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Functional Magnetic Resonance Imaging and Diffusion Tensor Imaging for Language Mapping in Brain Tumor Surgery: Validation With Direct Cortical Stimulation and Cortico–Cortical Evoked Potential

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Objective: Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging-derived tractography (DTI-t) contribute to the localization of language areas, but their accuracy remains controversial. This study aimed to investigate the diagnostic performance of preoperative fMRI and DTI-t obtained with a simultaneous multi-slice technique using intraoperative direct cortical stimulation (DCS) or corticocortical evoked potential (CCEP) as reference standards.
Materials and Methods: This prospective study included 26 patients (23–74 years; male:female, 13:13) with tumors in the vicinity of Broca's area who underwent preoperative fMRI and DTI-t. A site-by-site comparison between preoperative (fMRI and DTI-t) and intraoperative language mapping (DCS or CCEP) was performed for 226 cortical sites to calculate the sensitivity and specificity of fMRI and DTI-t for mapping Broca's areas. For sites with positive signals on fMRI or DTI-t, the true-positive rate (TPR) was calculated based on the concordance and discordance between fMRI and DTI-t.
Results: Among 226 cortical sites, DCS was performed in 100 sites and CCEP was performed in 166 sites. The specificities of fMRI and DTI-t ranged from 72.4% (63/87) to 96.8% (122/126), respectively. The sensitivities of fMRI (except for verb generation) and DTI-t were 69.2% (9/13) to 92.3% (12/13) with DCS as the reference standard, and 40.0% (16/40) or lower with CCEP as the reference standard. For sites with preoperative fMRI or DTI-t positivity (n = 82), the TPR was high when fMRI and DTI-t were concordant (81.2% and 100% using DCS and CCEP, respectively, as the reference standards) and low when fMRI and DTI-t were discordant (≤ 24.2%).

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Conclusion: fMRI and DTI-t are sensitive and specific for mapping Broca's area compared with DCS and specific but insensitive compared with CCEP. A site with a positive signal on both fMRI and DTI-t represents a high probability of being an essential language area.
Keywords: Functional MRI; Broca's area; Diffusion tensor imaging; Direct cortical stimulation; Cortico–cortical evoked potential

INTRODUCTION

Language mapping reduces postoperative functional impairment and enables safe maximal resection [1]. Presurgical language mapping with functional magnetic resonance imaging (fMRI) and diffusion tensor imaging-derived tractography (DTI-t) enables a comprehensive understanding of the language network system [2] and localization of the language area [3,4]. Language mapping in fMRI is based on blood oxygen level dependence (BOLD) effects caused by increased local brain activity [5]. DTI-t can visualize the arcuate fasciculus (AF), the major white matter tract connecting Broca's area and Wernicke's area [6,7]. However, its diagnostic accuracy has not yet been established. The reported diagnostic performance of fMRI is inconsistent, with sensitivities ranging from 5% to 100%, and specificities ranging from 0% to 98% [4]. In addition, although several studies have reported the language localization accuracy of fMRI and DTI-t [4,8-10], few have investigated it by combining fMRI and DTI-t results.

The recently introduced simultaneous multi-slice (SMS) imaging technique for DTI and fMRI may improve preoperative language mapping. The SMS technique simultaneously acquires several two-dimensional (2D) slices [11-13] using a multiband composite radiofrequency pulse with a slice-selective gradient [12]. Therefore, this approach can achieve more detailed fMRI BOLD profiles with higher spatial and temporal resolutions than conventional 2D echo-planar imaging.

Direct cortical stimulation (DCS) during awake craniotomy is the standard method of language mapping. However, it prolongs the duration of surgery and increases the risk of intraoperative seizures. In 2004, Matsumoto et al. [14] introduced an electrical tracing method using corticocortical evoked potentials (CCEP) for intraoperative monitoring of AF under general anesthesia. It has been successfully applied in intraoperative language mapping with acceptable language function preservation outcomes [9,15,16] and CCEP monitoring can be used for language mapping when awake surgery is not applicable.

The purpose of this study was to 1) investigate the accuracy of fMRI and DTI using DCS or CCEP as reference standards, and 2) suggest a method for the comprehensive interpretation of fMRI and DTI-t results.

MATERIALS AND METHODS

Study Population

This prospective study was approved by the Institutional Review Board (IRB No. H-1702-051-832) at Seoul National University Hospital, and written informed consent was obtained from all participants. All of the study designs were conducted following the Helsinki Declaration. Twenty-eight patients who met the following inclusion criteria were initially enrolled between June 2017 and September 2021: 1) preoperative diagnosis of glioma located adjacent to Broca's area requiring surgical treatment with intraoperative DCS or CCEP, and 2) feasibility of performing the fMRI task. Among the 28 patients, two had illegible results for the analysis. One patient had unsuccessful intraoperative language mapping using CCEP, and the other showed suboptimal image quality on DTI. Therefore, 26 patients were included in the study (Fig. 1).

All patients underwent fMRI and DTI-t examinations on the day before surgery. DCS during awake surgery was chosen if the tumor was small or focal without any signs of increased intracranial pressure, and CCEP under general anesthesia was chosen if the patient was ineligible for awake anesthesia or if the tumor was large or diffuse.

Magnetic Resonance Imaging

All magnetic resonance imaging (MRI) scans were performed using a 3T MRI scanner (Skyra, Siemens). The MR protocol included sagittal 3-dimensional (3D) T1-weighted imaging, sagittal 3D fluid-attenuated inversion recovery (FLAIR) with fat suppression, axial 2D DTI-t with SMS spin-echo EPI, and axial 2D fMRI with SMS gradient-echo EPI. Detailed acquisition parameters are listed in Supplementary Table 1.

