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# Eye Movement Network Originating from Frontal Eye Field: Electric Cortical Stimulation and Diffusion Tensor Imaging

Yusuke KIMURA,<sup>1</sup> Rei ENATSU,<sup>1</sup> Rintaro YOKOYAMA,<sup>1</sup> Hime SUZUKI,<sup>1</sup>  
Ayaka SASAGAWA,<sup>1</sup> Tsukasa HIRANO,<sup>1</sup> Masayasu ARIHARA,<sup>1</sup>  
Tomoyoshi KURIBARA,<sup>1</sup> Satoko OCHI,<sup>1</sup> and Nobuhiro MIKUNI<sup>1</sup>

<sup>1</sup>Department of Neurosurgery, Sapporo Medical University, Sapporo, Hokkaido, Japan

## Abstract

This study investigated the networks originating from frontal eye fields (FEFs) using electric cortical stimulation and diffusion tensor imaging (DTI). Seven patients with intractable focal epilepsy, in which FEFs were identified by electrical cortical stimulation, were enrolled in this study. Electric stimulation at 50 Hz was applied to the electrodes for functional mapping. DTI was used to identify the subcortical fibers originating from the FEFs with two regions of interests (ROIs) in the FEF and contralateral paramedian pontine reticular formation (PPRF). FEFs were found in the superior precentral sulcus (pre-CS) in six patients and superior frontal gyrus (SFG) in three patients. DTI detected fibers connecting FEFs and contralateral PPRFs, passing within the internal capsule. The fibers were located close to the lateral antero-superior border of the subthalamic nucleus (STN) and medial posterior border of the globus pallidus internus (GPi). This study found the characteristic subcortical networks of the FEF. These tracts should be noted to prevent complications of deep brain stimulation (DBS) of the STN or GPi.

Keywords: frontal eye field, electric cortical stimulation, eye movement, diffusion tensor imaging

## Introduction

Two control areas of eye movement have been previously identified in the frontal lobe in animal studies.<sup>1)</sup> The first area resides in the dorsolateral frontal areas and is termed the frontal eye field (FEF),<sup>1–4)</sup> and the second is located medially and dorsally and is termed the supplementary eye field.<sup>5,6)</sup> Although the precise location and function of the supplementary eye field are still under debate, the FEF has been reported in humans. Previous studies reported that the electrical stimulation of the human dorsolateral frontal cortex induced eye movements in epileptic patients undergoing presurgical evaluation.<sup>1,4,7,8)</sup> However, the

subcortical network of the FEF remains unclear. In addition, contralateral conjugate eye deviation has been reported as a complication of deep brain stimulation (DBS) due to electrical current spread to the axons from FEFs coursing close to the subthalamic nucleus (STN)<sup>9)</sup> and globus pallidus internus (GPi).<sup>10)</sup> The investigation of FEF networks could provide useful information not only for clarifying complicated control systems of eye movement but also for establishing safe and effective procedures for DBS.

Diffusion tensor imaging (DTI) is a non-invasive technique that has enabled us to visualize in vivo white matter pathways in the living human brain by calculating the anisotropic diffusion of water molecules.<sup>11)</sup> The combination of electric cortical stimulation and DTI could provide new information on human brain networks. We studied the networks associated with the FEF and associated neuronal fiber projection using a combination of electric cortical stimulation and DTI in this study.

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**Table 1 Patient profile**

| Case | Age/sex | Diagnosis | Epileptogenic zone | FEF location             | Stimulation intensity |
|------|---------|-----------|--------------------|--------------------------|-----------------------|
| 1    | 28/F    | Lt. FLE   | Lt. inf. Pre-CG    | Lt. sup. Pre-CS, Lt. SFG | 3–15 mA               |
| 2    | 17/M    | Lt. FLE   | Lt. mid Cing. G    | Lt. sup. Pre-CS          | 12 mA                 |
| 3    | 25/M    | Lt. TLE   | Lt. lat T          | Lt. sup. Pre-CS          | 10 mA                 |
| 4    | 11/F    | Lt. FLE   | Lt. inf. Pre-CG    | Lt. sup. Pre-CS          | 8 mA                  |
| 5    | 8/F     | Rt. FLE   | Rt. frontal pole   | Lt. sup. Pre-CS          | 12 mA                 |
| 6    | 17/M    | Rt. FLE   | Rt. SMA            | Rt. sup. Pre-CS, Rt. SFG | 6 mA                  |
| 7    | 43M     | Rt. OLE   | Rt. Occipital      | Rt. SFG                  | 3–10 mA               |

Cing. G: cingulate gyrus, F: female, FLE: frontal lobe epilepsy, inf: inferior, lat: lateral, Lt: left, M: male, mid: middle, OLE: occipital lobe epilepsy, Pre-CG: precentral gyrus, pre-CS: precentral sulcus, Rt: right, SFG: superior frontal gyrus, SMA: supplementary motor area, sup.: superior, TLE: temporal lobe epilepsy.

