

# Critical Neural Networks in Awake Surgery for Gliomas

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## Abstract

From the embarrassing character commonly infiltrating eloquent brain regions, the surgical resection of glioma remains challenging. Owing to the recent development of *in vivo* visualization techniques for the human brain, white matter regions can be delineated using diffusion tensor imaging (DTI) as a routine clinical practice in neurosurgery. In confirmation of the results of DTI tractography, a direct electrical stimulation (DES) substantially influences the investigation of cortico-subcortical networks, which can be identified via specific symptoms elicited in the concerned white matter tracts (eg., the arcuate fascicle, superior longitudinal fascicles, inferior fronto-occipital fascicle, inferior longitudinal fascicle, frontal aslant tract, sensorimotor tracts, optic radiation, and so forth). During awake surgery for glioma using DES, it is important to identify the anatomo-functional structure of white matter tracts to identify the surgical boundaries of brain regions not only to achieve maximal resection of the glioma but also to maximally preserve quality of life. However, the risk exists that neurosurgeons may be misled by the inability of DTI to visualize the actual anatomy of the white matter fibers, resulting in inappropriate decisions regarding surgical boundaries. This review article provides information of the critical neuronal network that is necessary to identify and understand in awake surgery for glioma, with special references to white matter tracts and the author's experiences.

Key words: glioma, awake surgery, white matter tract, tractography

## Introduction

Owing to recent developments in functional brain imaging, human cerebral neuronal and functional networks have been investigated, and this knowledge has contributed to neurosurgical fields, including brain tumor surgery.<sup>1)</sup> A glioma, which arises from glial cells, is a brain primary neoplasm invading the central nervous system. The tendency of this tumor type to infiltrate cortical and subcortical functional structures renders its treatment is challenging, and treatment has therefore been widely debated. The extended surgical resection of the glioma has been suggested to contribute to improvement of the prognosis;<sup>2)</sup> however, the functional connectivity, which is complex and composed of both cortical and subcortical networks, should be preserved to maintain functional outcomes.<sup>3)</sup> In order to take maximal advantage of the plasticity of the brain, “hodotopy,” named for the Greek “hodos” (path, referring to the subcortical fibers) and “topos” (place, referring to the cortex) is critically important to the surgical strategy for the treatment of gliomas.<sup>4)</sup>

It has been recently elucidated that cerebral functional cortical regions, which constitute a so-called “eloquent area,” have the potential to move and change dynamically, facilitated by subcortical white matter pathways.<sup>5)</sup> Direct electrical stimulation (DES) is a useful tool for brain mapping to investigate the cortical and subcortical functional complexity associated with brain plasticity. Stimulation under appropriate conditions interferes locally and transiently with a small cortical or axonal site, which might be connected only to a part of the network.<sup>1,6)</sup> Using this technique, an awake surgery for glioma in eloquent areas is now the gold standard, developed by the contribution not only of advancements in anesthesiology and electrophysiology but also of dedicated clinical neurosurgical experience.<sup>7–9)</sup> In addition to classic anatomical information regarding cerebral white matter connectivity, subcortical networks have been extensively elucidated by additional contributions from the awake brain mapping undertaken in glioma surgeries. Furthermore, the original methodology has provided new insights into the functional connectivity underlying not only sensorimotor and visuospatial language systems but also sociocognitive and multimodal systems such

**Table 1 Subcortical tracts, mapping tasks, and symptoms induced by the direct electrical stimulation**

Subcortical tracts	Tasks	Symptoms <sup>*</sup> )
<b>Arcuate fascicle</b>	<ul style="list-style-type: none"> <li>• Picture naming</li> <li>• Word repetition</li> </ul>	<ul style="list-style-type: none"> <li>• Phonemic paraphasia<sup>24)</sup></li> <li>• Repetition disturbance<sup>26)</sup></li> </ul>
<b>IFOF</b>	<ul style="list-style-type: none"> <li>• Picture naming</li> <li>• PPTT</li> </ul>	<ul style="list-style-type: none"> <li>• Semantic paraphasia<sup>44,45)</sup></li> </ul>
<b>Fronto-striatal tract</b>	<ul style="list-style-type: none"> <li>• Spontaneous movement</li> </ul>	<ul style="list-style-type: none"> <li>• Inhibition of movement<sup>67,72)</sup></li> </ul>
<b>SLF</b>	<p><b>I</b></p> <ul style="list-style-type: none"> <li>• Spatial 2-back test</li> </ul> <p><b>II</b></p> <ul style="list-style-type: none"> <li>• Line bisection test</li> </ul> <p><b>III</b></p> <ul style="list-style-type: none"> <li>• Picture naming</li> </ul>	<ul style="list-style-type: none"> <li>• Spatial working memory disturbance<sup>38)</sup></li> <li>• Visuospatial agnosia<sup>35)</sup></li> <li>• Articulatory disturbance<sup>24,29,31)</sup></li> </ul>
<b>Frontal aslant tract</b>	<ul style="list-style-type: none"> <li>• Picture naming</li> </ul>	<ul style="list-style-type: none"> <li>• Inhibition of speech<sup>72,75)</sup></li> </ul>
<b>Optic radiation</b>	<ul style="list-style-type: none"> <li>• 4-screen picture naming</li> </ul>	<ul style="list-style-type: none"> <li>• Phosphenes<sup>66)</sup></li> <li>• Blurred vision<sup>66)</sup></li> </ul>
<b>ILF (posterior part)</b>	<ul style="list-style-type: none"> <li>• Picture naming</li> <li>• Word reading</li> </ul>	<ul style="list-style-type: none"> <li>• Visual paraphasia<sup>55)</sup></li> <li>• Dyslexia<sup>50)</sup></li> </ul>
<b>Pyramidal tract</b>	<ul style="list-style-type: none"> <li>• Spontaneous movement</li> </ul>	<ul style="list-style-type: none"> <li>• Muscle contraction<sup>67)</sup></li> </ul>
<b>Somatosensory tract</b>	<ul style="list-style-type: none"> <li>• Subjective sensation</li> </ul>	<ul style="list-style-type: none"> <li>• Dysesthesia<sup>24)</sup></li> </ul>

IFOF: inferior fronto-occipital fascicle, ILF: inferior longitudinal fascicle, PPTT: pyramids and palm trees test, SLF: superior longitudinal fascicle. An asterisk shows reference numbers.

as working memory, attention, executive functions, and even consciousness.<sup>1)</sup>

In this study, we review reports of the critical neural networks investigated and identified via awake surgery for gliomas, with special reference to white matter tracts and our clinical experiences.