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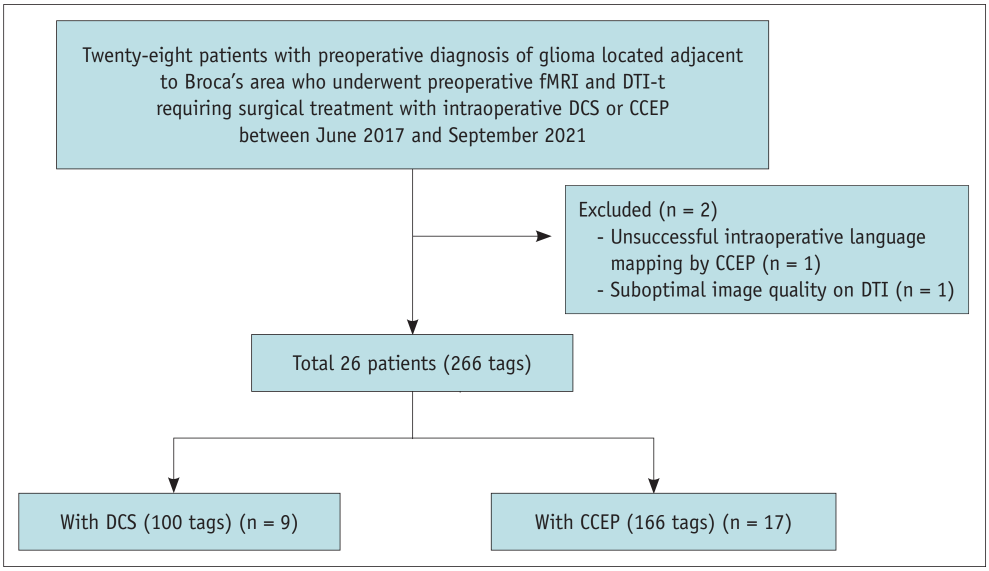

Fig. 1. Flowchart for the inclusion and exclusion criteria of our study population. A total of 26 patients were tested intraoperatively comprising direct cortical stimulation (DCS) in 9 patients and corticocortical evoked potential (CCEP) in 17 patients. DTI-t = diffusion tensor imaging-derived tractography, fMRI = functional magnetic resonance imaging

Functional MRI Paradigms and Analysis

A block design alternating four active and four rest periods was used for each of the two visually presented language tasks (verb generation and sentence completion) [17,18]. The remaining block consisted of 80 measurements lasting for 40 s, and the active block consisted of 40 measurements lasting for 20 s with tasks. This was the default setting of the clinical software (NordicActiva v.1.2.0, NordicNeuroLab), the paradigms of which follow recommendations from the American Society for Functional Neuroradiology. The fMRI stimulus was presented visually through a 4K LCD screen in front of the participants. Visual verb generation was as follows: Pictures of the noun were shown, and the participants were required to silently generate the corresponding verb for the noun shown on the screen. Each noun was presented for 5 seconds, and each active block consisted of four different nouns. Sentence completion was as follows: Pictures of a simple sentence with one blank space were shown, and participants were required to silently read and fill in an appropriate word to complete the sentence on the screen. Each sentence was presented for 5 s and each active block consisted of four different sentences. During the remaining phase of both tasks, meaningless symbols were displayed. fMRI data were analyzed using Food and Drug Administration–approved software (NordicBrainEx v.2.3.9, NordicNeuroLab). After removing the three initial volumes to reach signal equilibrium, a 6-parameter rigid realignment for motion correction, rigid co-registration with the 3D FLAIR sequence, and spatial smoothing (Gaussian kernel, full width at half maximum = 8 x 8 x 8 mm) were performed. Using a general linear model, the signal time course was correlated with the expected hemodynamic response function on a voxel-by-voxel basis. Automatic thresholding in NordicBrainEx (NordicNeuroLab) was set to 40% of the maximum *t*-value for a given BOLD dataset (activation mapping as percentage of local excitation [AMPLE] normalization) [19]. BOLD fMRI activities during the verb generation task ($fMRI_{verb}$) are presented in red, whereas those during the sentence completion task ($fMRI_{sentence}$) are shown in blue (Fig. 2).

DTI-t Analysis

DTI data were processed and analyzed using NordicBrainEx v.2.3.9 (NordicNeuroLab), using the Fiber Assignment Continuous Tracking (FACT) algorithm to calculate fiber tracking [20,21]. White matter tracts were generated on each voxel based on the direction and magnitude of maximum water diffusion. Six-parameter rigid realignment for motion correction and Gaussian smoothing were performed for preprocessing. The fiber tracking termination criteria included a fractional anisotropy below 0.2, an angle threshold greater than 41.4°, a minimum fiber length of 20 mm, and the number of seeds per voxel. Fiber tracts that passed through both the seed region of interest (ROI) and the target ROI were classified as AF tracts [7]. ROI placement was performed by a neuroradiologist (K.M.Kang,