## Materials and Methods

### Patient population

Seven patients (four males and three females, age: 8–43 years old) with refractory focal epilepsy were retrospectively enrolled in this study (Table 1). Six patients underwent craniotomies to implant subdural electrodes, and one underwent stereotactic electroencephalography (SEEG) placement to locate the epileptogenic zone and functional areas for presurgical evaluation. FEFs were identified during the electrical cortical stimulation between October 2014 and March 2020. Written informed consent was obtained from all the patients, and the study protocol was approved by the institutional Review Board Committee of our institution (No. 23-161).

### Image acquisition and processing

All patients underwent preoperative neuroimaging using a 3 T MR scanner (Signa HDxt 3.0 T version 16; GE Healthcare, Fairfield, CT, USA) equipped with an eight-channel head coil. Diffusion-weighted images were obtained using the 18-direction diffusion-encoding scheme with a 220-mm field of view, a  $128 \times 128$  matrix ( $1.72 \times 1.72$  mm pixels), a 2.4-mm slice thickness, and a maximum b-value of  $1000 \text{ s/mm}^2$ . Anatomical MRI for each patient was used to construct skull-stripped three-dimensional anatomical MR images, and individual diffusion-weighted image volumes were realigned to the subject's skull-stripped anatomical MR image using iPLAN Cranial 3.0 (Brainlab, Feldkirchen, Germany).

### Implantation of electrodes

In six patients, strip or grid subdural electrodes were implanted on the surface of the hemispheres covering the lateral frontal lobe. The grids were composed of two or four lines, each line comprising 5–8 electrodes made of platinum, a recording

diameter of 3 mm and a center–center interelectrode distance of 1 cm (Unique Medical Co., Ltd., Tokyo, Japan). The strips were composed of  $1 \times 4$  or  $1 \times 6$  electrodes with the same composition as grids. One patient underwent SEEG implantation. The SEEG electrodes consisted of 10 cylindrical 2.3-mm-long platinum contacts with a diameter of 0.89 mm and a recording length of 47 or 65 mm (Ad-Tech, Racine, WI, USA). The electrodes were implanted in the planned target using the Leksell frame-based technique through 2.5-mm-diameter drill holes. The positions of the electrodes were confirmed using a pre-surgical three-dimensional reconstructed MR image along with a postoperative high-resolution volumetric computed tomography (CT) image (1-mm-thin slice) to supply a visual correlation between the location of each electrode and the corresponding cortical area or deep structure.

