The ability to read and write is associated with a widely distributed cortical or subcortical neuro-network. Brain lesions in cases of acquired alexia or agraphia are distributed throughout the dominant network of the frontal to occipital lobes. These lesions are thought to be related to various subcortical fibers. Previous reports of alexia and agraphia have localized the disorders to a restricted area, the left inferior parietal lobule and, more specifically, the angular and supramarginal gyri. These findings imply that lesions resulting in alexia with agraphia may be related to damage in common subcortical pathways necessary for reading and writing, including cerebral white matter tracts.

Recent noninvasive diagnostic techniques such as functional MRI (fMRI) and diffusion tensor imaging (DTI) have enabled characterization of the neuroanatomical distribution of various functions within the brain. Regarding reading and alexia, previous fMRI studies have revealed that reading is performed by a dominant-hemisphere network of inferior frontal and temporoparietal areas that constitute a dorsal phonological route and occipitotemporal cortical regions that form a ventral orthographic reading route. The arcuate fasciculus (AF), which is part of the superior longitudinal fasciculus (SLF), may subserve the dorsal phonological route, while the inferior frontooccipital fasciculus (IFOF) and the inferior longitudinal fasciculus (ILF) may subserve the ventral orthographic route. However, DTI fiber tracking studies for reading are relatively sparse, and most prior studies have made assumptions regarding the specific white matter tracts that may be involved.

In terms of functional and structural aspects, the writing process has been associated with the lateral posterior parietal cortex in the dominant hemisphere. Within the lateral posterior parietal cortex, lesions in-
volving the angular gyrus have been reported to produce a writing impairment along with a disruption in reading, that is, agraphia with alexia.5,10,16 Conversely, damage to areas involving the superior parietal lobe only produce impaired writing, that is, apraxic agraphia.2,28 Previous functional studies using fMRI have identified several writing-related areas, including the superior parietal lobe, the supramarginal gyrus of the inferior parietal lobe, and the intraparietal sulcus.19,25,43 However, little is known about how these cortical regions interact with other cortical or subcortical sites and what the most crucial white matter tracts are in relation to the writing process.

Even though noninvasive fMRI was developed to study brain organization of cognitive function, it is still a relatively limited tool because the functional approach sometimes fails to demonstrate sufficient accuracy compared with direct brain stimulation during an awake craniotomy.

Here, we describe a case of transient alexia and agraphia elicited by intraoperative direct subcortical electrostimulation of a specific white matter tract in a patient who underwent an awake craniotomy for a left inferior parietal lobule glioma. To our knowledge, this is the first report to identify the subcortical fibers associated with both reading and writing via direct subcortical stimulation.

Case Report

History and Neuroimaging Findings. A 48-year-old right-handed businessman, with no remarkable medical history, presented with the chief complaint of a generalized seizure attack and was admitted to a neurosurgical department. Magnetic resonance imaging of his brain showed an abnormality of the left inferior parietal lobule, which was suspected to be a low-grade diffuse glioma (Fig. 1A). He was transferred to our neurosurgery department, and surgery was scheduled for 2 months later. Approximately 1 month later, however, T1-weighted MRI with Gd enhancement revealed enlarged regions inside the area that had the abnormality (Fig. 1B). The area with the highest uptake on PET with 11C-methionine (MET) appeared in the superficial part of the lesion (Fig. 1C), corresponding largely with the enhanced area seen on MRI. By contrast, PET with FDG revealed a region of high uptake in this lesion (Fig. 1D).

Neuropsychological Assessment. The third edition of the Wechsler Adult Intelligence Scale (WAIS-III) was administered to the patient before surgery, and it revealed impaired writing, that is, apraxic agraphia.5,28 Previous functional studies using fMRI have identified several writing-related areas, including the superior parietal lobe, the supramarginal gyrus of the inferior parietal lobe, and the intraparietal sulcus.19,25,43 However, little is known about how these cortical regions interact with other cortical or subcortical sites and what the most crucial white matter tracts are in relation to the writing process.

