Supratotal resection of diffuse frontal lower-grade gliomas with awake brain mapping while preserving motor, language, and neurocognitive functions: Technical note

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Abstract

Objective

An extended margin tumor resection beyond the abnormal area detected by magnetic resonance imaging, defined as supratotal resection, could improve the outcome of patients with lower-grade gliomas (LGGs).

The aim of this study was to assess the surgical outcomes of awake brain mapping in order to achieve a supratotal resection while determining the normal brain tissue boundaries beyond the tumor of frontal LGGs, in both dominant and non-dominant hemispheres.

Methods

We analyzed nine patients with diffuse frontal LGGs who achieved supratotal resection with awake surgery between January 2016 and November 2017.

Results

The frontal aslant tract was identified as the functional boundary in four out of five left frontal tumor cases (80%). Notably, working memory impairments during dorsolateral prefrontal cortex stimulation with digit span and/or visual N-back tasks, were detected in all four (100%) right-frontal tumor cases.

Regarding post-resection neurocognitive outcomes, the mean Wechsler adult intelligence scale-III scores for verbal IQ ($p = 0.04$) and verbal comprehension ($p = 0.03$) and the mean Wechsler memory scale-revised scores for generalized memory ($p = 0.04$), and delayed recall ($p = 0.04$), were significantly improved after surgery.

Conclusions

This study provides evidence that awake mapping can enable the preservation of higher neurocognitive functions, including working memory and spatial cognition in patients with non-dominant right frontal tumors. Despite the small number of cases, our findings suggest the surgical benefit of awake surgery for the supratotal resection of diffuse frontal LGGs.

Introduction

Lower-grade gliomas (LGGs), including the World Health Organization (WHO) classification of grade II-III gliomas, are slow-growing tumors that arise from supporting glial cells of the central nervous system[1,2]. In particular, isocitrate dehydrogenase (IDH) gene mutations are potential prognostic markers for LGGs and have been included in the updated WHO classification[3]. As previously described[1,2], Diffuse LGGs, including grade II and III gliomas, are genetically classified into three distinct subtypes based on IDH mutation status and codeletion of chromosome 1p and 19q (1p/19q). Patients with LGGs are often young adults and have a median overall survival (OS) of ten years or longer. Nevertheless, LGGs have been associated with potential features that lead to inevitable malignant transformation and progression to highly malignant gliomas[4,5].

Due to the lack of well-designed randomized controlled clinical trials with adequate follow-up to account for the longer survival of patients with LGGs, the optimal management of LGGs remains controversial in clinical neuro-oncology, with respect to the surgical and oncological management and the timing of radiotherapy and chemotherapy[6-9]. In fact, due to ethical considerations, no randomized controlled trial comparing radical surgical resection to no surgery has been performed for patients with LGGs.

However, recent large observational studies and literature reviews based on objective evaluation of the extent of resection (EOR) for gliomas, revealed that maximal tumor resection and early surgical intervention are significantly associated with better outcomes for LGGs[10-16]. In a retrospective study with 216 hemispheric LGGs cases, patients with more than 90% EOR had 5-year OS rates of 97%, whereas patients with less than 90% EOR had 5-year OS rates of 76%[10]. Furthermore, population-based parallel cohorts of LGGs in Norway showed that the survival of the ‘early surgical resection’ group was significantly greater than the ‘biopsy and watchful waiting’ group with LGGs[14,15]. Interestingly, it was reported that extended tumor resection beyond the margins of the abnormal magnetic resonance imaging (MRI)-verified area, also known as supratotal resection, improves the outcome of LGG patients[17]. Although it is not curative, of course, supratotal resection performed prevents or delays malignant transformation which is a new concept in the surgical management of LGGs[17-19]. Therefore, greater EOR, including total or supratotal surgical LGG resection can significantly increase survival.

In the current study, we performed awake brain mapping with cortical and subcortical stimulation for diffuse frontal LGGs, in order to achieve a supratotal resection while determining the functional brain tissue boundaries beyond the tumor margin. Regarding frontal tumors of the left dominant hemisphere, we could preserve language function mainly by using counting and picture-naming tasks. On the other hand, when the tumor affected the right frontal dominant hemisphere, we performed electrical brain stimulation, so as to preserve the sensorimotor and neurocognitive functions, including working memory and spatial awareness.

We aimed to investigate the surgical outcomes of awake brain mapping to accomplish a supratotal resection of frontal LGGs in both the dominant and nondominant hemisphere.

Materials & Methods

Patient selection

We have retrospectively collected data from nine patients with diffuse frontal LGGs of the dominant and non-dominant hemisphere, who achieved supratotal resection. All patients underwent awake brain surgery at the Nagoya University Hospital between January 2016 and November 2017. This study has been approved by the ethics committee of Nagoya University Hospital (approval number: 2017-0459) and we obtained written informed consent from all patients.