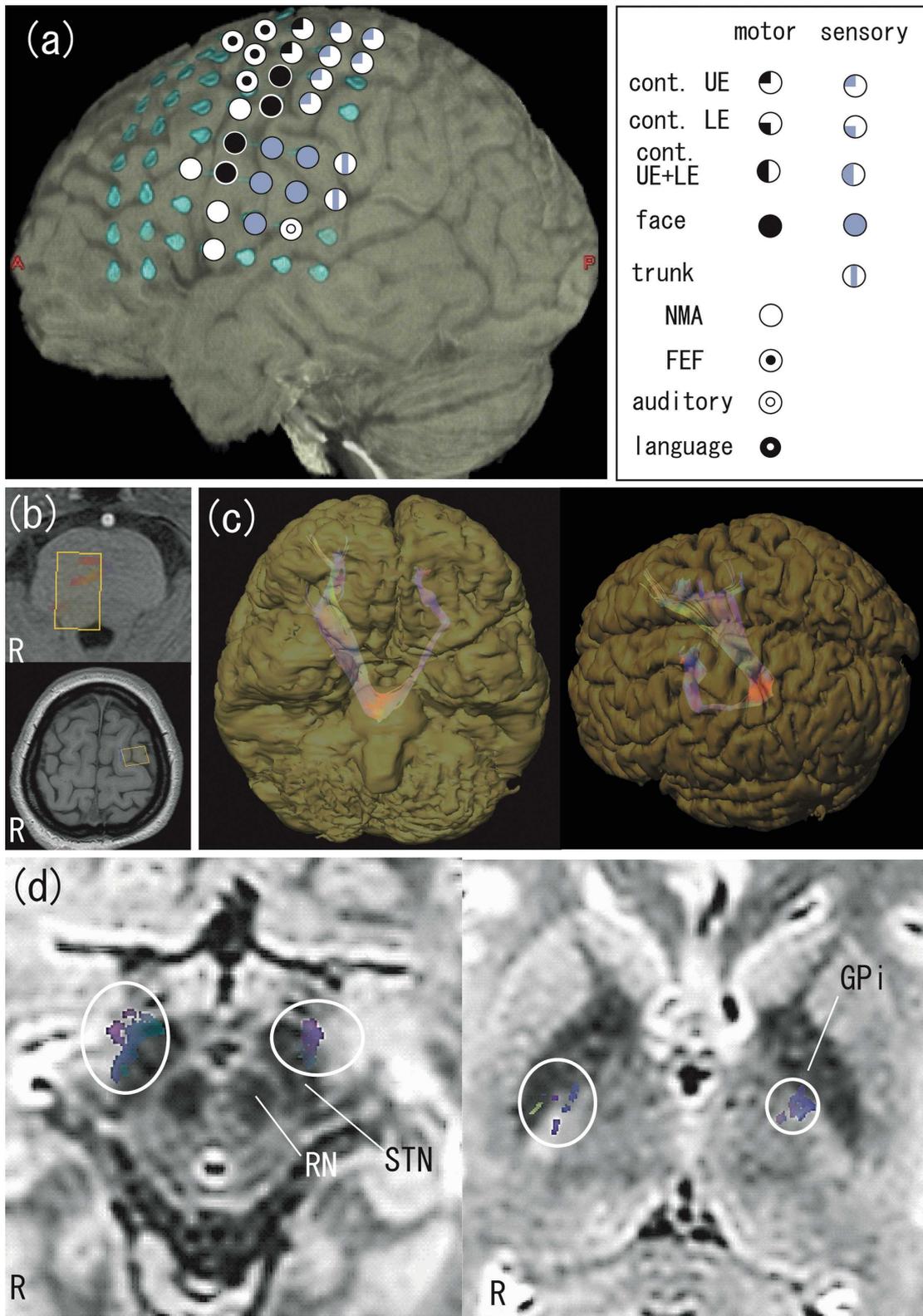
### Electrical cortical stimulation

Cortical electrical stimulation was performed for functional mapping as part of the routine pre-surgical evaluation. Repetitive square-wave electrical currents of alternating polarity, with a pulse width of 0.3 ms, were delivered at a frequency of 50 Hz for 5 s. The current was stepped up from 0 mA to 15 mA for the subdural electrode and 0–12 mA for SEEG, in steps of 1–2 mA, until a behavioral response was observed.

The FEF was defined as the lateral frontal cortices in which the electrical stimulation induced contralateral eye version.<sup>12)</sup> In all the trials, the stimulation was performed at least twice to confirm reproducibility.

### Tractography of FEF network

A fractional anisotropy (FA) value was computed at each voxel from the normalized variance of the eigenvalues of each diffusion tensor. Deterministic fiber tracking was performed with iPLAN Cranial 3.0 (Brainlab), using the streamline tracking algorithm.



**Fig. 1** Case 1: (a) A summary of electrical cortical stimulation. (b) Two seed ROIs (FEF and contralateral PPRF) for tractography. (c) Tractography showing bilateral descending pathways connecting left FEFs and right superior frontal areas with the right PPRF. (d) The locational relationship of the depicted fibers to STN and GPi. Cont.: contralateral, FEF: frontal eye field, GPi: globus pallidus internus, LE: lower extremity, NMA: negative motor area, PPRF: paramedian pontine reticular formation, RN: red nucleus, ROI: region of interest, STN: subthalamic nucleus, UE: upper extremity.

An FA termination threshold of 0.2 was used to generate a set of whole-brain fiber pathways. A two region of interest (ROI) approach was employed for fiber tracking, using a preoperative axial T1-weighted MR image with information from a reconstructed three-dimensional image coordinated with postoperative thin slice CT scans. Seed ROIs included the electrodes of the FEFs and contralateral paramedian pontine reticular formation (PPRF) (Fig. 1b). The ROI of the PPRF included the inferior pontine tegmentum.<sup>13,14</sup> Since the surface of brain could be distorted due to compression of electrodes, the location of the FEF was visually corrected to the corresponding gyrus in the preoperative MRI based on the postoperative CT and the intraoperative photograph. The ROI of the FEF included the corrected locations of all FEF electrodes with the depth of 1 cm.