## Clinical Procedures

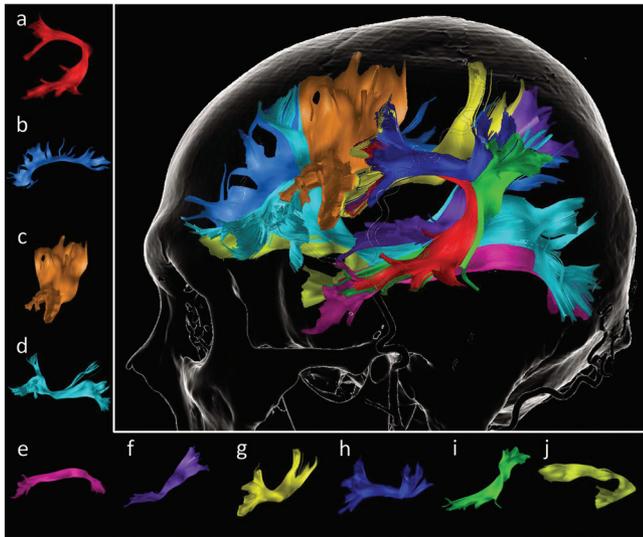
### Awake surgery and functional mapping

All surgical procedures were performed using an asleep–awake–asleep technique with DES mapping.<sup>10–12)</sup> A bipolar electrode with 5-mm spaced tips delivering a biphasic current (pulse frequency 60 Hz; single-pulse phase duration 1 ms; amplitude 1.5–5 mA) was used in all cases. During the awake phase, the intensity threshold was set either by evoking speech arrest when stimulating the ventral premotor cortex, or by evoking motor disorder via the stimulation of the primary motor cortex within the pre-central gyrus. Complete cortical mapping was achieved using the picture-naming, motor, passive sensory, line bisection, spatial 2-back, and facial expression and emotional tasks, after which resection was begun. Subcortical resection was stopped when DES reproduced specific findings and disorders during task execution. As shown in Table 1, task selection was determined by which white matter tracts and structures that needed to be preserved to maintain tract-specific functions were present near

the resection site. Positive mapping areas induced by DES on cortical and subcortical regions were marked via number tags and video-recorded.

### Tractography

Diffusion weighted (DW)-MR images were acquired preoperatively using a 3.0 Tesla MRI scanner (Signa Excite HDx 3.0T, General Electric Medical Systems). A series of diffusion-weighted axial images with (b-value = 1,000 s/mm<sup>2</sup>) and without (b-value = 0) a diffusion-sensitizing gradient along 30 directions were obtained. The other diffusion parameters were as following: time of repetition (TR) = 14,000 ms, time of echo (TE) = 69.6 ms, number of excitations (NEX) = 2, 60 axial slices with slice thickness = 2.5 mm with no interslice gap, and field of view (FOV) = 220 × 220 mm with a matrix = 88 × 88, resulting in an effective resolution of 2.5 mm<sup>3</sup> isotropic voxels. The DW-MR images were transferred to a workstation using iPlan Cranial 3.0 software (BrainLab, Feldkirchen, Germany), which reconstructed qualitative maps. Regions of interest targeting each white-matter tract were selected manually by referring to the diffusion tensor imaging (DTI)-tractography atlas and to results of previous studies.<sup>13,14)</sup> All three-dimensional tracts were reconstructed with fiber propagation stopped at a fractional anisotropy threshold of <0.18. An illustrative case with the tractography of a healthy adult is presented in Fig. 1.



**Fig. 1** An illustrative case of diffusion tensor imaging tractography in the left cerebral hemisphere of a healthy adult. Each tract is shown in a–j: a, arcuate fascicle (red); b, cingulate fascicle (sky blue); c, frontal aslant tract (brown); d, inferior fronto-occipital fascicle (cyan); e, inferior longitudinal fascicle (magenta); f, middle longitudinal fascicle (purple); g, superior longitudinal fascicle II (yellow); h, superior longitudinal fascicle III (blue); i, superior longitudinal fascicle-temporoparietal component (green); j, uncinate fascicle (yellowish green).

## White Matter Tracts and DESs

Specific symptoms could be transiently elicited by subcortical DES on the relevant subcortical white matter regions using appropriate tasks (Table 1). In this section, we describe the anatomo-functional characters of each white matter tract with reference to DES. Four illustrative cases of patients who underwent awake surgery for gliomas are presented with pre- and post-operative MRI, tractography, and intraoperative photographs in Figs. 1–4.

### Arcuate fascicle

Burdach (1822) was the first to designate the peri-sylvian tract, a group of fibers running deeply around the sylvian fissure, collectively as the “Fasciculus Arcutus” based on the shape of the long arch.<sup>15)</sup> The classic arcuate fascicle had been believed to connect Broca’s area in the frontal lobe to Wernicke’s area in the temporal lobe. Recent information regarding the arcuate fascicle suggest that the frontal terminations broadly include the pars opercularis and triangularis of the inferior frontal gyrus and the ventral premotor cortex, although most of the arcuate fascicle terminates

