Modification of electrophysiological activity pattern after anterior thalamic deep brain stimulation for intractable epilepsy: report of 3 cases

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OBJECTIVE Thalamic stimulation can provoke electroencephalography (EEG) synchronization or desynchronization, which can help to reduce the occurrence of seizures in intractable epilepsy, though the underlying mechanism is not fully understood. Therefore, the authors investigated changes in EEG electrical activity to better understand the seizure-reducing effects of deep brain stimulation (DBS) in patients with intractable epilepsy.

METHODS Electrical activation patterns in the epileptogenic brains of 3 patients were analyzed using classical low-resolution electromagnetic tomography analysis recursively applied (CLARA). Electrical activity recorded during thalamic stimulation was compared with that recorded during the preoperative and postoperative off-stimulation states in patients who underwent anterior thalamic nucleus DBS for intractable epilepsy.

RESULTS Interictal EEG was fully synchronized to the β frequency in the postoperative on-stimulation period. The CLARA showed that electrical activity during preoperative and postoperative off-stimulation states was localized in cortical and subcortical areas, including the insular, middle frontal, mesial temporal, and precentral areas. No electrical activity was localized in deep nucleus structures. However, with CLARA, electrical activity in the postoperative on-stimulation period was localized in the anterior cingulate area, basal ganglia, and midbrain.

CONCLUSIONS Anterior thalamic stimulation could spread electrical current to the underlying neuronal networks that connect with the thalamus, which functions as a cortical pacemaker. Consequently, the thalamus could modify electrical activity within these neuronal networks and influence cortical EEG activity by inducing neuronal synchronization between the thalamus and cortical structures.

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KEY WORDS deep brain stimulation; intractable epilepsy; anterior thalamic nucleus; electroencephalography; functional neurosurgery
cortical areas, whereas high-frequency (> 60 Hz) stimulation of the thalamus provoked desynchronization of intrinsic cortical activity. High-frequency stimulation of the ATN is considered to induce desynchronization in electroencephalography (EEG) activity, which is thought to increase cortical susceptibility to seizures. An epileptogenic pathogenesis of the ATN is supported by the increased metabolic activation of the ATN during seizures and by observations in animal experiments in which lesioning or high-frequency stimulation of the ATN and its corresponding pathways can reduce seizure activity. However, the electrical activation patterns that occur during ATN stimulation have not been identified yet. Therefore, in this study we investigated the chronological changes in the electrophysiological activation resulting from ATN stimulation in patients with intractable epilepsy who underwent ATN DBS.

Methods
Patients and Surgical Procedures
We enrolled 3 patients with intractable epilepsy who underwent ATN DBS. A satisfactory reduction in seizure frequency in these patients could not be achieved with medical treatment administered by an expert epileptologist. For each patient, we performed 24-hour video EEG monitoring to determine the appropriate surgical treatment. The patients did not show specific epileptic foci eligible for resection. Therefore, we informed the patients and their families about their ineligibility for resection and presented other surgical options, such as corpus callosotomy, vagus nerve stimulation, and DBS. Each of the patients opted for DBS. Informed consent for ATN DBS was obtained from the patients and their families, and they agreed to undergo follow-up EEG evaluation as well.

The ATN DBS procedures were performed using a routine protocol. A Leksell G stereotactic frame (Elekta) was mounted on the patient’s head after a local anesthetic was applied. Preoperative MRI (GE Signa HDxt 1.5-T) was performed for stereotactic determination of the anterior and posterior commissural line and surgical targets. Intracranial electrodes were implanted under a local anesthetic through bur holes made bilaterally anterior to the coronal suture and using scalp EEG monitoring via needle electrodes. We performed microelectrode recordings before inserting the intracranial electrodes to confirm that they were not positioned in a ventricle. We used the recordings to differentiate the border between the ventricle and the thalamus. We obtained CT images (GE Discovery CT750 HD) and merged them with preoperative MRI to confirm that the electrode (DBS electrode model 3387, Medtronic Inc.) positions were correct before removing the stereotactic frame. On the same day, we inserted implantable programmable generators (IPGs; Soletra, Medtronic Inc.) in both subclavian regions while the patient was under general anesthesia. The patients were hospitalized until they recovered.

We turned on the stimulator 6 weeks after the DBS surgery once we confirmed that the patient had fully recovered. The patients visited our outpatient department every 2–3 months. We asked the patients and their families or caregivers to maintain a seizure diary from 3 months before to 6 months after the surgery. We then reprogrammed the IPGs according to the frequency of seizures documented in these diaries. The final stimulation parameters are shown in Table 1, which were determined after the stimulator was reprogrammed over 1–2 months of trial and error modifications to accomplish optimum control of seizure activity. Electroencephalography recordings were performed 2 years after surgery at the follow-up.