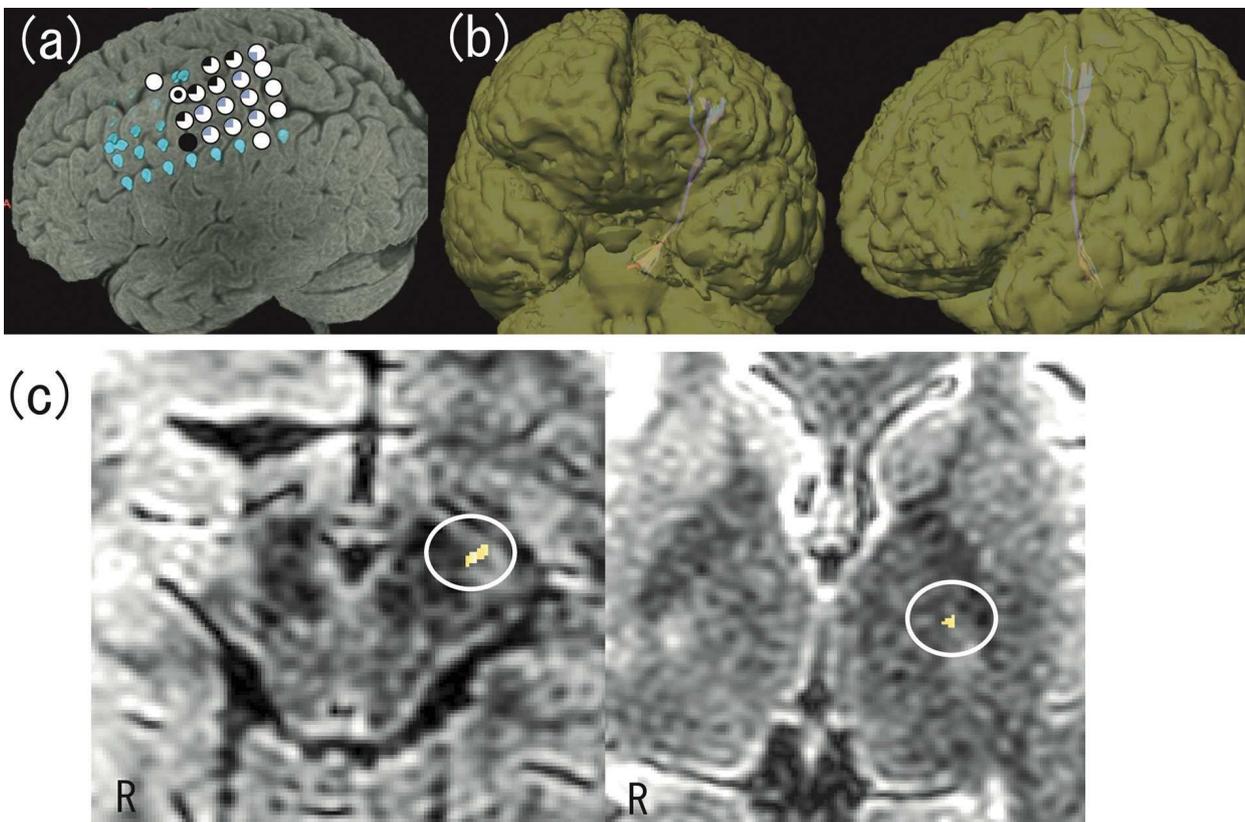
## Results

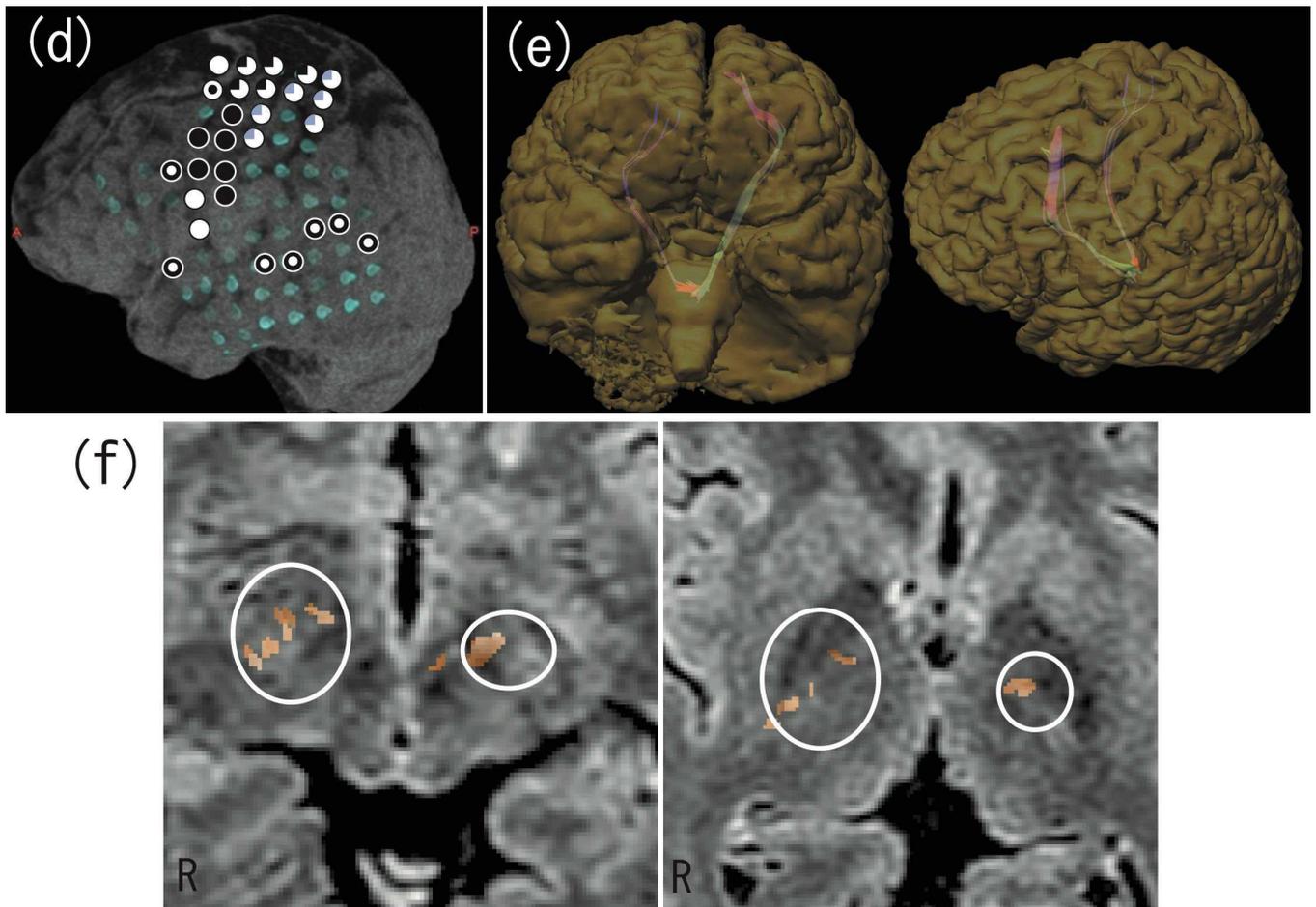
FEFs were found in the superior precentral sulcus (pre-CS) in six patients (Cases 1–6) and in the superior frontal gyrus (SFG) in three patients (Cases 1, 6, 7) (Figs. 1–3, Table 1). These areas were identified adjacent to hand motor areas with stimulus intensities of 3–15 mA.

In seven patients, diffusion tensor images were available in five patients (Cases 1–5). Tractography

from FEFs was successfully visualized in all five patients, and the fibers originating from FEFs descended via the ipsilateral internal capsule and projected to the contralateral PPRFs. In addition, four patients (Cases 1, 3, 4, and 5) showed a contralateral tract connecting the PPRF and the superior posterior frontal areas (Figs. 1–3). With respect to the locational relationship to the STN and GPi, these descending fibers were located close to the lateral anterior border of the STN and medial middle border of the GPi (Table 2).

In Case 1, left FEFs were identified on the posterior SFG and pre-CS at the level of the SFG and the middle frontal gyrus (MFG) located anterior to the hand and face motor areas (Fig. 1a). Tractography depicted bilateral descending pathways connecting left FEFs and right superior frontal areas with the right PPRF (Fig. 1c). These fibers were located in the lateral anterior side of the STN and the medial middle-posterior side of the GPi within the internal capsule (Fig. 1d). In Case 2, left FEFs were identified on the pre-CS at the level of the MFG located anterior to the hand motor areas (Fig. 2a). Tractography depicted a left descending pathway located in the lateral anterior side of the STN and the medial middle-posterior side of the GPi within the internal capsule (Fig. 2c). In Case 3, left FEFs were identified on the pre-CS at the level of the superior