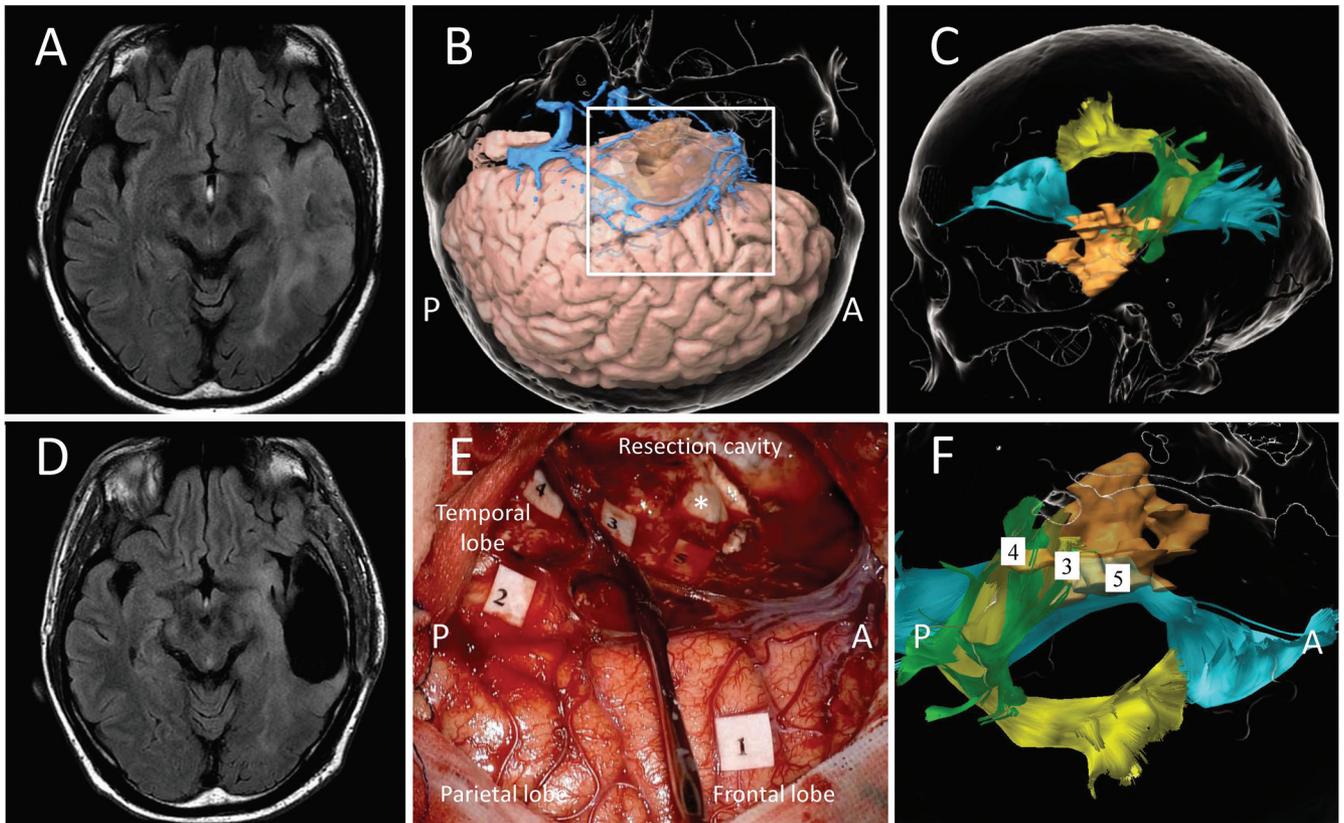
in the premotor area, as indicated by the results of recent postmortem fiber dissection and DTI/diffusion spectrum imaging (DSI) tractography studies.<sup>16–19)</sup> In contrast, the major temporal termination of the arcuate fascicle is in the posterior superior temporal gyrus and middle temporal gyrus; furthermore, cortex-sparing fiber dissection and DTI studies suggest that the arcuate fascicle may have extensions to the caudal inferior temporal gyrus (Fig. 2).<sup>20,21)</sup>

A dual-stream model of speech processing has been postulated, one stream of which is the dorsal stream involved in mapping phonological representation onto articulatory motor representations by connecting cortical regions in the frontal, temporal, and the parietal lobes.<sup>22)</sup> The left arcuate fascicle has been proposed to be the white matter fiber system most prominently related to auditory-motor integration in the dorsal stream. The disconnection syndrome of this bundle is thought to lead to conduction aphasia, characterized as a deficit in the ability to encode phonological information for production.<sup>23)</sup> During intra-operative subcortical mappings using the picture-naming task, DES along the arcuate fascicle exactly reproduces transient phonological paraphasia and repetition disturbance, rather than the articulatory disorders demonstrated via the stimulation of the superior longitudinal fascicle (SLF) III described below.<sup>24–26)</sup> An anomia, a symptom characteristic of conduction as reported in some studies, is also induced (Fig. 2).<sup>24,25)</sup>

### Superior longitudinal fascicle (SLF)

Dejerine, in 1852, was the first to use the term SLF and arcuate fascicle interchangeably.<sup>27)</sup> According to recent interpretations, however, the SLF does not appear to accurately coincide with the arcuate fascicle. The first tractography studies revealed that the “classic” arcuate fascicle was composed of three subcomponents—the anterior short segment, posterior short segment, and long segment.<sup>19,28)</sup> These are now called, respectively, SLF III, SLF-tp (temporo-parietal component), and the arcuate fascicle in the narrow sense. In the most recent anatomical conception of the peri-sylvian network, the SLF is a large tract composed of four subparts—SLF I, II, and III and SLF-tp.<sup>29)</sup> They run parallel with each other longitudinally from the parietal to the frontal lobe, except for SLF-tp, which vertically connects the temporal and parietal lobes (Fig. 2).

SLF III is the most lateral subpart of the SLF (also called the lateral, horizontal, or anterior segment of the SLF), which connects the supra-marginal gyrus