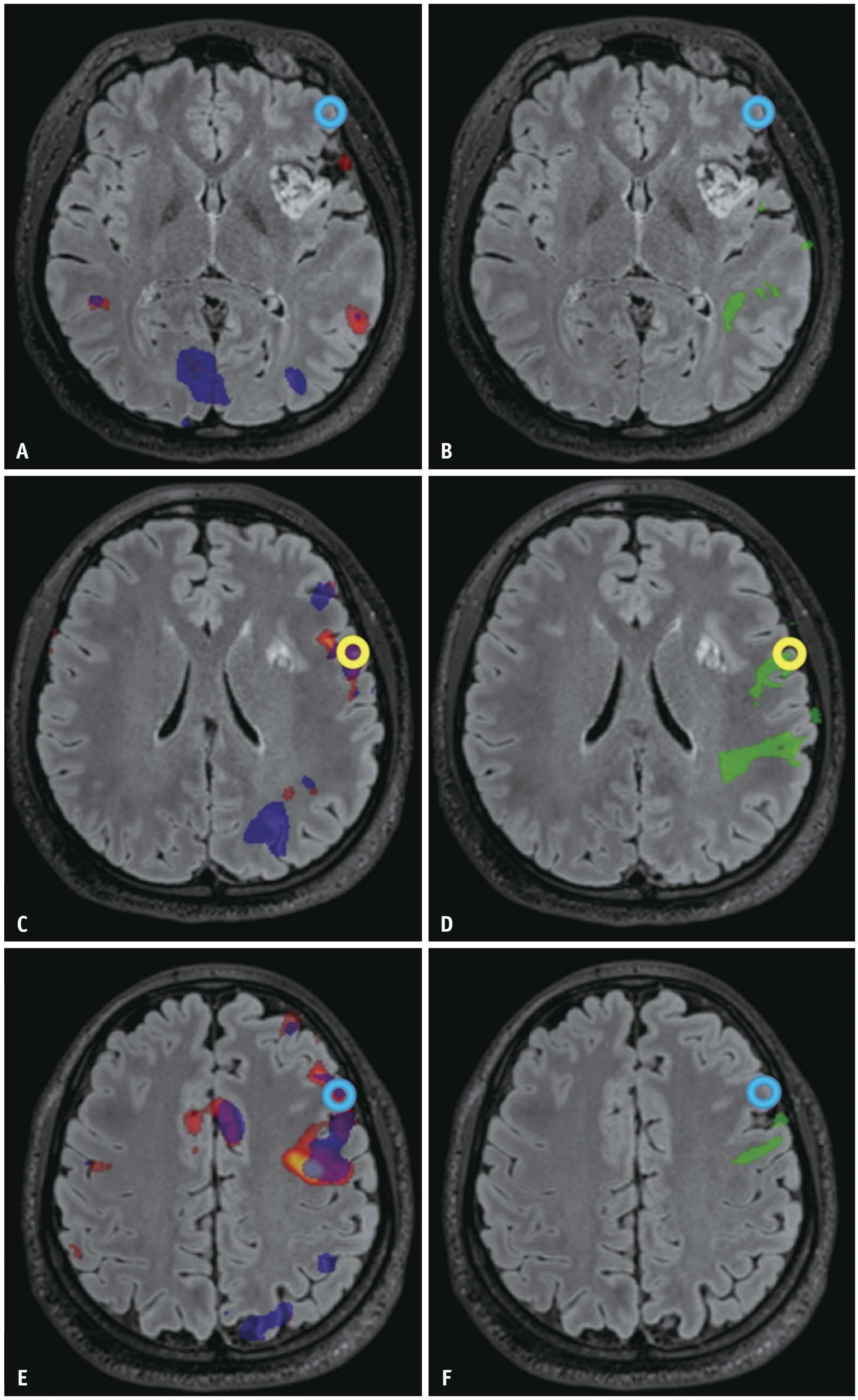

Fig. 2. Axial fMRI **(A, C, E)** and DTI-t **(B, D, F)** images are overlaid on 3D-FLAIR images in a 24-year-old female with a papillary glioneuronal tumor in the left insula. BOLD fMRI activities with the verb generation task ($fMRI_{verb}$) are presented in red, and fMRI activities with the sentence completion task ($fMRI_{sentence}$) are shown in blue. The AF on DTI-t is shown in green. DCS tag locations are indicated in yellow if positive and in sky-blue if negative. No overlapping sky-blue DCS sphere with fMRI signal **(A)** and DTI-t **(B, F)** was counted as TN. Overlap of the yellow DCS sphere with $fMRI_{verb}$ and $fMRI_{sentence}$ **(C)** and DTI-t **(D)** was counted as TP. Overlap of the sky-blue DCS sphere with the $fMRI_{verb}$ and $fMRI_{sentence}$ **(E)** was counted as FP. AF = arcuate fasciculus, DCS = direct cortical stimulation, DTI-t = diffusion tensor imaging-derived tractography, fMRI = functional magnetic resonance imaging, FP = false positive, TN = true negative, TP = true positive, FLAIR = fluid-attenuated inversion recovery, BOLD = based on blood oxygen level dependence

with 13 years of neuroimaging experience). The seed ROI was placed in the deep white matter of the posterior parietal portion of the superior longitudinal fasciculus, which appeared as a green structure in the coronal plane. The target ROI was placed on the descending portion of the superior longitudinal fasciculus in the posterior temporal lobe, which is visible as the blue lateral aspect of the splenium of the corpus callosum in the transverse plane. The mean volume ± standard deviations of seed and target ROIs were 47.02 ± 13.80 mm^3 and 35.55 ± 13.78 mm^3, respectively. On DTI-t, the cortical endpoint of the AF in the inferior frontal region was considered the Broca's area.

Intraoperative DCS

DCS was executed with the "asleep-awake-asleep" protocol [22]. After the craniotomy, the patient awakened, and DCS was performed to identify the speech arrest site. The initiating gyrus of DCS was at the preoperative fMRI- or DTI-t-positive site. Tumor resection was performed to avoid candidates for Broca's area localized using preoperative language mapping and DCS.

Intraoperative CCEP

The CCEP monitoring was performed under total intravenous anesthesia with continuous infusion of propofol (effect site concentration: 3–5 µg/mL) and remifentanil (effect site concentration: 3–5 ng/mL). The details of the CCEP procedure have been described previously [15]. After the dural incision, electrical stimulation was applied to the preoperative positive language sites in the frontal lobe. The electrical strip of the frontal lobe was repositioned to stimulate a different frontal gyrus, and a positive potential signal was detected using an electrical grid in the temporal lobe.

Comparative Analysis between Preoperative and Intraoperative Language Mapping

The tags were defined as all sites intraoperatively stimulated by DCS or CCEP confirmed after the operation video review. The tags were registered and numbered on the reconstructed brain images using Mango software (http://ric.uthscsa.edu/mango/), which automatically showed tags on the corresponding axial, sagittal, and coronal MR images. Several preoperatively positive language sites away from the craniotomy that were not exposed during surgery, making surface stimulation impossible, were excluded from the analysis. A site-by-site comparison between preoperative (fMRI or DTI-t) and intraoperative (DCS or CCEP) language mapping allowed us to categorize tags as true positive (TP), false negative (FN), true negative (TN), or false positive (FP): "TP" if the DCS or CCEP positive tag is within the same gyrus and less than 1 cm from the fMRI or DTI-t positive site; "FN" if the DCS or CCEP positive tag is located in a different gyrus or 1 cm away from the fMRI or DTI-t positive site; "TN" if the DCS or CCEP-negative tag is located in a different gyrus or 1 cm apart from the fMRI or DTI-t positive site; and "FP" if the DCS or CCEP-negative tag is located within the same gyrus and less than 1 cm from the fMRI or DTI-t positive site (Fig. 2). The same comparative analysis was performed in previous studies [5,23,24].