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Preoperative DTI. Three-dimensional T1-weighted MRI, conventional MRI (T1- and T2-weighted), and diffusion-weighted imaging data were acquired on a 3.0-T scanner (Trio, Siemens). All of the procedures for DTI were performed as described previously.45 The location of the white matter tracts, pyramidal tract, SLF, and IFOF were computed from the DTI data set as previously described using BrainLAB iPlan Cranial 2.6 (Fig. 2).27 Seeding was performed using two regions of interest (ROIs) for each fiber tracking for these tracts. The fractional anisotropy threshold and minimum fiber length were individually defined; these remained constant for the patient and were all below 0.2 and around 30 mm, respectively.

Operation. Because the tumor was located in the dominant hemisphere, the patient underwent an awake craniotomy while under local anesthesia. A wide parieto-occipital craniotomy was performed, and intraoperative neuronavigation was used to delineate the tumor. This technique allowed us to use intraoperative functional mapping, especially language mapping, cortical mapping, and subcortical mapping, using direct electrical stimulation. We used a bipolar stimulator with a 1-mm diameter...
and a 5-mm interelectrode distance (Unique Medical) to deliver a biphasic current (pulse frequency 60 Hz, single pulse phase duration 0.5 msec, amplitude 4–8 mA) to the brain of the awake patient.

First, cortical mapping was performed after opening the dura mater. We used object-naming tasks presented on a monitor to identify the cortical language sites affected by electrical stimulations. In succession, the patient was asked to perform an oral reading task, including the use of two types of Japanese words, “kanji” (Japanese morphograms) and “kana” (Japanese syllabograms), and a writing task. Speech and occupational therapists were present in the operating room to evaluate any disturbances of language, movement, reading, or writing. Awake cortical mapping allowed us to detect the postcentral gyrus, whose stimulation elicited a convulsion around the mouth (Fig. 3), as well as the posterior portion of the superior temporal gyrus, whose stimulation generated phonemic paraphasia on the object-naming task. In addition, stimulation over the left superior parietal lobule induced a cessation of movement in the right upper limb. Oral reading and writing tasks did not induce any disturbance in the cortical mapping.

After cortical mapping was complete, the lesion resection was started at the anterior border of the tumor (Tags B and C, Fig. 3). We removed the tumor to the level of the white matter under the angular gyrus, while frequently checking the patient’s response using subcortical stimulation. At the end of the resection, approximately 4 cm in depth from the brain surface, stimulation was applied over the medial, anterior, and superior parts of the tumor cavity; this resulted in semantic paraphasia when stimulated during the picture-naming task (Tag 31, Fig. 4). We also had the patient perform a sentence-repetition task to assess whether this part of the tumor cavity was related to the SLF and found that he was able to repeat sentences when the site was stimulated. A semantic test of association, the pyramid and palm tree test, was visually presented to the patient, and we found that there were no disturbances in the test during stimulation of this site. The patient participated in an oral reading task in which sentences written in Japanese words were presented on a screen. The patient’s task was to read aloud all of the displayed sentences. Upon stimulation of this site, the patient abruptly stopped speaking. Lastly, the writing task required the patient to write down a kanji. For example, if the cue read “grass,” the patient might write the “草” kanji. When we electrically stimulated the patient’s brain just after we started giving a cue, the patient did not write any characters at all. Likewise, when we stimulated the brain region after we finished giving a cue, the patient’s writing would stop midcourse. Tumor removal was completed using subcortical mapping to identify the deep boundaries of the tumor.

Postoperative Course. Just after the surgery, the patient experienced a worsening in calculation; however, this symptom gradually resolved in 2 weeks. There were no remarkable deteriorations regarding language, oral reading, and writing or in movement of the upper and lower extremities. On postoperative MRI, we were able to confirm the subtotal resection, as more than 90% of the tumor was resected and tumor residue was located deep within the anterior, superior, and deep part of the angular gyrus. This produced disruptions of language, oral reading, and writing during intraoperative subcortical stimulation (Fig. 5). The neuropathological examination revealed a WHO Grade IV glioblastoma. Postoperative
neuropsychological assessment was performed with the use of the WAIS-III, SLTA, and WMS-R 3 months after the awake craniotomy.