Source Localization Using CLARA
Preoperative and postoperative EEGs were analyzed for source localization. Electrical activity was recorded using a digital EEG acquisition system (Grass-Telefactor, Astro-Med Inc.). Twenty-one electrodes were positioned at standard scalp spots and both mastoids, according to the international 10-20 system. Recordings were performed with a sampling rate of 200 Hz. Postoperative EEG recordings were performed for the off- and on-stimulation states at 2 years after stimulator implantation. The EEG data were exported to the European Data Format (EDF), which was subsequently imported into Brain Electrical Source Analysis (BESA) Research 6.0 (BESA GmbH). Epochs that did not show an epileptogenic discharge on preoperative EEG, from EEG data recorded 10 minutes after the off-stimulation state began, and from EEG data recorded postoperatively 1 minute after the on-stimulation state began. To remove the DBS stimulation artifact, we used an online low-pass filter provided by our EEG system. The duration of each epoch was 500 msec. We adapted the epochs that were suitable after removing the artifacts made by eyeball and muscle movement. Low-resolution electromagnetic tomography (LORETA) implemented in BESA software was used to analyze the epochs and to obtain source localization. LORETA has been previously used to localize the generator of epileptogenic discharge in electrical cortical activity recorded on scalp EEG. To obtain a more focused source image, classical LORETA analysis recursively applied (CLARA), the iterative method, was used for source localization. CLARA can localize a deep source correctly and resolve closely neighboring sources. Moreover, it can be reliably performed over a wide range of noise levels. The regularization value is used in the iteration stage, and the default setting is 0.003% for singular value decomposition to improve the calculation of imaging. Talairach coordinates were used in anatomical sites containing the maximal activity with a voxel size of 7 mm.

Results
The patients were women with ages between 36 and 38 years, and their duration of epilepsy was nearly lifelong.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Magnitude (V)</th>
<th>Pulse Width (usec)</th>
<th>Frequency (Hz)</th>
<th>Stimulation Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.3</td>
<td>270</td>
<td>20</td>
<td>Intermittent</td>
</tr>
<tr>
<td>2</td>
<td>3.2</td>
<td>210</td>
<td>20</td>
<td>Intermittent</td>
</tr>
<tr>
<td>3</td>
<td>3.3</td>
<td>270</td>
<td>25</td>
<td>Intermittent</td>
</tr>
</tbody>
</table>

TABLE 1. Deep brain stimulation parameters
The demographics of the patients and overall clinical results are shown in Table 2. We followed the patients for at least 2 years after surgery. The overall decrease in seizure frequency relative to the preoperative state for all patients was 54.7%–81.8%. Moreover, interictal EEG in the postoperative on-stimulation period was fully synchronized to the β frequency (Fig. 1).

**Electroencephalography Source Analysis With CLARA**

The EEG source imaging showed different localizations between the preoperative and postoperative off-stimulation and on-stimulation states. Case 1 showed localizations in the anterior cingulate (activity: 72%), middle frontal (66%), and precentral and mesial temporal areas (63%) in the off-stimulation state and localizations in the basal ganglia (36%), anterior cingulate area (41%), and midbrain (43%) in the on-stimulation state. Case 2 showed localization in the medial frontal (100%), posterior cingulate (100%), mesial temporal (64%), and insular areas (67%) in the off-stimulation state and localizations in the anterior cingulate area (100%), the basal ganglia (42%), and the cerebellum (100%) in the on-stimulation state. Case 3 showed localizations in the medial frontal (100%), medial occipital (100%), and mesial temporal areas (65%) in the off-stimulation state and localizations in the anterior cingulate area (94%), the midbrain (66%), and the cerebellum (100%) in the on-stimulation state.

It is meaningful that CLARA localized electrical activity during the off-stimulation states in cortical and subcortical areas including the insular, middle frontal, mesial temporal, and precentral areas (Fig. 2). There was no localized activity in deep nuclei. Otherwise, CLARA localized electrical activity postoperatively during thalamic stimulation in the anterior cingulate area, basal ganglia, and midbrain (Fig. 3). There was no electrical activity localized in the cortex and subcortical area.