When analyzing fMRI positivity, verb generation ($fMRI_{verb}$) and sentence completion tasks ($fMRI_{sentence}$) were considered separately and in combination ($fMRI_{any}$ and $fMRI_{both}$), where $fMRI_{any}$ indicates the area in which $fMRI_{verb}$ or $fMRI_{sentence}$ activity was positive, and $fMRI_{both}$ indicates the area in which both $fMRI_{verb}$ and $fMRI_{sentence}$ activities were positive.

Statistical Analysis

The numbers of TP, TN, FP, and FN tags were computed for each patient. The sensitivity and specificity for preoperative Broca's area mapping were calculated on a per-tag basis according to the imaging methods and fMRI tasks.

For tags with fMRI- or DTI-t-positive signals (TP or FP tags), the rate of TP tags was calculated based on the concordance or discordance between fMRI and DTI-t. When fMRI and DTI-t results were concordant (TP or FP), the proportion of TP tags indicated a perfect match. When fMRI and DTI-t results were discordant, TP tag rates were calculated for fMRI and DTI-t, respectively.

Differences in sensitivity and specificity between fMRI and DTI-t, and between low- and high-grade gliomas, were compared using logistic regression with a generalized estimating equation to account for multiple data within a subject. The Bonferroni correction method was applied for multiple comparisons, with $P < 0.0125$ (= 0.05/4). Statistical analyses were performed using SAS 9.4 (SAS Institute). All statistical analyses were performed in the DCS or CCEP subgroups.

RESULTS

Twenty-six patients were enrolled and the relevant clinical characteristics of the study population are presented in Supplementary Table 2. There were 13 males and 13 females with ages ranging from 23 to 74 years (median, 57 years).

Table 1. Per-tag Basis Analysis for Sensitivity and Specificity

	$fMRI_{sentence}$	$fMRI_{verb}$	$fMRI_{any}$	$fMRI_{both}$	DTI-t	*P*			
						$fMRI_{sentence}$ vs. DTI-t	$fMRI_{verb}$ vs. DTI-t	$fMRI_{any}$ vs. DTI-t	$fMRI_{both}$ vs. DTI-t
All (DCS + CCEP), n = 266									
Sensitivity	34.0 (18/53) [21.5–48.3]	30.2 (16/53) [18.3–44.3]	43.4 (23/53) [29.8–57.7]	20.8 (11/53) [10.8–34.1]	52.8 (28/53) [38.6–66.7]	0.073	0.018	0.350	0.002*
Specificity	84.0 (179/213) [78.4–88.7]	91.1 (194/213) [86.4–94.5]	81.7 (174/213) [75.8–86.6]	93.4 (199/213) [89.2–96.4]	94.8 (202/213) [90.9–97.4]	0.001*	0.112	< 0.001*	0.498
DCS, n = 100									
Sensitivity	69.2 (9/13) [38.6–90.9]	38.5 (5/13) [13.9–68.4]	76.9 (10/13) [46.2–95.0]	30.8 (4/13) [9.1–61.4]	92.3 (12/13) [64.0–99.8]	0.299	0.003*	0.367	0.006*
Specificity	77.0 (67/87) [66.8–85.4]	83.9 (73/87) [74.5–90.9]	72.4 (63/87) [61.8–81.5]	88.5 (77/87) [79.9–94.3]	93.1 (81/87) [85.6–97.4]	0.001*	0.013	< 0.001	0.166
CCEP, n = 166									
Sensitivity	22.5 (9/40) [10.8–38.5]	27.5 (11/40) [14.6–43.9]	32.5 (13/40) [18.6–49.1]	17.5 (7/40) [7.3–32.8]	40.0 (16/40) [24.9–56.7]	0.134	0.259	0.530	0.046
Specificity	88.9 (112/126) [82.1–93.8]	96.0 (121/126) [91.0–98.7]	88.1 (111/126) [81.1–93.2]	96.8 (122/126) [92.1–99.1]	96.0 (121/126) [91.0–98.7]	0.101	> 0.999	0.079	0.729

$fMRI_{any}$ indicates any region with $fMRI_{verb}$ or $fMRI_{sentence}$ activity; $fMRI_{both}$ is defined as a region with both $fMRI_{verb}$ and $fMRI_{sentence}$ activity. For sensitivity and specificity, data are presented as percentages with the numerator/denominator in parentheses. Numbers in brackets indicate 95% confidence intervals. *$P < 0.0125$ (Bonferroni corrected $P < 0.05/4 = 0.0125$ was used as a statistical threshold). CCEP = corticocortical evoked potential, DCS = direct cortical stimulation, DTI-t = diffusion tensor imaging-derived tractography, fMRI = functional magnetic resonance imaging

Table 2. Number and Proportion of Tags According to fMRI and DTI-t Positivity

	All	DCS	CCEP
Tags with $fMRI_{any}$ or DTI-t positive	30.8 (82/266)	41 (41/100)	24.7 (41/166)
Tags with the same category for $fMRI_{any}$ and DTI-t	23.2 (19/82)	26.8 (11/41)	19.5 (8/41)
Tags with different categories for $fMRI_{any}$ and DTI-t	76.8 (63/82)	73.2 (30/41)	80.5 (33/41)
Tags with $fMRI_{both}$ or DTI-t positive	19.5 (52/266)	25.0 (25/100)	16.3 (27/166)
Tags with the same category for $fMRI_{both}$ and DTI-t	21.2 (11/52)	24.0 (6/25)	18.5 (5/27)
Tags with different categories for $fMRI_{both}$ and DTI-t	78.8 (41/52)	76.0 (19/25)	81.5 (22/27)