Preoperative neuropsychological evaluation

All patients underwent neuropsychological testing and preoperative neurological findings were assessed at admission, before the awake brain surgery. Handedness was assessed using the Edinburgh inventory standardized questionnaire[20]. Hemispheric language dominance was determined according to the comprehensive interpretation of the results of both functional MRI and navigated repetitive transcranial magnetic stimulation (nrTMS)[21]. Functional MRI studies were performed using a Siemens Magnetom Verio (Siemens, Erlangen, Germany) 3.0 T scanner with a 32-channel head coil. The nrTMS language mappings with the use of picture-naming tasks were performed with the Magstim Rapid (Magstim Co., UK). Neuropsychological status and language function were evaluated by speech and occupational therapists. The neuropsychological tests that were used included the standard language test of aphasia (SLTA), the third edition of the Wechsler adult intelligence scale (WAIS-III), the Wechsler memory scale–revised (WMS-R) and the frontal assessment battery (FAB). FAB is a cognitive and behavioral test to assess frontal lobe functions[22]. This consists of six subtests that detect the following frontal functions: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy[22].

Surgery

Preoperative anatomical images with 3D T1-weighted images, conventional MRI (T1- and T2-weighted images), and diffusion-weighted imaging data which were acquired on a 3.0-Tesla scanner (Trio Siemens, Germany) were sent to the navigation system (BrainLAB, Vector Vision Compact)[23]. In all nine cases, intraoperative awake brain mapping with direct brain stimulations was performed using an asleep-awake-asleep protocol, as previously reported[24-27]. Briefly, a wide craniotomy was performed, and in accordance with the neuronavigational system, we initially placed letter tags along the tumor borders before the occurrence of brain shifts. The awake surgery was performed under cortical and subcortical mapping by using direct electrical stimulation. Standard number tags were used to identify several brain functions, including motor and language on the brain surface. Moreover, somatosensory-evoked potentials were recorded using a strip electrode for the identification of the central sulcus. Continuous electrocorticograms (ECoGs) were performed by using strip electrodes, in order to detect discharge phenomena during direct brain stimulation and tumor resection. After tumor resection, during awake craniotomy, all patients were subjected to intraoperative MRI (iMRI) using a 0.4-Tesla vertical field MRI scanner (Aperto Inspire, Hitachi, Tokyo, Japan), installed in the operating room of the Brain THEATER in Nagoya University Hospital.

Mapping tasks in awake brain surgery

Preferred testing tasks for the right and left frontal regions are shown in Table 1. For the patients with frontal tumor in the language dominant hemisphere, we used counting tasks and picture-naming tasks presented on a monitor, in order to identify the cortical language sites and subcortical fibers affected by electrical stimulations. Speech therapists evaluated the type of language disorder, such as speech arrest, anomia, dysarthria, anarthria, speech slowness, initiation troubles, perseveration or paraphasia. In particular, subcortical brain mapping enabled the surgeons to decide on the functional boundary inside the normal tissue and beyond the tumor margin for achieving supratotal resection. On the other hand, working memory has been especially investigated in patients with right non-dominant frontal tumors. To assess verbal working memory, patients were subjected to digit span testing during awake surgery[28]. Speech therapists requested the repetition of three or four strings of digits in forward and/or reverse order. Furthermore, the spatial working memory performance of the patients was tested using the visual N-back task[29]. This task comprised of 1-back or 2-back tasks during which plane figures were presented on the monitor. In the line bisection task in order to recognize the brain areas of spatial awareness, patients were asked to mark the center of the presented image[30]. Lateral midline deviation from the mark of approximately 5 mm was regarded as a positive response and was associated with a functionally spatial region. Therefore, awake brain mapping for the evaluation of working memory and spatial awareness could define the functional resection boundaries in right frontal lesions.

Postoperative outcome evaluation

All patients underwent MRI scanning one week postoperatively, to assess EOR. The EOR volume was subtracted from the preoperative tumor volume to provide volumetric EOR data on a three-dimensional basis, by using the iPlan® cranial planning software included in BrainLAB iPlan® Cranial 3.0[23]. A supratotal resection was defined as a tumor resection extending beyond the abnormal MRI-verified area, which indicated that the volume of the postoperative cavity was larger than the preoperative tumor volume[17,19]. Furthermore, resection of normal brain tissue surrounding radiographically abnormal tissue was also defined as a supratotal resection. All patients were evaluated using postoperative neuropsychological assessments, including the WMS-R, SLTA, FAB and WAIS-III, six months after surgery.

Statistical analysis

All statistical analyses were performed using the statistical software IBM SPSS Statistics for Windows, version 24.0 (IBM Corporation, Armonk, NY). To compare preoperative and postoperative neurocognitive function data acquired from neuropsychological assessments, including WMS-R, SLTA, and FAB, nonparametric statistics were applied (Wilcoxon signed rank test, 2-tailed, a level < 0.05). Significance of $p = 0.05$ was assumed.

