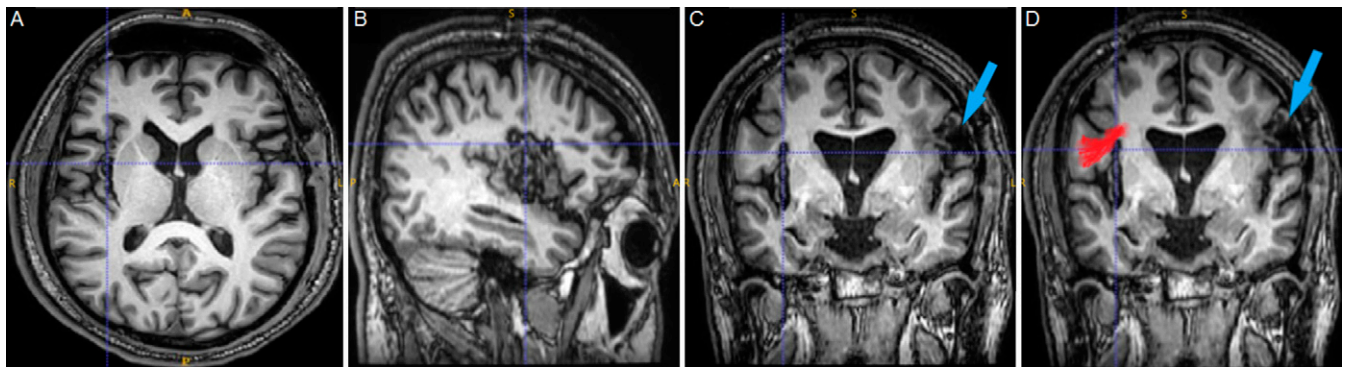
## Postoperative Course

Post-vRFA of the right insula, the patient was noted to have sialorrhea, dysarthria, and dysphagia for liquids, along with upper motor neuron facial palsy affecting the left side. Taken to represent a bilateral opercular Foix–Chavany–Marie syndrome (FCMS), this gradually improved by the third postablative month. By the sixth month, he was noted to have only very minimal dysarthria and no dysphagia. By the ninth month, all deficits resolved completely. He has remained free of habitual auras and seizures for 20 months following the right insular vRFA, while maintained on the same two anticonvulsants, and was fully back to his occupation. Interval MRI, done 8 months postablation, is shown in Fig. 5. Volumetric MRI analysis (ITK-SNAP 3.8.0 software, <http://www.itksnap.org>) revealed total volume of ablation measured as 6.275 mL (each target of vRFA measuring 0.241 mL).

## Discussion

### Observations

We report this interesting case from the standpoint of 1) potential epileptogenicity distant from an FCD focus, 2) management strategies for failed epilepsy surgery in cryptic MRI cases, and 3) technical details of a novel non-SEEG-based RFA technique, which we designate as “vRFA.” The patient initially responded to resection of a lesion from the left operculum, which was demonstrated pathologically to be a type 2A focal cortical dysplasia. His first SEEG study had already demonstrated significant bilateral ictal synchronization of the right posterior insular cortex immediately following an ictal onset localized more anteriorly in the left frontal operculum. This area was later confirmed as an epileptogenic zone by resection, with seizure freedom lasting 9 months and histopathological evidence of type 2A FCD. Recurrence of his seizures with known



**FIG. 5. A–D:** MRI taken 8 months post-vRFA with ablated right insula (blue crossbars) and left insular resection cavity (blue arrows in C and D). D: Right opercular white matter fibers (diagrammatically represented in red) partially disconnected by the superior extension of ablation cavity (crossbars).

pathological substrate was suspected to represent relapse due to incomplete resection of an imaging subtle/negative dysplasia in the eloquent cortex. However, there were significant changes in the relapsed seizure semiology. The semiological shift in lateralization combined with initial SEEG evidence of bilateral insular synchrony prompted us to include extensive contralateral insular sampling in addition to circumferential sampling of the resection cavity margins during the second SEEG study. Surprisingly, there was no evidence of seizure onset from the previous resection margin on the left side and the contralateral posterior insular epileptogenicity, which was seen 2 years prior, appeared to be responsible for the seizures upon relapse. vRFA of this region led to sustained seizure freedom. As the second intervention was only a stereotactic ablative procedure, tissue biopsy was not performed, and we unfortunately lack a tissue diagnosis of the contralateral focus responsible for seizure relapse. This perhaps represents an interesting case of the previously studied phenomenon of epileptogenicity remote and, in fact, even contralateral to an FCD.<sup>1</sup>

Quantified SEEG analysis by Wang et al.<sup>2</sup> suggested that pure insular epilepsy is rare, and the close connection between insular and opercular cortex makes them a single entity. Propagation of insuloopercular seizures to other regions of the brain including contralateral insula can cause false lateralization of an epileptogenic zone,<sup>3,4</sup> and corticocortical-evoked potential studies have shown that both insulae are closely connected and the latency period of propagation is only 8–24 msec to the contralateral homotopic insula.<sup>5</sup>