Data are percentages of the numerator/denominator in parentheses. The tags indicate the intraoperative stimulation sites using DCS or CCEP. Positive tags indicate intraoperative speech arrest sites on DCS and localized language areas on CCEP. The categories indicate true positives, true negatives, false positives, and false negatives. $fMRI_{any}$ indicates any region with $fMRI_{verb}$ or $fMRI_{sentence}$ activity, and $fMRI_{both}$ was defined when a region had both $fMRI_{verb}$ and $fMRI_{sentence}$ activity. CCEP = corticocortical evoked potential, DCS = direct cortical stimulation, DTI-t = diffusion tensor imaging-derived tractography, fMRI = functional magnetic resonance imaging

A total of 226 tags were tested intraoperatively, comprising DCS in nine patients (34.6%) with 100 sites (44.2%) and CCEP in 17 patients (65.4%) with 166 sites (73.5%). Among the 226 sites, 13 of 100 tags (13.0%) were DSC-positive, and 40 of 166 tags (24.1%) were CCEP-positive. The results of the preoperative language mapping for Broca's area are listed in Supplementary Table 3.

Performance of Preoperative Language Mapping

All 26 patients were right-handed, and fMRI revealed successful lateralization of the Broca's area in the left hemisphere. The sensitivity and specificity of preoperative Broca's area mapping based on the per-tag analysis are presented in Table 1. For all 266 intraoperative stimulation sites, t-DTI showed the highest specificity (94.8% [202/213]). The specificities of $fMRI_{both}$ (93.4% [199/213]) and $fMRI_{verb}$ (91.1% [194/213]) were not significantly different from those of DTI-t ($P = 0.498$ and $P = 0.112$, respectively). However, the specificities of $fMRI_{sentence}$ (84.0% [179/213]) and $fMRI_{any}$ (81.7% [174/213]) were significantly lower than those of DTI-t ($P = 0.001$ and $P < 0.001$, respectively). The sensitivities of fMRI and DTI-t were both < 53%.

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Table 3. The Rate of True Positive According to fMRI and DTI-t Positivity

	All	DCS	CCEP
Tags with $fMRI_{any}$ or DTI-t positive			
Tags with the same category for $fMRI_{any}$ and DTI-t	89.5 (17/19)	81.2 (9/11)	100 (8/8)
Tags with different categories for $fMRI_{any}$ and DTI-t			
For $fMRI_{any}$	9.5 (6/63)	3.3 (1/30)	15.2 (5/33)
For DTI-t	17.5 (11/63)	10.0 (3/30)	24.2 (8/33)
Tags with $fMRI_{both}$ or DTI-t positive			
Tags with the same category for $fMRI_{both}$ and DTI-t	81.8 (9/11)	66.7 (4/6)	100 (5/5)
Tags with different categories for $fMRI_{both}$ and DTI-t			
For $fMRI_{both}$	4.9 (2/41)	0 (0/19)	9.1 (2/22)
For DTI-t	46.3 (19/41)	42.1 (8/19)	50 (11/22)

Data are percentages, that is, the true positive rate, with the numerator/denominator in parentheses. The tags indicate the intraoperative stimulation sites using DCS or CCEP. Positive tags indicate intraoperative speech arrest sites on DCS and localized language areas on CCEP. The categories indicate true positives, true negatives, false positives, and false negatives. $fMRI_{any}$ indicates any region with $fMRI_{verb}$ or $fMRI_{sentence}$ activity, and $fMRI_{both}$ was defined when a region had both $fMRI_{verb}$ and $fMRI_{sentence}$ activity. CCEP = corticocortical evoked potential, DCS = direct cortical stimulation, DTI-t = diffusion tensor imaging-derived tractography, fMRI = functional magnetic resonance imaging

In the subgroup analysis of 100 DCS tags, DTI-t demonstrated the highest sensitivity (92.3% [12/13]) and specificity (93.1% [81/87]). The specificities of $fMRI_{both}$ (88.5% [77/87]) and $fMRI_{verb}$ (83.9% [73/87]) were not significantly different from those of DTI-t (*P* = 0.166 and 0.013). The sensitivities of $fMRI_{any}$ (76.9% [10/13]) and $fMRI_{sentence}$ (69.2% [9/13]) were not significantly different from those of DTI-t (*P* = 0.367 and *P* = 0.299, respectively). However, the specificities of $fMRI_{any}$ and $fMRI_{sentence}$, and the sensitivities of $fMRI_{both}$ and $fMRI_{verb}$ were significantly lower than those of DTI-t (all *P* < 0.0125) (Table 1).

In the subgroup analysis of the 166 CCEP tags, all fMRI and DTI-t showed specificities ranging from 88.1% [111/126] to 96.8% [122/126], with no significant differences between fMRI and DTI-t (all *P* ≥ 0.079). However, the sensitivities of all the methods were less than 40% (Table 1). The sensitivities and specificities of fMRI and DTI-t according to the aggressiveness of tumors are listed in Supplementary Table 4.

The Rate of True Positive According to fMRI and DTI-t Positivity

The number and proportion of tags according to fMRI and DTI-t positivity are presented in Table 2. Table 3 shows the rate of TP in tags with fMRI- or DTI-t-positive signals by dividing them into subgroups based on concordance or discordance between fMRI and DTI-t. A combination of fMRI tasks ($fMRI_{any}$ and $fMRI_{both}$) was used because the sensitivity was the highest in $fMRI_{any}$, and the specificity was the highest in $fMRI_{both}$.

The first analysis used $fMRI_{any}$ for fMRI. Among the 266 tags, 82 (30.8%) had a signal on preoperative $fMRI_{any}$ or DTI-t and 19 of the 82 tags (23.2%) showed the same tag category (TP or FP) for $fMRI_{any}$ and DTI-t. Seventeen of the 19 tags (89.5%) were TP tags, indicating perfect matches. In the subgroup analysis for DCS, 41 of 100 tags (41%) had a signal on preoperative $fMRI_{any}$ or DTI-t, 11 of 41 tags (26.8%) revealed an identical category for $fMRI_{any}$ and DTI-t, and nine of 11 tags (81.8%) were TP. Among the 166 tags with CCEP, 41 (24.7%) were $fMRI_{any}$ or DTI-t positive, and eight of the 41 (19.5%) tags were in the same category as $fMRI_{any}$ and AF positive. All eight tags (100%) were TP. On the other hand, when tags had different categories for $fMRI_{any}$ and DTI-t, the rate of TP tags was low (< 25%) in all as well as in the subgroup analyses.