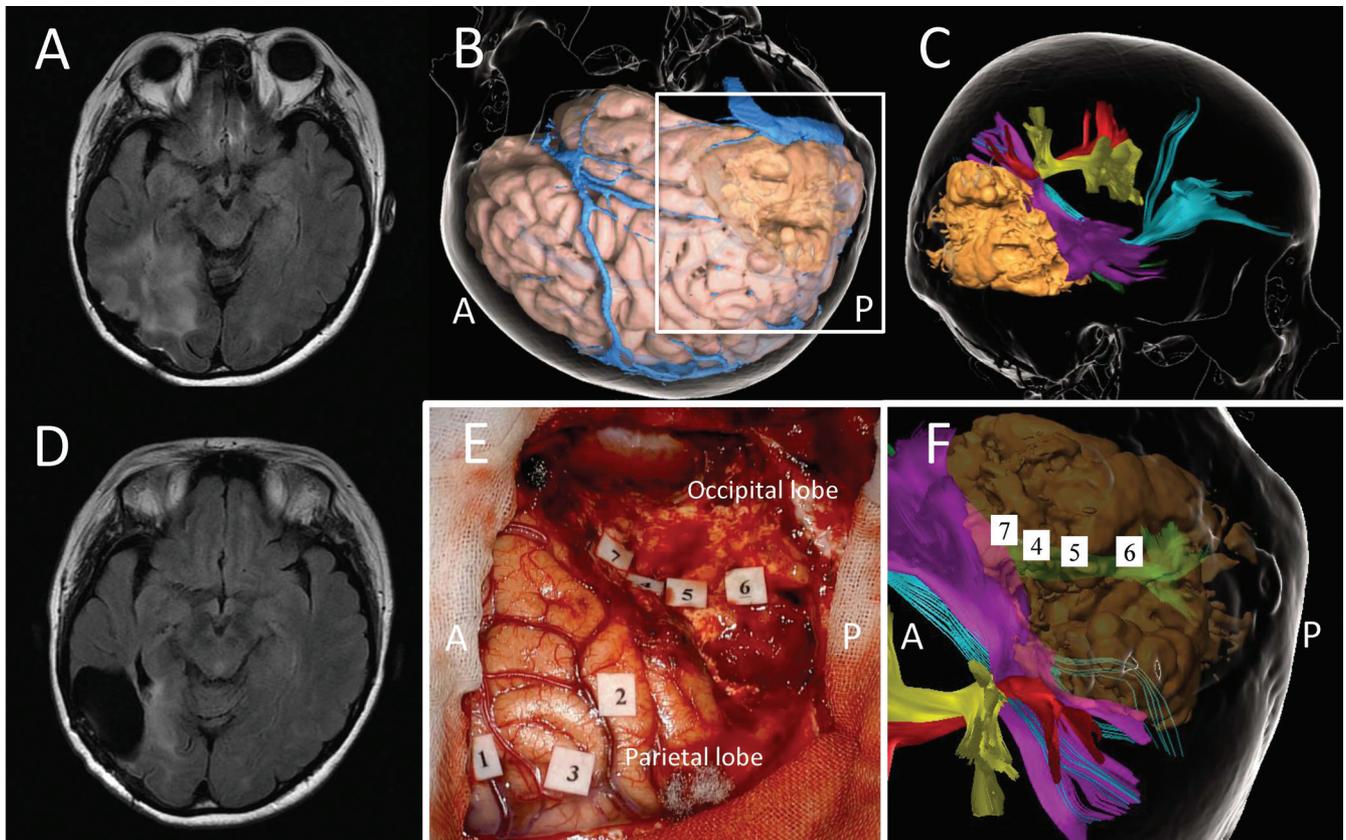
**Fig. 2** A case of left temporal low-grade glioma with intraoperative direct electrical stimulations. **A:** Preoperative FLAIR axial MRI showing a recurrent hyper lesion in left temporal lobe. **B:** Three-dimensional cortical image in operative view. **C:** Tractography showing the tumor (*beige*) infiltrating into the inferior fronto-occipital fascicle (*cyan*), the superior longitudinal fascicle-temporoparietal compartment (*green*), and the arcuate fascicle (*yellow*). **D:** Postoperative FLAIR axial MRI. **E and F** show an intraoperative photo and preoperative tractography within the *white square* in **B**. **E:** An intraoperative photo taken after surgical resection of tumor with preservation of positive mapping areas elicited by cortical and subcortical electrical stimulations. Anarthria was elicited in ventral region of precentral gyrus (tag 1), and anomia in the angular gyrus (tag 2); phosphene in right inferior quadrant area (tag 3) and right half area (tag 4) on the left optic radiation; semantic paraphasia on the inferior fronto-occipital fascicle (tag 5). An *asterisk* shows the head of hippocampus. **F:** Tags 3–5 in the subcortical positive mapping areas are overlapped on the preoperative tractography. **A** and **P** indicate the anterior and the posterior side, respectively.

and the ventral prefrontal cortex.<sup>19,30</sup> The stimulation of the left SLF III causes dysarthria and other impairments in articulatory processing in coordination with SLF II.<sup>14,24,29,31</sup> Repetition errors could also be interpreted as perturbations of articulatory and phonological processing caused by DES of SLF III and SLF-tp, respectively.<sup>29,32</sup>

SLF II connects the dorsal and prefrontal areas to the angular gyrus. The most prominent role of SLF II is in the processing of spatial awareness in the right hemisphere. Anatomical disconnections of the fronto-parietal network result in chronic left spatial neglect, especially in cases with damage to SLF II, which is the best predictor of this morbidity.<sup>33,34</sup> It is also possible to identify the subcortical SLF II *in vivo* by DES during awake craniotomy using

a line bisection task (Fig. 3).<sup>35</sup> Stimulation of SLF II can cause rightward deviations when DES transiently induces a left spatial unawareness. Successful examinations could spare postoperative neglect by detecting not only rightward but also leftward deviations even in the right hemisphere.<sup>36</sup>

Not only the function of SLF I but also its existence encompass some unverified issues. In a fiber dissection study, the SLF, including segments of I and II, could be dissected, with the exception of the SLF I.<sup>37</sup> However, DSI and spherical deconvolution tractography studies could demonstrate that the SLF I connects the precuneus with the superior frontal and anterior cingulate areas on the dorsal aspect of the main cingulum fibers, in a paracingulate or supracingulate location.<sup>21,37</sup> Our previous study



**Fig. 3** A case of recurrent low-grade glioma in the right temporal lobe. **A:** Preoperative FLAIR axial MRI showing a hyper lesion in right temporo-occipital area. **B:** Three-dimensional cortical image in operative view. **C:** Tractography with a recurrent tumor (*beige*); the inferior fronto-occipital fascicle (*cyan*), the superior longitudinal fascicle II (*red*) and III (*yellow*), and middle longitudinal fascicle (*purple*). **D:** Postoperative FLAIR axial MRI. **E** and **F** show an intraoperative photo and preoperative tractography within the *white square* in **B**. **E:** An intraoperative photo taken after surgical resection of tumor with preservation of positive mapping areas elicited by cortical and subcortical electrical stimulations. Cortical mappings: Dysesthesia of left hand in the postcentral gyrus (tag 1), and rightward deviation in the line bisection task (tags 2 and 3). Subcortical mappings: phosphene in the left superior quadrant area (tags 4–6) and topographical disorientation (tag 7). **F:** Tags 4–6 in the subcortical positive mapping areas are overlapped on the optic radiation (*green*) in the preoperative tractography. **A** and **P** indicate the anterior and the posterior side, respectively.