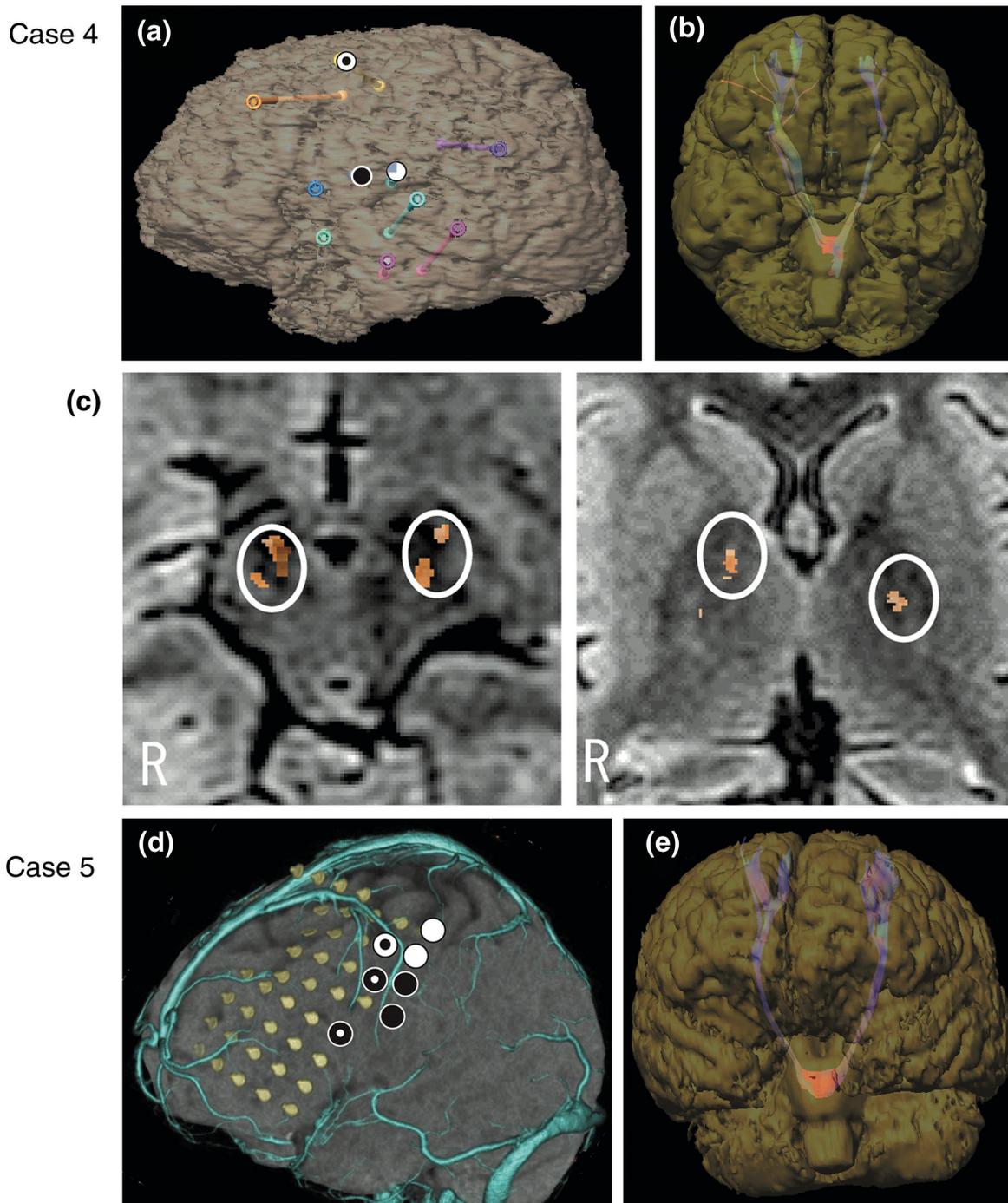
**Fig. 2** In Case 2, left FEFs were identified on the pre-CS at the level of the MFG located anterior to the hand motor areas (a, double circle). Tractography depicted a left descending pathway located in the lateral anterior side of the STN and the medial middle-posterior side of the GPi within the internal capsule (b, c). In Case 3, left FEFs were identified on the pre-CS at the level of the SFS located anterior to the hand motor areas (d). Tractography depicted bilateral descending pathways connecting left FEFs and right superior frontal areas with the right PPRF (e). These fibers were located in the lateral anterior side of the STN and the medial middle-posterior side of the GPi within the internal capsule (f). FEF: frontal eye field, GPi: globus pallidus internus, MFG: middle frontal gyrus, PPRF: paramedian pontine reticular formation, Pre-CS: precentral sulcus, STN: subthalamic nucleus.

frontal sulcus (SFS) located anterior to the hand motor areas (Fig. 2d). Tractography depicted bilateral descending pathways connecting left FEFs and right superior frontal areas with the right PPRF (Fig. 2e). These fibers were located in the lateral anterior side of the STN and the medial middle-posterior side of the GPi within the internal capsule (Fig. 2f). In Case 4, left FEFs were identified on the pre-CS at the level of the SFG with an SEEG electrode (Fig. 3a). Tractography depicted bilateral descending pathways connecting left FEFs and right superior frontal areas with the right PPRF (Fig. 3b). These fibers were located in the lateral anterior side of the STN and the medial anterior side of the right GPi and the medial middle side of the left GPi (Fig. 3c). In case 5, left FEFs were identified on the posterior SFG and pre-CS at the level of the SFG (Fig. 3d).

Tractography depicted bilateral descending pathways connecting left FEFs and right superior frontal areas with the right PPRF (Fig. 3e). Similar to these cases, these fibers were located in the lateral anterior side of the STN and the medial middle-posterior side of the GPi within the internal capsule (Fig. 3f). Right FEFs were identified on a posterior SFG and pre-CS at the level of the SFG located anterior to the hand motor areas in Case 6 (Fig. 3g) and at the posterior SFG in Case 7 (Fig. 3h). In Cases 6 and 7, tractography was not available.