In conventional SEEG electrode-based RF thermocoagulation, the ablation is done at the bedside with SEEG electrodes in situ, and ablation of targets is feasible only around the intended contact sites.<sup>6</sup> At most, ablation can be done along the longitudinal axis of the SEEG electrode. Our lack of ability to do bedside SEEG electrode-based RFA serendipitously led to design of a stereotactic technique that allows more freedom in designing the ablation zone based on SEEG electrode position combined with functional and anatomical patterns. A similar technique of multitrajectory stereotactic RF thermocoagulation of 100 hypothalamic hamartomas has been reported by Kamayama et al.,<sup>7</sup> where priority was given to disconnection of the lesion from the surrounding normal brain tissue. In the present vRFA case, our entry is from a single dural entry point, a volumetric cone can be constructed such that ablation is carried over in three dimensions, and ablation can be extended based on the intended region of interest so that the epileptic focus/lesion is ablated, as well as perhaps some additional white matter

disconnection. Present evidence support the use of thermocoagulation only for 1) perinodular heterotopias<sup>8</sup> and 2) in difficult, poorly localized focal epilepsies as a “therapeutic challenge” to be followed by a later stage resection based on the response to this challenge.<sup>6</sup> Our volumetric ablative technique approximates lesion sizes and locations achieved using the more modern laser interstitial thermal therapy (LITT) technique. LITT has the advantage of using a single trajectory with real-time lesion imaging using MR thermography but comes with significant cost escalation.<sup>9</sup> In the healthcare system of our country, the impetus for developing this vRFA was that the cost-per-single use probe of the LITT system is, at present, prohibitive for wide adoption of laser ablative technology here. Hence, the first benefit in our scenario is one of cost savings on a per-patient basis. The overhead cost for robotic stereotaxy is already calculated and, at present, not prohibitive in our scenario.<sup>10</sup> Theoretically, these larger volumes of ablation may allow this minimally invasive technique to provide seizure-freedom rates above the conventional bedside SEEG electrode-based RFA.<sup>11</sup>

The bilateral opercular syndrome, also known as FCMS, was first reported in 1926 but was first described by Magnus in 1837.<sup>12</sup> It is a clinical syndrome of bilateral corticobulbar involvement of a cortical or subcortical region involving the anterior opercular region presenting as faciolabio-glossopharyngo-laryngobrachial paralysis on voluntary movement of these muscles but well-preserved automatic and reflex movements.<sup>13</sup> Careful review of the postablation imaging in this patient reveals that the probable cause of FCMS was due to ablation-driven edema and damage to the traversing frontal opercular white matter fibers during vRFA disconnection of the superior portion of the right insula in a scenario of already-resected left frontal operculum (Fig. 5D). Perhaps a more focused insular lesioning during the second intervention might have avoided this. A lesioning plan avoiding the opercular white matter is probably advisable if undertaking similar cases in the future. The functional disability from this known complication has since resolved but is noteworthy when planning bilateral insuloopercular intervention.

### Limitations of the vRFA Technique

Wider surface epileptic focus ablation is theoretically difficult but feasible with multiple entry drills adjacent to each other. A biopsy sample was not available in this case, but biopsy is still possible before commencement of the procedure. Our primary stereotactic objective in this situation is lesioning more than histopathological diagnosis. Biopsy alongside RF

lesioning poses technical issues by creating heat sinks, which potentially interfere with the local heat generation required for thermoablation. Furthermore, the yield of stereotactic biopsy in MRI-negative cryptogenic cases remains uncertain, and the ideal biopsy target for histopathology within the ablative cone in a normal MRI is unknown. vRFA requires general anesthesia in the operating room with stereotactic guidance and additional registration imaging, as opposed to the bedside technique of SEEG electrode-guided RFA done without anesthesia. The multiplicity of trajectories usually requires robotic stereotaxy, which is costly, although frame-based multiple trajectories are still possible. With respect to outcome, the seizure-freedom rates and sustainability are less when compared to resective surgery in focal epilepsy. The benefits of lesioning therapy would include 1) avoiding craniotomy when uncertain about the location and extent of epileptogenic zone and 2) minimally invasive nature allowing more rapid recovery.

## Lessons

We herein report an interesting case of focal cortical dysplasia causing insuloopercular epilepsy with bilateral insular synchrony initially and contralateral insular epileptogenicity upon relapse. We highlight the utility of bilateral insular SEEG coverage and provide evidence that bilateral intervention can be effective in seizure control in such rare cases. With respect to the bilateral opercular syndrome, careful white matter-sparing ablation is advised. We also describe the application of a novel stereotactic technique of stacked RF lesions in multiple cortical trajectories to ablate larger volumes of epileptogenic cortex in a minimally invasive procedure, similar to that used in deeper stereotactic ablative procedures of the thalamus and hypothalamus. To our knowledge, this is the first case report of surgical intervention in bilateral insuloopercular focus for seizures and also the first report on FCMS following bilateral insuloopercular epilepsy surgery. FCMS is a concerning but potentially reversible complication following bilateral insuloopercular surgery.

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## Disclosures

Dr. Pillai reports personal fees from Medtronic and honorarium and other support from Sutarasi Pvt. Ltd. outside the submitted work. Dr. Pillai also has a pending United States patent (no. US20190110854) and is Director of Sutarasi Medical Solutions, Pvt. Ltd. (Registered in India), a company working on research and development of stereotactic apparatus in addition to other stereotactic neurosurgical applications.

## Author Contributions

Conception and design: Pillai, Jayapaul, Rajamma, Gopinath. Acquisition of data: Pillai, Jayapaul, Rajamma, Gopinath. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Pillai, Jayapaul, Rajamma. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Pillai. Statistical analysis: Rajamma. Administrative/technical/material support: Pillai, Aslam, Rajamma, Gopinath. Study supervision: Rajamma, Gopinath. Pathology: Rajamma.

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