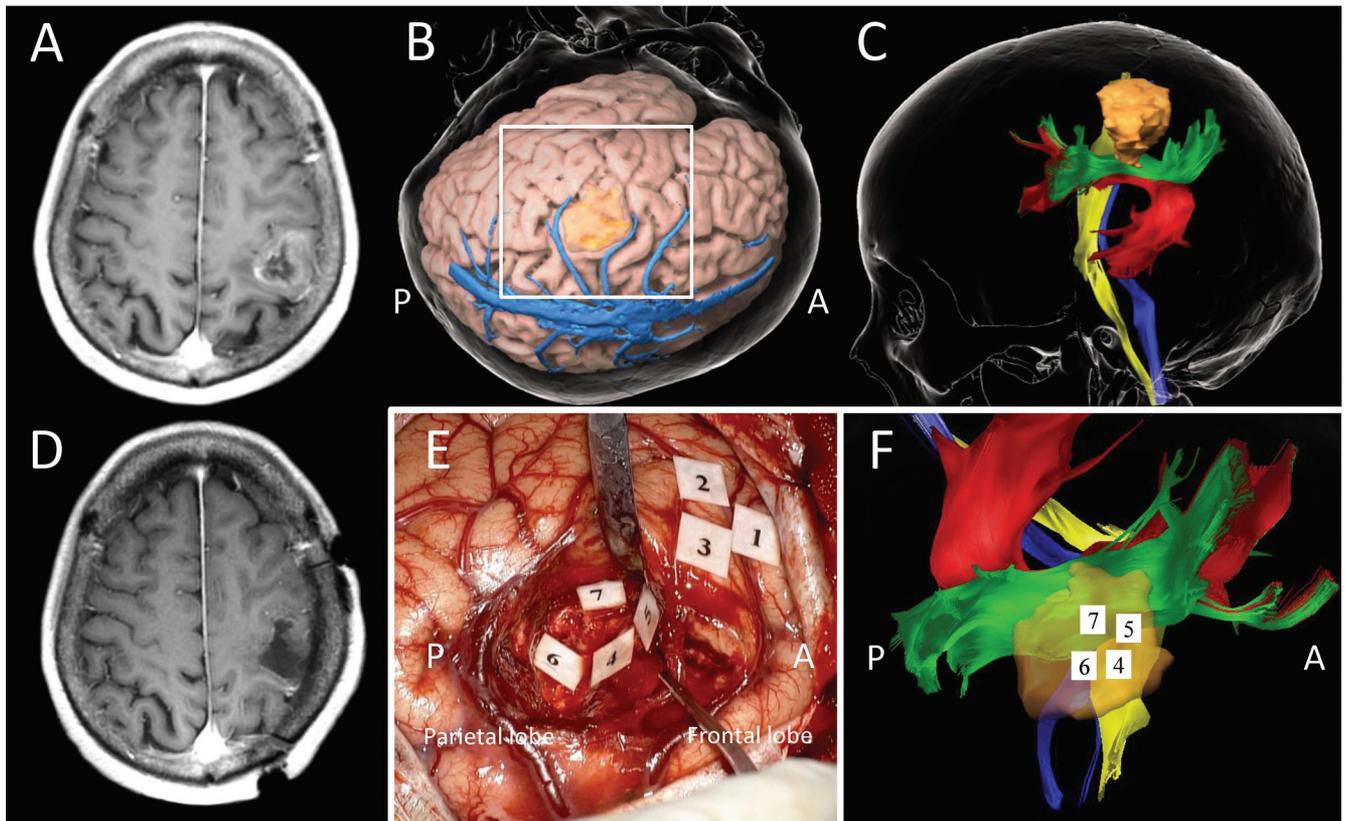
suggested that spatial working memory would be performed via parieto-frontal networks, especially with the right SLF I and II, damage to which caused chronic impairment of this function.<sup>38)</sup>

The SLF-tp, which is also called the vertical or posterior segment of the classic arcuate fascicle, connects the posterior temporal and inferior parietal lobes. This bundle may not be included in SLF subcomponents based on the anatomical feature of the “superior longitudinal” fascicle; however, it plays a role in phonological processing along with the arcuate fascicle as a part of dorsal stream of speech processing (Fig. 2).<sup>11,32,39,40)</sup> Some authors designate the arcuate fascicle as SLF-IV.<sup>40,41)</sup> These differing interpretations of peri-sylvian white matter pathways have caused unresolved confusion without enough

integration, also due to recent rapid advancements in white matter tractography studies.

#### Inferior fronto-occipital fascicle (IFOF)

The IFOF is an anterior–posterior white matter tract consisting of two layers; the superficial and deep layers. The former connects the temporo-basal and posterior occipital lobes with the inferior frontal gyrus, and the latter connects the middle frontal and dorso-lateral prefrontal cortex. Based on its wide distribution to the frontal cortices, the IFOF can be considered a “multi-function” bundle.<sup>42)</sup> In contrast to the dorsal stream of speech subserving phonological processing, the ventral stream, composed of the IFOF, predominates in language semantics.<sup>43)</sup>



**Fig. 4** A case of high-grade glioma located in left parietal lobe. **A:** Preoperative contrast enhanced- $T_1$  axial MRI showing an enhanced lesion in the left postcentral gyrus. **B:** Three-dimensional cortical image in operative view. **C:** Tractography showing the tumor (*beige*) near the pyramidal tract (*yellow*), somato-sensory tract (*blue*), the superior longitudinal fascicle III (*green*), and the arcuate fascicle (*red*). **D:** Postoperative FLAIR axial MRI. **E** and **F** show an intraoperative photo and preoperative tractography within the *white square* in **B**. **E:** An intraoperative photo taken after surgical resection of tumor with preservation of positive mapping areas elicited by cortical and subcortical electrical stimulations. Cortical mappings: Dysarthria was elicited in the precentral gyrus (tag 1), and dysesthesia in the postcentral gyrus (tags 2 and 3). Subcortical mappings: Involuntary movements of right arm (tag 4) and leg (tag 6) were reproduced on the pyramidal tract, and dysesthesias of right hand (tag 5) and fingers (tag 7) on the somatosensory tract. **F:** Subcortical positive mapping areas are overlapped on the preoperative tractography. **A** and **P** indicate the anterior and the posterior side, respectively.