## Discussion

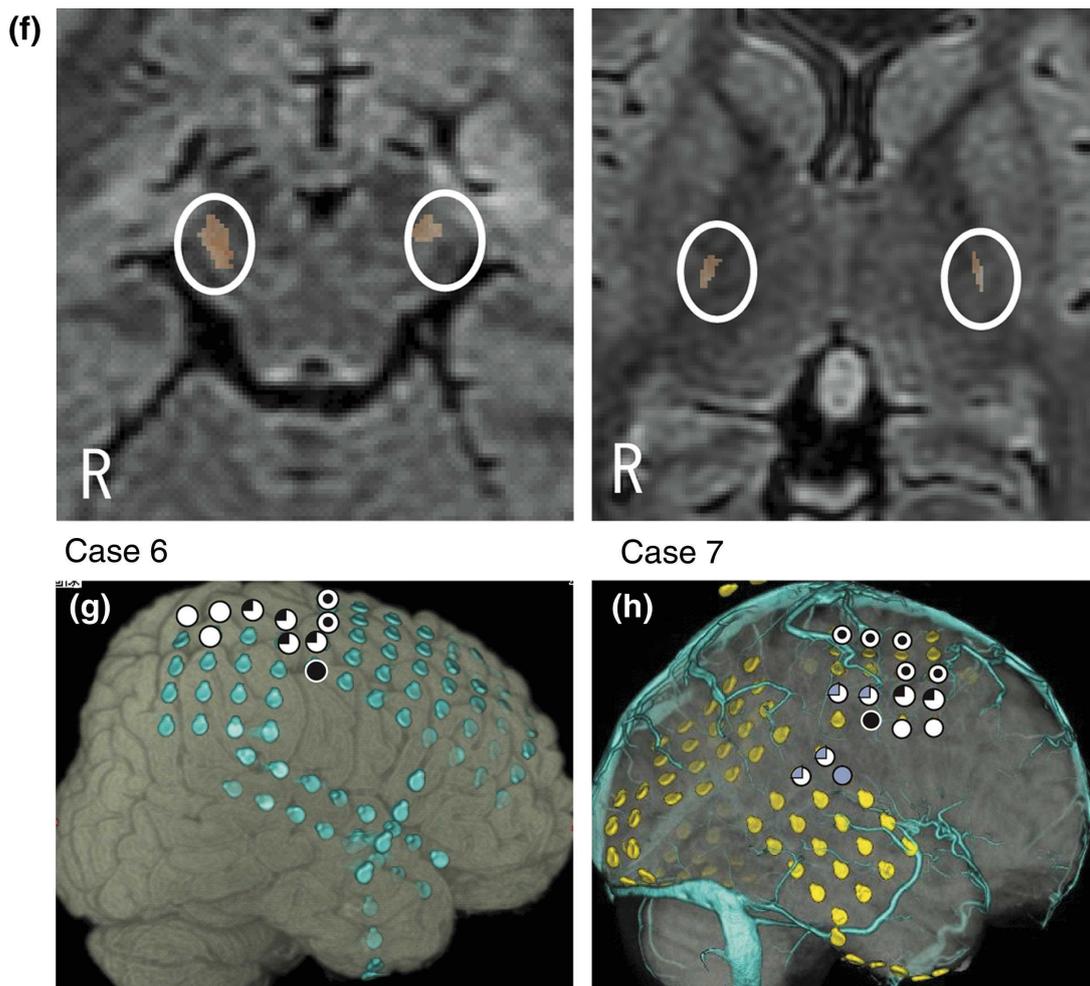
FEFs were identified in the posterior end of SFG and pre-CS at the level of the SFG and MFG adjacent to hand motor areas in the present study. A previous



**Fig. 3** In Case 4, left FEFs were identified on the pre-CS at the level of the SFG with a SEEG electrode (a, double circle). Tractography depicted bilateral descending pathways connecting left FEFs and right superior frontal areas with the right PPRF (b). These fibers were located in the lateral anterior side of the STN and the medial anterior side of the right GPi and the medial middle side of the left GPi (c). In case 5, left FEFs were identified on the posterior SFG and pre-CS at the level of the SFG (d, double circle). Tractography depicted bilateral descending pathways connecting left FEFs and right superior frontal areas with the right PPRF (e).

study reported that the human FEF is located either in the vicinity of the pre-CS and/or in the depth of the caudal-most part of the SFS.<sup>2)</sup> Blanke et al.<sup>4)</sup> reported that human FEFs were located at the posterior end of the MFG anterior to the pre-CS and in

proximity of the SFS. Tehovnik et al.<sup>1)</sup> summarized the previous reports and claimed that the human FEF lies within the pre-CS just caudal to the MFG. The FEF locations in the present study are nearly consistent with those of previous reports, yet they