Although the WAIS-III showed almost the same average verbal, performance, and full-scale IQs as the preoperative values, the score for processing speed deteriorated from 102 to 81. On the SLTA test, the ability for multiplication and division was not changed. On the other hand, verbal memory (from 88 to 101) and visual memory (from 98 to 108) on the WMS-R were rather improved compared with the preoperative scores.

**Postoperative DTI.** As previously reported,\textsuperscript{21,42,51} we combined postoperative DTI tractography with the results of intraoperative mapping. The subcortical fibers were constructed from DTI data by positioning the ROI within the anterior, superior, and deep part of the angular gyrus. This was done in an attempt to identify the white matter fibers associated with language, oral reading, and writing. Notably, the calculated fiber tracts were deep parts of IFOF fibers from the temporal stem, toward the superior parietal lobule (Fig. 5).

**Discussion**

**Judgment of No Reading or Writing**

In the current case, the patient completely stopped both reading and writing tasks on direct subcortical stimulation at the deep part of the surgical cavity. When the patient was asked why he had stopped writing any words, he explained that he did not know what next step to take, although he was able to move his hands to write. In addition, he was able to move his upper and lower extremities for a simple movement task. These findings suggest that this symptom was not related to the specific hand movement necessary in forming letter shapes, meaning that a disruption in subcortical activity might not be associated with the negative motor network.\textsuperscript{37}

With respect to the patient's cessation of reading following stimulation, it was difficult to assess whether this symptom was due to alexia or to complete anarthria. However, the brain region that was responsible for producing the disruption in reading (as assessed through response to stimulation) was very close to the deep parts of the IFOF, far apart from the SLF III (the main pathway connecting the superior marginal gyrus to the ventral premotor and prefrontal areas) according to postoperative DTI tractography.\textsuperscript{20} Therefore, our results demonstrate that the dorsal IFOF fibers in the deep parietal lobe are associated with both reading and writing processes.

**Reading and Alexia**

Reading and writing constitute a way to represent language in the physical environment. The left inferior parietal lobule (angular and supramarginal gyri) is known to contain regions in which alexia and agraphia have been localized; however, the anatomical connectivity of the subcortical fibers involved is still poorly understood.

Two distinct neural routes have been shown to be involved in reading processes: a dorsal phonological route and a ventral orthographic route.\textsuperscript{18,36} The dorsal phonological route involves the left temporoparietal junction, including the posterior superior temporal gyrus, angu-
lar gyrus, supramarginal gyrus, and opercular part of Broca’s area. This dorsal route has been associated with phonological processing and grapheme-to-phoneme mapping in phonological analysis. Therefore, it has been associated with word decoding through the indirect graphophonological route. In contrast, the ventral orthographic system is in the left occipitotemporal region near the fusiform gyrus. This region is often referred to as the “visual word form area” (VWFA) and has been associated with fluent reading and the automatic processing of visual word form perception. Based on the location of these two routes, it was thought that the AF might serve as the dorsal phonological route and that the IFOF and ILF might serve as the ventral orthographic route.

Furthermore, Vandermosten et al. suggested that the dorsally located AF seems to be implicated in the phonological aspects of speech perception, whereas the ventrally running IFOF may be implicated in semantic aspects of speech recognition. However, it is still unclear how the AF or IFOF are directly related to reading processes, because the current technique of standard DTI tractography is not sufficient for investigating the functional information of tracts. In the current report, we integrated the intraoperative functional mapping findings with the results of postoperative DTI fiber tracking studies. Although all of these fascicles—AF, IFOF, or ILF—are very close to the surgical cavity, the DTI study revealed that the deeper IFOF runs around the medial, anterior, and superior parts of the tumor cavity. The dorsal IFOF fibers connecting the frontal lobe to the superior parietal lobule may play a significant role in the reading-related process.