Interestingly, the IFOF does not seem to exist in non-human primates, and could thus be considered the most important bundle in humans.<sup>1)</sup> In a picture-naming task, DES to this tract generates semantic paraphasia or anomia (Fig. 2), which can be confirmed to be disturbances of comprehension, including non-verbal semantic processing, using a semantic task such as the Pyramids and Palm Trees Test (PPTT).<sup>44,45)</sup> Multimodal participation in verbal and non-verbal semantic processing originates in the deep and superficial layers of the IFOF, respectively.<sup>46)</sup> As observed in the head of the caudate, verbal perseveration could also be induced by stimulation of the IFOF, but this does not persist until 3 months.<sup>47)</sup> In addition to language functions, furthermore, Duffau and his colleagues have made

the interesting suggestion that the IFOF might play a crucial role in the awareness of amodal semantic knowledge, which contributes to make the human what he is.<sup>1,45)</sup>

### Inferior longitudinal fascicle (ILF)

The ILF runs parallel to a direct pathway of the ventral stream as an indirect pathway with the uncinate fascicle (UF). A predominant part of the terminations lies in the occipito-parietal region and the ventral aspect of the temporal lobes. In the posterior region, the fibers, which are bound medially by the IFOF and laterally by the subcortical U fibers, run vertically from the posterior lingual and fusiform gyri and cuneus. At the ventral aspect of the occipito-temporal junction, the ILF changes

direction and runs horizontally in the white matter of the inferior temporal lobe, amygdala, and parahippocampal gyrus, and then connects to the origin of the uncinate fasciculus.<sup>28,41,48,49)</sup> The posterior part of the ILF is implicated in reading,<sup>50)</sup> and face and object recognition,<sup>51)</sup> whereas both the anterior and posterior parts of the ILF are involved in the processing of names,<sup>52)</sup> reading,<sup>53)</sup> and spoken language.<sup>54)</sup> In conclusion, the posterior “visual” part is involved in visual processing of objects or pictures, whereas the anterior part is involved in linking object representations to their lexical labels.<sup>54)</sup>

Intraoperative DES can induce alexia in the posterior part of ILF, frequently with anomia or phonemic paraphasia caused by simultaneous stimulation of the posterior segment of the arcuate fascicle (SLF-tp).<sup>50)</sup> The ILF does not seem to be essential in language semantic processing because the IFOF running above the ILF was shown to mainly function as a direct pathway in other intraoperative DES studies.<sup>55,56)</sup>

### Uncinate fascicle (UF)

The UF is one of the indirect pathways of the semantic ventral stream. It originates in the temporal pole, aggregates lateral to the ventral part of the claustrum, moves medially through the limen insula, and then relays information from the visual object form area via ILF to the pars orbitalis of the inferior frontal gyrus.<sup>28,49)</sup> The results of several studies suggested that the UF plays a potential role not only in semantics<sup>57)</sup> but also in auditory stimuli, recognition memory,<sup>58)</sup> and emotion.<sup>59)</sup> Nonetheless, the UF does not seem to be essential for language, and does not generate semantic paraphasia in DES due to IFOF compensation.<sup>60)</sup>

### Middle longitudinal fascicle

A temporo-parietal fiber bundle was first identified in a rhesus monkey in 1984 by using an *in vivo* technique with radioisotope injections, and named the middle longitudinal fasciculus (MdLF).<sup>61)</sup> The MdLF connects the angular gyrus with the superior temporal gyrus up to the temporal pole (Fig. 3). The tract could be a part of the ventral semantic route, but its functional role has not been elucidated despite recent evidence showing its existence by using fiber dissection.<sup>62)</sup> In addition, intraoperative DES on MdLF does not seem to generate any disorders.<sup>63)</sup>

### Optic radiation (OR)

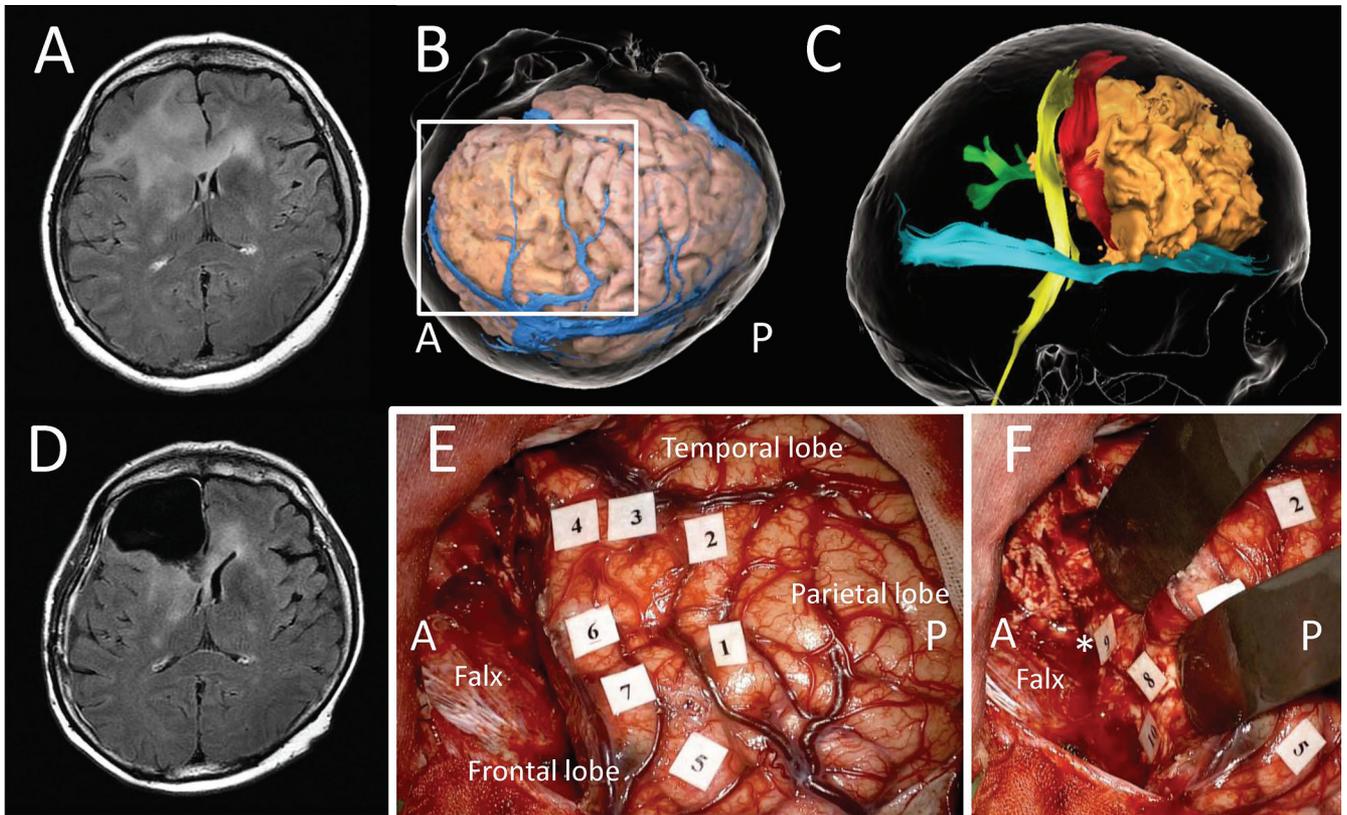
The OR comprises three bundles of visual fibers (direct, central, and Meyer loop) emerging from the lateral geniculate body, running around the roof of the occipital horn, and terminating at the primary visual cortex. This bundle runs through