Second, fMRI was used to obtain the fMRI results (Fig. 3). Among the 266 tags, 52 (19.5%) were $fMRI_{both}$ or DTI-t positive. Eleven of the 52 tags (21.2%) showed an identical category for the $fMRI_{both}$ and DTI-t, and nine of the 11 identical tags (81.8%) were TP. In the subgroup analysis of 100 DCS tags, 25 tags (25%) were $fMRI_{both}$ or DTI-t positive, and six of the 25 tags (24%) had the same tag category for $fMRI_{both}$ and DTI-t, resulting in TP in four of the six tags (66.7%). Of the 166 CCEP tags, 27 of 166 (16.3%) were $fMRI_{both}$ or DTI-t-positive. In five of the 27 tags (18.5%) for which the fMRI signal and AF on DTI-t were identical, the rate of TP was 100% (five of five tags). However, in the tags with discordant results between $fMRI_{both}$ and DTI-t, the rate of TP tags was 50% or less for both $fMRI_{both}$ and DTI-t.

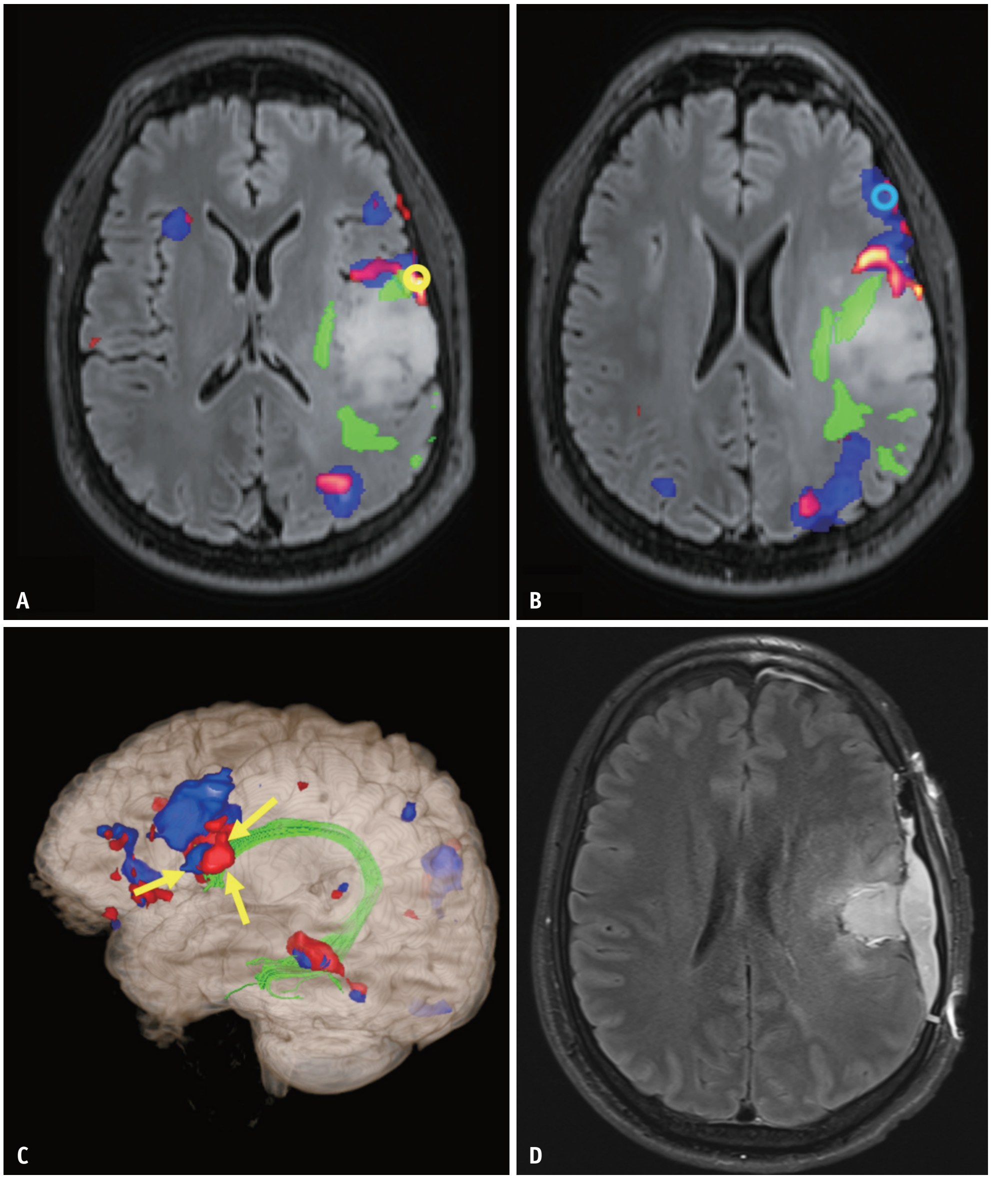

Fig. 3. We present the results of fMRI and DTI-t overlaid on 3D-FLAIR images in a 41-year-old male with oligodendroglioma, isocitrate dehydrogenase mutant and 1p/19q codeleted. BOLD fMRI activities with the verb generation task ($fMRI_{verb}$) are presented in red, while fMRI activities with the sentence completion task ($fMRI_{sentence}$) are shown in blue. AF on DTI-t is shown in green. CCEP tag locations are indicated in yellow if positive and in sky-blue circle if negative. **A:** The tag that shows both fMRI signal and DTI-t is considered a TP and is represented by the yellow CCEP sphere. **B:** The tag that only shows the fMRI signal is considered a FP and is represented by the sky-blue CCEP sphere. **C:** The fMRI and DTI-t results are overlaid on a sagittal view of the volume rendering image. The yellow arrows indicate the TP site, the same site as the yellow CCEP sphere in **A. D:** Immediate postoperative MRI reveals sub-totally resected tumors. Since the tumor involved the language area, maximal safe resection was performed to preserve the localized language area. AF = arcuate fasciculus, CCEP = corticocortical evoked potential, DTI-t = diffusion tensor imaging-derived tractography, fMRI = functional magnetic resonance imaging, FP = false positive; TP = true positive, FLAIR = fluid-attenuated inversion recovery, BOLD = based on blood oxygen level dependence, MRI = magnetic resonance imaging