**Writing and Agraphia**

Writing is also one of the complexities of language modalities, involving many different processes. Recently, fMRI studies confirmed that the act of writing activated a network in the dominant hemisphere, including the superior and inferior parietal lobules, second frontal convolution, premotor areas, and supplementary motor area. Furthermore, some studies have shown that the functional components of writing can be partially separated into selective pathways within the cerebral lobules. Similar to the brain networks responsible for reading, those responsible for writing have been postulated to involve a dual route model. While the supramarginal and posterior temporal gyrus could be the neuroanatomical substrates of the phonological process (sound-letter or phoneme-grapheme conversion), lesions of the angular gyrus were more likely to be involved in symptoms of lexical agraphia (the whole-word retrieval process). Segal and Petrides demonstrated that the rostral part of the superior parietal lobule of the language-dominant hemisphere serves as the critical high-level motor control area in the context of a left hemisphere somatic motor circuit involved in the act of writing. Additionally, using intraoperative electrical mapping, Scarone and colleagues demonstrated that language and writing functions are associated with a network involving at least 5 zones: superior parietal region, superior marginal gyrus, insula, second and third frontal convolutions, and supplementary motor area. However, most of the previous studies have been unable to identify the specific subcortical fibers associated with the writing system.

**Inferior Frontooccipital Fasciculus**

The IFOF is a ventral white matter tract that directly connects the frontal lobe (orbitofrontal cortex and prefrontal region) with the posterolateral temporal and occipital lobes. This bundle crosses the temporal stem to pass from the ventral insular region to the temporal lobe. The IFOF was reported to be an important subcortical component of the semantic system given that intraoperative electrical stimulation of this fascicle induces semantic paraphasia with high reproducibility. Sarubbo et al. suggested that the IFOF consists of 2 layers: a superficial dorsal segment, which is anterosuperiorly directed and terminates in the inferior frontal gyrus, and a deep ventral segment, which consists of 3 portions (posterior, middle, and anterior). The superficial portion of the IFOF was connected to the superior parietal lobule and the posterior portion of the superior and middle occipital gyri, whereas the deep portion of the IFOF was connected to the posterior and basal temporal regions and the posterior portion of the inferior occipital gyrus. Of these, the posterior and middle portions of the deep fibers connecting the superior parietal lobule to the frontal lobe are involved in the semantic elaboration of language and visual recognition, or in the integration of the multimodal sensory inputs and motor planning functions, respectively. Therefore, Sarubbo et al. concluded that the IFOF may play a role in multimodal integration among the brain neuro-network.

With regard to reading, the deep ventral segment connecting the frontal lobe with the inferior occipital gyrus is particularly interesting as it connects the VWFA with the inferior frontal gyrus. In a tractography study of a patient with alexia, Epelbaum et al. suggested that there might be direct connections between the VWFA and the frontal semantic areas, sustained by the IFOF. In our case, we found transient alexia and agraphia elicited by intraoperative direct subcortical stimulation over the medial, anterior, and superior parts of the tumor cavity. Interestingly, the DTI fiber tracking study that followed intraoperative stimulation confirmed that the subcortical fiber in this region corresponded to the left IFOF connecting the frontal lobe to the superior parietal lobule and that this fiber is crucial for semantic processing. This part of the IFOF was consistent with deeper portions of the IFOF bundle in terms of anatomical structure. In conclusion, these findings suggest that intraoperative electrical stimulation in patients undergoing awake craniotomy can be a powerful tool to directly verify anatomical and functional connectivity.

Although this report provides novel information on a fiber tract responsible for reading and writing function, some limitations should be discussed. First, one limitation is associated with the inherent inaccuracy of coregistering intraoperative photographs with the fiber tracts created on preoperative MRI. If an ROI could be accurately positioned at the location of these fibers, which was identified with subcortical stimulation, and if we could map them back to the preoperative MR images, we would
obtain better knowledge about the cortical or subcortical neural network. Second, this report features only a single case, and thus a larger-scale study is required to further establish the role of this subcortical fiber pathway in semantic processing, writing, and reading. Therefore, the accumulation of additional evidence by brain mapping will be essential for our understanding of the subcortical network and will, we hope, become a useful guide for glioma surgeons.

Conclusions

We report the first case in which subcortical stimulation enabled the identification of the white matter tracts associated with reading and writing. These tracts were found to be deep portions of the dorsal IFOF that connects the frontal lobe to the superior parietal lobule. Although there are still unknown functional networks of the left inferior parietal lobule, this report may shed light onto the complex mechanisms underlying the reading and writing processes.

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Disclosure

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