the sagittal stratum, which is a sheet-like structure located lateral to the atrium of the lateral ventricle, and passes close to the IFOF and ILF. The OR is located just medially and above the ILF, which runs laterally and inferiorly to the lateral wall of the temporal horn, and deeply and inferiorly to the IFOF.<sup>64)</sup> Intraoperative stimulation of the OR can elicit transient phosphene, blurred vision, or visual loss in the contralateral visual field (Fig. 3).<sup>65)</sup> A 4-screen picture-naming task is very useful to detect which part of the OR would be stimulated up to details with quadrant visual level. The disturbance of visual perception is very different from a disorder of visual recognition, which can be elicited by DES of the ILF connecting the visual cortex and visual object form area.<sup>1)</sup>

### Sensori-motor tracts

The sensori-motor system is composed mainly of projection fibers including pyramidal cortico-spinal and somato-sensory thalamo-cortical tracts. All spontaneous body movements are controlled by initiation, execution, and inhibition. Notably, this motor control is enabled by a complex circuit, which comprises multiple complex networks including paracentral U fibers and short frontal association fibers (frontal aslant tract [FAT]),<sup>66)</sup> and other projection fibers (fronto-striatal tract [FST]).<sup>67)</sup> Especially, the supplementary motor area (SMA), which is located rostral to the medial region of primary motor area, has an important role as a hub of these fibers described below.

DESs of the pyramidal tract induce involuntary muscle contraction (Fig. 4),<sup>68)</sup> which should be distinguished from the negative motor response (NMR) that is reproduced on negative motor areas (Fig. 5). Motor-evoked potentials using single-pulse electrical cortical stimulation can be useful for distinguishing primary motor area and negative motor area represented by SMA.<sup>69)</sup> NMR caused by DES with high-frequency stimulation is a disorder of motor initiation and control, which ranges from complete arrest of movement to involuntary acceleration of movement without loss of consciousness.<sup>70)</sup> The negative motor network has been reported by some DES studies using cortico-cortical evoked potential<sup>71)</sup> and subcortical DES mapping.<sup>67,70)</sup> The FST, which is also called the anterior short fiber of subcallosal fascicle, forms a veil-like stream running from the SMA to the head of the caudate nucleus.<sup>72)</sup> The FAT, which connects the posterior part of the inferior frontal gyrus with the pre-SMA, runs slightly anterior and lateral to the FST. DESs can reproduce NMR contralaterally or in both upper and/or lower limbs in the FST (Fig. 5), and NMR of speech in the



**Fig. 5** A case of high-grade glioma originating from right frontal lobe. **A:** Preoperative FLAIR axial MRI showing diffuse hyper lesion in bilateral frontal lobes. **B:** Three-dimensional cortical image in operative view. **C:** Tractography showing the tumor (*beige*) near the pyramidal tract (*yellow*), the frontal aslant tract (*red*), the cingulate fascicle (*green*), and the inferior fronto-occipital fascicle (*cyan*). **D:** Postoperative FLAIR axial MRI showing no residual-enhanced lesion. **E** and **F** show intraoperative photos within the *white square* in **B**, and were taken after surgical resection of tumor with preservation of positive mapping areas elicited by cortical and subcortical electrical stimulations. **E:** Cortical mappings; anarthria was elicited in ventral part of the precentral gyrus (tags 1 and 2), negative motor response in the pars triangularis (tag 3), errors in emotional task on the pars orbitalis (tag 4) and superior frontal gyrus (tag 5), and rightward deviation in line bisection task on the posterior region of the middle frontal gyrus (tags 6 and 7). An *asterisk* shows the anterior horn of lateral ventricle. **F:** Subcortical mappings; rightward deviation in line bisection task on the posterior boundary of resection cavity (tag 8), and motor inhibition of left upper-limb on the fronto-striatal tract (tags 9 and 10). **A** and **P** indicate the anterior and the posterior side, respectively.

FAT.<sup>72,73</sup>) Stimulations of both these tracts converging in deep regions can generate cessation of combined movements with a specific somatotopic feature.<sup>67</sup>

#### Frontal aslant tract (FAT)

The FAT is a frontal association white matter tract recently named after the structural characteristic of running in the “aslant (oblique)” direction at coronal section. This pathway connects the inferior frontal gyrus with the superior frontal gyrus including both medial and dorsolateral parts,<sup>66,72,74</sup> and likely subsumes the subcallosal fascicle.<sup>29</sup> Its function has been recently described by a DES study; it seems to have a role in the control of language especially the planning of articulation, disruption of which results

in disorders of initiation of speech (Fig. 5).<sup>72,75</sup> This is also demonstrated by previous reports indicating that the disturbance of verbal fluency and errors in initiation of speech were involved in primary progression aphasia, Foix–Chavany–Marie syndrome, and stuttering, in which the FAT was shown to be damaged in tractographic studies.<sup>76–78</sup> These data indicate that FAT may be also a part of the negative motor network, especially with regard to speech function.