DISCUSSION

In our study of Broca's area mapping, DTI-t showed high specificity with DCS and CCEP and high sensitivity with DCS. However, fMRI provided the most important information on the lateralization of language areas in the first stage. In addition, the specificities of $fMRI_{both}$ and $fMRI_{verb}$, and the sensitivities of $fMRI_{any}$ and $fMRI_{sentence}$ were not significantly different from those of DTI-t for DCS. In addition, the sensitivities and specificities of all fMRI tasks

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were not significantly different from those of DTI-t for CCEP. Furthermore, in the tags with preoperative fMRI or DTI-t positivity, the rate of TP was high when fMRI and DTI-t were concordant, but the rate of TP was low when fMRI and DTI-t were discordant. This suggests that the combined use of fMRI and DTI-t indicates a high probability of identifying language areas.

DTI-t showed the highest specificity for both DCS and CCEP. This result agrees with several previous studies that showed good performance of DTI-t compared with intraoperative stimulation [9,25-27]. The sensitivity of DTI-t differed depending on whether DCS or CCEP was used. The sensitivity of DTI-t for detecting DCS was high (93%). However, the sensitivity of DTI-t to CCEPs was low (40.0%). The low sensitivity of CCEP can be explained by the fact that CCEP was applied to a higher proportion of malignant gliomas with an extensive infiltrative nature, and the ratio of positive tags was larger in CCEP than in DCS. In addition, we applied the consistent TP definition for DCS and CCEP: "TP" if the DCS or CCEP-positive tag was within the same gyrus and less than 1 cm from the DTI-t positive site, the cortical endpoint of the AF. However, in contrast to Broca's area in the cortex, the AF is a white matter tract that spreads away from the cortex. Therefore, our results suggest that the criteria for comparing CCEP and DTI-t require further investigation in future studies.

The specificities of fMRI were 72.4%–96.8%. Among the fMRI tasks, the specificities of $fMRI_{both}$ and $fMRI_{verb}$ were as high as those of DTI-t. The sensitivity of fMRI was 20%–76.9%. Although the sensitivities of $fMRI_{any}$ and $fMRI_{sentence}$ were 76.9% and 69.2% for DCS, respectively, all fMRI tasks revealed low sensitivities of 17.5%–32.5% for CCEP. Similar to this, fMRI results for evaluating eloquent language areas have been heterogeneous [5,23,24,28-32]. Significant limitations of clinical fMRI include the intrinsic foundation of the BOLD signal, neurovascular uncoupling, and venous signal bias [28]. In addition, the tasks, acquisition, processing, and interpretation of fMRI data were not standardized. Despite these limitations, previous studies have suggested that the combined use of various fMRI tasks might increase the sensitivity and specificity of language site detection [24]. Our results agree with these results because $fMRI_{any}$ showed higher sensitivity and $fMRI_{both}$ demonstrated higher specificity than $fMRI_{verb}$ or $fMRI_{sentence}$.

In clinical practice, the comprehensive interpretation of positive signals from variable preoperative imaging (i.e., fMRI signals during sentence completion tasks, fMRI signals during verb generation tasks, and AF on DTI-t) is challenging. It is difficult to find studies investigating the possibility of a language area at a site with both fMRI and t-DTI positivity. Therefore, we attempted to clarify the significance of fMRI- or DTI-t-positive sites by investigating the rate of TP according to the concordance of the tag categories between fMRI and DTI-t. First, tags with concordant fMRI and DTI-t results showed much higher TP rates than tags with discordant results. This suggests that a region with both fMRI and DTI-t-positive signals represents a high possibility of being an essential language. Second, we recommend the use of $fMRI_{both}$ and $fMRI_{any}$ for the combined interpretation of fMRI and DTI-t, because tags with $fMRI_{any}$ and DTI-t positivity represented a higher rate of TP than those with $fMRI_{both}$ and DTI-t positivity.

This study had several limitations. First, only a small number of patients were included. However, this number was similar to that reported in a recent meta-analysis [4]. Second, although we acquired fMRI and DTI-t in one patient, DCS and CCEP were not performed in the same patient. Therefore, we do not fully understand the discordant sensitivity between DCS and CCEP. Third, we applied the SMS technique to DTI-t and fMRI, which may have improved preoperative language mapping. Because we did not compare DTI-t and fMRI with and without the SMS technique, its added value could not be fully evaluated. Finally, we used CCEP and DCS as reference standards. Although language mapping with CCEP monitoring is not generally used, several studies have validated it as an alternative method when DCS is not feasible [9,15,16].

In conclusion, fMRI enabled the lateralization of the language area in the first stage. Both fMRI and DTI-t are specific and sensitive methods, except for the low sensitivity when compared with CCEP. Among the variable positive signals from the fMRI tasks and DTI-t, the site with both fMRI and DTI-t positivity was the most important candidate for an essential language area. Therefore, combining fMRI and DTI-t can help to target intraoperative stimulation sites and improve surgical efficiency.