**Fig. 3** These fibers were located in the lateral anterior side of the STN and the medial middle-posterior side of the GPi within the internal capsule (f). In Case 6, right FEFs were identified on a posterior SFG and pre-CS at the level of the SFG located anterior to the hand motor areas (g, double circle). In Case 7, right FEFs were identified on a posterior SFG (h, double circle). FEF: frontal eye field, GPi: globus pallidus internus, PPRF: paramedian pontine reticular formation, Pre-CS: precentral sulcus, SFG: superior frontal gyrus, STN: subthalamic nucleus.

were located in a relatively superior position. Tehovnil and Paus reviewed the FEF location using positron emission tomography (PET), and Blanke et al. carried out testing similar to ours using electrodes. We generated the three-dimensional model of the brain using MRI and the site of the electrode based on CT. We believe that electrical cortical stimulation is superior to PET and functional MRI in terms of the spatial resolution. Because the techniques differ, positions of the FEF in this study are thought to be slightly different from those of past reports.

Tractography from FEFs revealed the descending fibers via the ipsilateral internal capsule in one patient and the bilateral internal capsule in three patients, projecting to contralateral PPRFs. These fibers were located at the lateral anterior side of the STN and medial middle side of the GPi. Several previous studies assumed that the fiber originating

from the FEF descends within the internal capsule medial to the cortical motor neuron and projects to the brainstem.<sup>1,5,9)</sup> In addition, previous lesion studies reported that patients with a lesion in the internal capsule involving the FEF efferent pathways experienced a decreased gain in eye control.<sup>3,15)</sup> The present results support these previous assumptions and findings.

Three patients showed a contralateral tract connecting the PPRF and superior posterior frontal areas via the contralateral internal capsule. In Cases 1 and 5, fiber was projected on the SFG, and in Cases 3 and 4, fiber was projected on the inferior frontal gyrus. In Cases 1 and 5, the contralateral FEF may be reflected in this fiber. However, the inferior frontal gyrus and the oculomotor association are not clear, and the results of two other cases may reflect another fiber.

**Table 2 Characteristics of fibers from frontal eye field**

| Case | Ipsilateral fiber depiction | Contralateral fiber depiction | Anatomical relationship to STN | Anatomical relationship to GPi |
|------|-----------------------------|-------------------------------|--------------------------------|--------------------------------|
| 1    | +                           | +                             | Anterolateral                  | Medial                         |
| 2    | +                           | -                             | Anterolateral                  | Medial                         |
| 3    | +                           | +                             | Anterolateral                  | Medial                         |
| 4    | +                           | +                             | Anterolateral                  | Medial                         |
| 5    | +                           | +                             | Anterolateral                  | Medial                         |
| 6    | -                           | -                             | NA                             | NA                             |
| 7    | -                           | -                             | NA                             | NA                             |

GPi: globus pallidus internus, NA: not available, STN: subthalamic nucleus.

Furthermore, contralateral eye deviation has been reported as a rare complication of DBS of the STN and GPi.<sup>10,9)</sup> These phenomena are explained by the spreading of electrical current to the projecting fibers from the FEF to the brainstem within the internal capsule. In terms of the anatomical aspect, the FEF projection is supposed to be located at the lateral anterosuperior border of the STN and the medial border of the GPi, and electrode placement of these areas might cause contralateral eye deviation.<sup>9,10)</sup> The surrounding fibers include corticospinal tract/corticobulbar tracts/FEF projection of the internal capsule and medial lemniscus; therefore, the deviation of DBS electrodes toward specific direction could correlate with specific symptoms. Although a precise locational definition was difficult to obtain due to the limitations of spatial resolution, our results are nearly consistent with these reports.

In this study, the number of patients and electrode coverage was limited, and more data need to be accumulated to confirm our findings. Furthermore, methodological limitations (e.g., fusion error between preoperative MR and postoperative CT scans, inaccessibility of sulcal cortex, and inappropriate FA threshold and seed ROI) and epileptogenicity might affect the results. In addition, a quantitative analysis of fibers (e.g., fiber numbers, FA values) was not available in this study and should be considered for the future analysis.

Despite these limitations, however, this study could provide new information regarding the human eye control networks, and serve as a locational guide for electrode placement in DBS.

### Conflicts of Interest Disclosure

No disclosures to declare.

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Corresponding author: Nobuhiro Mikuni, MD, PhD  
Department of Neurosurgery, Sapporo Medical University, South 1 West 16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan.  
*e-mail*: mikunin@sapmed.ac.jp