#### Vertical occipital fascicle

Due to modern *in vivo* tractographic techniques, the vertical occipital fascicle (VOF) has recently reappeared after a century, stirring debate among some of the most prominent neuroanatomists of the

19th century.<sup>79,80</sup> The bundle, previously named Wernicke's perpendicular fasciculus, connects the occipito-temporal sulcus with the lateral portion of the occipito-parietal junction.<sup>81</sup> VOF likely plays a role in the integration of perception of visual categories at the ventral termination, and the control of eye movements, attention, and motion perception in the dorsal termination.<sup>79</sup> Disorders due to DESs of this tract have not been well studied; therefore, this bundle should be investigated further in awake mappings.

### Cingulate fascicle

The cingulate fascicle is the largest white matter tract of the limbic system after the cingulate and the parahippocampal gyri. Many studies have investigated its function but few have examined the effects of DES of the cingulate fascicle in awake craniotomy. Intraoperative DES of the anterior cingulate cortex could reproduce executive errors in the Stroop test during awake surgery for frontal glioma.<sup>82</sup> Similarly, in the posterior cingulate cortex, DES induced a breakdown in conscious experience characterized by a transient behavioral unresponsiveness with loss of external connectedness.<sup>83</sup> The author suggests that the cingulate network is involved in high-level mentalization and consciousness of environment from his experiences of intraoperative DES.<sup>1</sup> Further research is needed to elucidate this aspect of the multimodal system.

## Tractography: Light and Darkness

Recent developments in DTI tractography have enabled a better understanding of subcortical networks not only in the field of neuroscience but also in neurosurgical practice. This visualization technique is especially beneficial for preoperative planning for brain tumor surgery as a noninvasive and simple method by using established software. However, despite rapid adoption of this method in clinical practice, DTI should not be used as the basis of any decisions in neurosurgery because of the inaccurate profile it provides.<sup>84</sup>

First, DTI tractography is not a tool to directly visualize the actual anatomy of fibers, but only provides an indirect reconstruction ("shadow" in other words) based on measuring the diffusion of water molecules. Tractography does not show the actual size of the fiber bundle evaluated in the cortico-spinal tract.<sup>85</sup> Second, the degree of white matter tracts depends on data acquired parameters (MR scanner, magnetic field, and scan parameter) and the kind of algorithms used for the analysis of the data.<sup>8</sup> Third, DTI has technical limitations,

although the fiber-tracking software used in this report is one of the most accurate methods.<sup>86</sup> It is difficult to visualize some subcortical tracts in some conditions: 1) tracts running within glioma-infiltrating lesions and edema (e.g., OR unable to be visualized in case 1); 2) Sharply curving tracts like the Meyer loop; and 3) tracts crossing in a complex manner with other fibers (e.g., lateral parts of the sensori-motor tracts, which direct to the upper-limb and facial area, intersected by SLFs in case 4). In particular, the strong intersection of fibers at the frontal operculum would explain the controversy regarding the results of DTI studies considering the terminations of the peri-sylvian white matter tracts.<sup>16</sup> In our experiences, the SLF I and II, Meyer loop, lateral part of the sensori-motor tracts, FST, and VOF are difficult to visualize using popular DTI methodology alone. From the limitation of DTI visualization and unverified characters of these subcortical tracts, there are still some problems remained in identification of those pathways only by intraoperative DESs.

In order to solve the micro-anatomical problems, newly developed methods including Q-ball imaging,<sup>87</sup> DSI,<sup>88</sup> and spherical deconvolution tractography<sup>89</sup> have been used and have consequently contributed to recent neuroscience and brain studies investigating white matter networks and disorders. However, the main drawback of these methods is the extensive amount of data generated and scanning times. These issues will have to be resolved to enable clinical applications in the future.

## Preservation of White Matter Tracts

Acquired knowledge about white matter connectivity has enabled neurosurgeons to avoid a permanent neurofunctional deficit according to functional and structural boundaries of glioma excision. For the purpose of maximal resection of the lesion, however, it is unreasonable to preserve all of those white matter tracts, considering neuronal plasticity and compensation.

There is a dynamic functional redistribution that allows extended surgical excision of brain regions in patients with slow-growing lesions such as low-grade glioma.<sup>5</sup> This neuroplastic phenomenon also makes it possible to remove broadly the residual lesion in the second surgery of a glioma that had seemed unresectable in the previous operation.<sup>90</sup> The functional reshaping process might be elaborated by complimentary compensation of white matter networks such as a relationship between the direct IFOF pathway and the indirect ILF-UF pathway.<sup>91</sup> On the other hand, according to a probabilistic

atlas of functional resectability of low-grade glioma, there are crucial common regions, that is, “minimal common brain” that need to be preserved to retain homotopical functions even if involved by the tumor.<sup>92)</sup>

The dilemma regarding maximal tumor resection and functional preservation is always present in glioma surgery. From the perspective of quality of life (QOL), postoperative transient dysfunction such as akinesia due to SMA syndrome, most of which could completely improve by 1–3 months even after excision of SMA lesion, should be avoided to enable patients to return to their life as soon as possible.<sup>1)</sup> Dysfunction of negative motor network, partial defect of visual field, and hemi-spatial agnosia are also factors that might prevent patients from going back to their professional work completely. On the other hand, however, the transient nature of SMA syndrome might permit more removal of the tumor infiltrating to the SMA. A concept of “onco-functional balance” is important in the neuro-oncological treatment to accommodate better outcomes of overall survival and functional morbidity, and QOL.<sup>93)</sup> Therefore, a tailor-made surgical strategy should be systematically proposed especially in slow-growing low-grade glioma.

## Conclusion

A DES during awake surgery for the resection of glioma can identify cortical and subcortical eloquent structures by eliciting specific neurological symptoms, which originate from the transient disruption of cortico-subcortical axonal networks. Owing to the recent development of visualization techniques for white matter tracts, most of these bundles can be reconstructed and clearly visualized using DTI. Thus, DTI tractography provides neurosurgeons with knowledge that considerably aids preoperative planning for glioma surgery; however, the risk exists that neurosurgeons may be misled into inappropriate decisions during the surgical resection of brain structures, as DTI cannot visualize the actual anatomy of the white matter fibers. In addition to the critical information acquired via intraoperative DES, it is important to identify the surgical boundaries of brain regions not only with a view to achieve the maximal incision of the glioma but also with consideration to the concept of onco-functional balance.

## Conflicts of Interest (COI) Disclosure

The authors declare that they have no conflict of interest. All authors who are the members of The Japan Neurosurgical Society (JNS) have registered *Neurol Med Chir (Tokyo)* 56, November, 2016

online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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