Supplement

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Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Seung Hong Choi, a contributing editor of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

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REFERENCES

1. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med* 2008;358:18-27
2. Vassal F, Schneider F, Boutet C, Jean B, Sontheimer A, Lemaire JJ. Combined DTI tractography and functional MRI study of the language connectome in healthy volunteers: extensive mapping of white matter fascicles and cortical activations. *PloS One* 2016;11:e0152614
3. Costabile JD, Alaswad E, D'Souza S, Thompson JA, Ormond DR. Current applications of diffusion tensor imaging and tractography in intracranial tumor resection. *Front Oncol*

2019;9:426
4. Weng HH, Noll KR, Johnson JM, Prabhu SS, Tsai YH, Chang SW, et al. Accuracy of presurgical functional MR imaging for language mapping of brain tumors: a systematic review and meta-analysis. *Radiology* 2018;286:512-523
5. Bizzi A, Blasi V, Falini A, Ferroli P, Cadioli M, Danesi U, et al. Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. *Radiology* 2008;248:579-589
6. Hill VB, Cankurtaran CZ, Liu BP, Hijaz TA, Naidich M, Nemeth AJ, et al. A practical review of functional MRI anatomy of the language and motor systems. *AJNR Am J Neuroradiol* 2019;40:1084-1090
7. Smits M, Jiskoot LC, Papma JM. White matter tracts of speech and language. *Semin Ultrasound CT MR* 2014;35:504-516
8. Yamao Y, Matsumoto R, Kunieda T, Arakawa Y, Kobayashi K, Usami K, et al. Intraoperative dorsal language network mapping by using single-pulse electrical stimulation. *Hum Brain Mapp* 2014;35:4345-4361
9. Yamao Y, Suzuki K, Kunieda T, Matsumoto R, Arakawa Y, Nakae T, et al. Clinical impact of intraoperative CCEP monitoring in evaluating the dorsal language white matter pathway. *Hum Brain Mapp* 2017;38:1977-1991
10. Spena G, Nava A, Cassini F, Pepoli A, Bruno M, D'Agata F, et al. Preoperative and intraoperative brain mapping for the resection of eloquent-area tumors. A prospective analysis of methodology, correlation, and usefulness based on clinical outcomes. *Acta Neurochir* 2010;152:1835-1846
11. Setsompop K, Cohen-Adad J, Gagoski BA, Raij T, Yendiki A, Keil B, et al. Improving diffusion MRI using simultaneous multi-slice echo planar imaging. *Neuroimage* 2012;63:569-580
12. Feinberg DA, Setsompop K. Ultra-fast MRI of the human brain with simultaneous multi-slice imaging. *J Magn Reson* 2013;229:90-100
13. Xu J, Moeller S, Auerbach EJ, Strupp J, Smith SM, Feinberg DA, et al. Evaluation of slice accelerations using multiband echo planar imaging at 3 T. *Neuroimage* 2013;83:991-1001
14. Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibasaki H, et al. Functional connectivity in the human language system: a cortico-cortical evoked potential study. *Brain* 2004;127(Pt 10):2316-2330
15. Kim KM, Kim SM, Kang H, Ji SY, Dho YS, Choi YD, et al. Preservation of language function by mapping the arcuate fasciculus using intraoperative corticocortical evoked potential under general anesthesia in glioma surgery. *J Neurosurg* 2022;137:1535-1543
16. Saito T, Tamura M, Muragaki Y, Maruyama T, Kubota Y, Fukuchi S, et al. Intraoperative cortico-cortical evoked potentials for the evaluation of language function during brain tumor resection: initial experience with 13 cases. *J Neurosurg* 2014;121:827-838
17. Binder JR. *fMRI of language systems: methods and applications*. In: Faro S, Mohamed F, Law M, Ulmer J, eds. *Functional neuroradiology*. Boston: Springer, 2011:393-417
18. Zacà D, Jarso S, Pillai JJ. Role of semantic paradigms for optimization of language mapping in clinical FMRI studies. *AJNR Am J Neuroradiol* 2013;34:1966-1971
19. Voyvodic JT. Reproducibility of single-subject fMRI language mapping with AMPLE normalization. *J Magn Reson Imaging* 2012;36:569-580
20. Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol* 1999;45:265-269
21. Mori S, van Zijl PC. Fiber tracking: principles and strategies – a technical review. *NMR Biomed* 2002;15(7-8):468-480
22. Duffau H, Peggy Gatignol ST, Mandonnet E, Capelle L, Taillandier L. Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere. *J Neurosurg* 2008;109:461-471
23. Meier M, Ilmberger J, Fesl G, Ruge MI. Validation of functional motor and language MRI with direct cortical stimulation. *Acta Neurochir (Wien)* 2013;155:675-683
24. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery* 2003;52:1335-1347
25. Castellano A, Cirillo S, Bello L, Riva M, Falini A. Functional MRI for surgery of gliomas. *Curr Treat Options Neurol* 2017;19:34
26. Bello L, Gambini A, Castellano A, Carrabba G, Acerbi F, Fava E, et al. Motor and language DTI Fiber Tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. *Neuroimage* 2008;39:369-382
27. Leclercq D, Duffau H, Delmaire C, Capelle L, Gatignol P, Ducros M, et al. Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations. *J Neurosurg* 2010;112:503-511
28. Morales H. Current and future challenges of functional MRI and diffusion tractography in the surgical setting: from eloquent brain mapping to neural plasticity. *Semin Ultrasound CT MR* 2021;42:474-489
29. Pernet CR, Gorgolewski KJ, Job D, Rodriguez D, Storkey A, Whittle I, et al. Evaluation of a pre-surgical functional MRI workflow: from data acquisition to reporting. *Int J Med Inform* 2016;86:37-42
30. Ille S, Sollmann N, Hauck T, Maurer S, Tanigawa N, Obermueller T, et al. Impairment of preoperative language mapping by lesion location: a functional magnetic resonance imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation study. *J Neurosurg* 2015;123:314-324
31. Kuchcinski G, Mellerio C, Pallud J, Dezamis E, Turc G, Rigaux-Viodé O, et al. Three-tesla functional MR language mapping: comparison with direct cortical stimulation in gliomas. *Neurology* 2015;84:560-568
32. Trinh VT, Fahim DK, Maldaun MV, Shah K, McCutcheon IE, Rao G, et al. Impact of preoperative functional magnetic resonance imaging during awake craniotomy procedures for intraoperative guidance and complication avoidance. *Stereotact Funct Neurosurg* 2014;92:315-322