**Illustrative Cases**

**Case 1**

This 36-year-old woman with mental retardation experienced tonic drop attacks and complex partial seizures with secondary generalization. She experienced drop attacks 2–3 times per week, which were devastating seizures. Video EEG monitoring showed frequent, multifocal spike and wave discharge from the right hemisphere posterior temporal areas and occasionally from the left posterior temporal areas. Her complex partial seizures presented initially as hand grabbing bilaterally and evolved into trunk rotation toward the left side with jerking of the left arm and face. The ictal EEG failed to lateralize the seizure origin.

The patient showed no side effect during the stimulation period. We attempted high-frequency (70 and 130 Hz) stimulation, but this aggravated the seizure frequency. We also attempted continuous stimulation with 20 Hz, but this exacerbated her symptoms. After final programming, she experienced drop attacks once or twice a year. Even after surgery, she experienced them when she was tired or sleep deprived for some reason, which may have been troublesome episodes for her and her family.

**Case 2**

This 37-year-old woman with cognitive delay experienced tonic drop attacks and generalized tonic-clonic seizures. She experienced right hemiparesis with right hemianopia after her generalized tonic-clonic seizures began at the age of 6 months and were accompanied by fever. Her habitual seizures included 3 types. The first type was an epileptic spasm of the right hand with rotation to the left side and lasted a few seconds. The second type was a tonic drop attack, whereas the third type was a generalized tonic-clonic seizure. In the video EEG monitoring, ictal EEG showed synchronous and fast rhythmic activity in both cortical hemispheres, with the left frontal area showing the maximum activity (F7, F3, Fp1) for 1–2 seconds. In addition, she presented with clinical seizures that included right shoulder elevation and wrist flexion.

We began stimulation 6 weeks after surgery. Improvement in the frequency of her seizures was gradual and continuous. Although she experienced seizures several times a month with diurnal variations after surgery, she rarely experienced drop attacks, which delighted her and her family.

**Case 3**

This 38-year-old woman with moderate to severe cognitive delay suffered intractable seizures. Her symptoms began when she was 3 years old. Her seizures were stereotypical and characterized by tonic elevation of both arms with falling down. There was no evidence of atypical absence seizures. Electroencephalography showed features characteristic of Lennox-Gastaut syndrome, including generalized paroxysmal fast activity and generalized slow spike and wave discharges.

Thalamic stimulation was started under a typical protocol. We experienced some difficulty in counting the frequency of her seizures before surgery because they were frequent and she had moderate to severe cognitive delay. Before surgery, she experienced several traumatic episodes every month. However, after surgery, she experienced no major traumatic episodes and she showed more prominent diurnal variations in the frequency of her seizures because of a definite decrease in seizures during the daytime.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Age at Onset of Seizure</th>
<th>Seizure Type</th>
<th>3-Mo Average Before Surgery</th>
<th>3-Mo Average 2 Yrs after Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>Female</td>
<td>4 yrs</td>
<td>Tonic drop attacks, complex partial seizure secondarily generalized</td>
<td>28.6/mo</td>
<td>5.2/mo (81.8%)</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>Female</td>
<td>6 mos</td>
<td>Tonic drop attacks, generalized tonic clonic seizure</td>
<td>16.3/mo</td>
<td>4.8/mo (70.5%)</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>Female</td>
<td>3 yrs</td>
<td>Tonic drop attacks, partial &amp; generalized tonic seizure</td>
<td>52.3/mo</td>
<td>23.7/mo (54.7%)</td>
</tr>
</tbody>
</table>
Discussion

This study was based on clinical data and EEG source analyses in patients who underwent ATN DBS for intractable epilepsy. Thalamic stimulation provoked electrical changes in the brain, which could be detected with EEG. The EEG synchronization during ATN stimulation was detected. Electrical current generated by the DBS system is much stronger than electrical activities generated by neuronal structures. It is clear that neurons and their connections are influenced by the strong electrical currents of ATN stimulation during the on-stimulation state, a phenomenon revealed by EEG synchronization that was simultaneous with the stimulation parameters. The electrical current from the DBS system induced a functional depolarization block of the neurons and their connections and increased c-Fos expression in thalamic connections.17

Animal studies have shown that stimulation or lesioning of the ATN may suppress that structure’s ability to amplify, propagate, and synchronize seizure activity.5,40 Anterior thalamic nucleus stimulation also reduced glutamate levels and increased γ-aminobutyric acid (GABA) levels in the hippocampus; this suggests that ATN stimulation may restore the balance between excitatory and inhibitory neurotransmission in these connected brain regions.26 Consequently, ATN DBS could reset thalamic neurons and their connections and modify the connected brain regions.

The electrical activity localized by CLARA in this study was changed during the on-stimulation state compared with activity in the preoperative or off-stimulation states. After we reprogrammed several times for optimal results, the frequency of the stimuli was 20–25 Hz (β frequency). There have been various reports regarding stimu-
The β frequency that we achieved after trial and error over an average of 6 months was not an ideal parameter, but it was optimal in this study; EEG during the on-stimulation state was synchronized to this frequency. A common feature of β-band oscillations in the human brain is the critical involvement of cortical or thalamocortical networks of inhibitory interneurons that act as pacemakers gated by GABA. Actions of this pacemaker would control the intrinsic hyperexcitability that is prone to evoking paroxysmal activity, such as seizures. In another study, electrical stimulation induced hyperpolarization that reduced spontaneous epileptic activity by mediating GABA inhibitory postsynaptic potentials and the slow after-hyperpolarization. During the on-stimulation state, thalamic inhibitory interneurons could be modulated, and their connections could be influenced. Disputed electrical activity within the epileptic brain is capable of evoking consistent paroxysmal EEG activity. The enhanced inhibitory interneuron activity triggered by neurostimulation modified the disputed electrical activity. However, continuous forced synchronization by external currents may suppress physiological oscillations of thalamocortical networks. Normally, networks in the brain, including inhibitory and excitatory interneurons, show a wide range of oscillation. Although the brain networks of patients in this study were abnormal, the balance among interneurons that maintains their normal ability to control seizure activity may be reduced because of continuous stimulation. In this study, continuous stimulation with β-band frequency exacerbated the patients’ seizure frequencies. The thalamocortical circuit could be reset by intermittent stimulation, and it could work without disabling normal functions. Accordingly, the balance between excitation and inhibition within the brain networks is a key marker of seizure control.

One of the mechanisms that may explain the inhibition of epileptic activity via electrical stimulation of the brain is activation of an endogenous brain inhibitory system. It
FIG. 3. CLARA localized electrical activity during the on-stimulation state. Electroencephalography source imaging showed localization in the anterior cingulate area (Case 1, A; Case 2, B; Case 3, C) and deep brain nuclei (Case 1, D; Case 2, E; Case 3, F) during the on-stimulation state. Figure is available in color online only.
has been suggested that the ventral pontine reticular formation is an inhibitory brain structure.\textsuperscript{9} The inhibitory effect of the raphe nuclei and the locus coeruleus has also been reported.\textsuperscript{12,23,34} This inhibitory effect is thought to mediate the activity of several nuclei located primarily in the midbrain, as well as its mediators and corresponding pathways.\textsuperscript{3} Increased activity in the current study was observed in the basal ganglia and midbrain. The reticular activating system of the midbrain and pons is believed to play a key role in the diffuse inhibitory system.

**Study Limitations**

There are some limitations to this study. Three cases are a small sample for drawing strong conclusions in a clinical study. Moreover, we could not completely remove the stimulation artifact from the EEG source, which could attenuate the impact of the results. Our use of scalp EEG with 21 electrodes had high temporal resolution but limited spatial resolution, although our results showed concordant identification for the pulseless electrical activity. To increase spatial resolution, the number of electrodes may be an important factor. Source imaging for dense array EEG using 256 channels can provide high yield in presurgical planning and predict surgical prognosis. The EEG source localization method in this study, that is, CLARA, did not provide statistical reliability of the source or correspondence to the actual source location. We could detect a change of the global activity distribution before or after manipulation within the brain.

**Conclusions**

In the human brain, there is a wide range of electrical oscillations that are normally harmonized. Neurmodulation could partially modify the networks of epileptic brains by resetting via stimulation with externally generated current. Electroencephalography source images analyzed using CLARA showed changes in electrical activity in the brains of patients with intractable epilepsy. Although our sample size was small, it was thought that anterior thalamic stimulation could spread electrical current to the underlying neural networks that connect to the cortical pacemaker, the thalamus. Consequently, it might modify electrical activity within neural networks and influence cortical EEG by inducing neural synchronization of the thalamus and connected structures. Further investigations of brain connectivity with high-density EEG in a large sample are needed to improve spatial resolution of images and better understand the change of brain network activity after DBS.

**References**

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**Disclosures**

The authors report no confliction of interest concerning the material or methods used in this study or the findings specified in this paper.

**Author Contributions**

Acquisition of data: Hur, SE Kim, Hwang. Analysis and interpretation of data: Hur, HD Kim. Park. Drafting the article: HY Kim. Critically revising the article: Hur, HY Kim. Approved the final version of the manuscript on behalf of all authors: Hur. Administrative/technical/material support: HD Kim. Study supervision: Hur, SE Kim.

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