Results

Clinical characteristics

Patients' clinical characteristics are summarized in Table 2. From January 2016 to November 2017, we performed awake surgery for a total of 45 patients with brain tumors between January 2016 and November 2017. Of these, 22 patients had frontal gliomas. 9 patients with LGGs in the right or left frontal lobe who underwent awake brain surgery were analyzed in this study. There were 4 men and 5 women, aged between 17 and 49 years with a mean age of 34 years. Eight patients were right-handed and one was left-handed. In four patients, the first clinical symptom was seizure, the tumors of the other five patients were incidentally discovered by MRI due to complaints of headaches or dizziness. Histologically, this study included all patients with LGGs, including 8 WHO grade II gliomas (5 diffuse astrocytomas, 3 oligodendrogliomas), and 1 WHO grade III glioma (anaplastic astrocytoma). As indicated in Table 2, all patients (100 %) had IDH1 mutations. Frontal tumors were located in the left hemisphere in 5 cases (55.6%) and in the right hemisphere in 4 cases (44.4%). The gliomas were located at the superior frontal gyrus (SFG) in 7 patients, the middle frontal gyrus (MFG) in 2 patients and the inferior frontal gyrus (IFG) in 1 patient. Preoperative median tumor volume was 18.7 cm^3 (range, 7.8–55.2 cm^3). Final EOR $\geq$ 100%, that is, supratotal resection was achieved in all patients. iMRI confirmed no further tumor removal in all patients because all observable tumors had been already removed.

Intraoperative findings

In order to achieve both maximal tumor resection and preservation of brain function, including motor, language, and neurocognitive functions, awake surgery with intraoperative functional brain mapping using cortical and subcortical electrical stimulation was performed in all nine patients. The cortical and subcortical functional boundaries in the normal brain tissue outside the tumor border allowed us to define the resection limits (Fig. 1, 2, 3).

In 6 out of 9 patients (66.7%), positive cortical mapping sites were identified as functional boundaries over the exposed dorsolateral prefrontal cortex (DLPFC) by checking the function of verbal and spatial working memory, when using digit span testing and/or visual N-back tasks. Notably, working memory impairments during stimulation of DLPFC were detected as functional structures in all 4 (100%) right frontal tumor cases (Table 2, Fig 1, 2).

Subcortical mapping determined the posterolateral resection margin through language interferences inducing paraphasia, in six cases (66.7%). In these cases, postoperative MRIs indicated the frontal aslant tract (FAT) as the posterolateral resection margin. In particular, FAT was identified as a functional boundary by using subcortical electrostimulation in four out of five left frontal tumor cases (80%, Table 2, Fig. 1, 3). No spatial attention impairments were detected during cortical and subcortical mapping with the line bisection task, in any patient. No patients experienced procedure-related complications.

Neurocognitive outcomes after resection

Results of the preoperative and postoperative neuropsychological assessments are summarized in Table 3. When individual test results were evaluated to assess the outcome of individual cognitive functions, the mean verbal IQ (VIQ; $p = 0.04$) and verbal comprehension (VC; $p = 0.03$) WAIS-III scores were significantly improved for every test after surgery, as determined by the Wilcoxon signed rank test. Other postoperative index scores did not decrease after the removal of the frontal tumor. Interestingly, postoperative mean WMS-R scores for generalized memory (GM; $p = 0.04$) and delayed recall (DR; $p = 0.04$) significantly improved compared to their preoperative values. There was no statistically significant difference between preoperative and postoperative mean FAB scores.

Discussion

Although the survival benefit of surgical resection for LGGs has been debatable, some retrospective studies suggest that extensive tumor resection might be beneficial for patients with LGGs, in terms of relieving tumor burden and prolonging survival[10,14-16]. Furthermore, the French Glioma Network showed in a large series of LGGs cases (more than 1000) that EOR for these tumors was a strong favorable prognostic factor significantly associated with longer survival[31]. Although no randomized controlled trial for LGGs comparing surgical resection to no radical surgery (i.e. biopsy) has been carried out, Jakola et al. published a retrospective population-based study comparing two Norwegian hospitals with different management strategies. One hospital strategy favored early surgical tumor resection whilst the other favored watchful waiting in LGGs. Interestingly, Jakola et al. reported a significantly increased survival benefit for patients treated with the early surgical resection strategy[14,15] with a 5-year OS rate of 74%, compared to 60% for the 'watchful waiting' group. Moreover, another group demonstrated that in two departments that acted independently at the same university medical center, a significant survival benefit was detected for patients with an early resection tumor management, as compared to those with a biopsy tumor management (5-year OS 82% *vs* 54%)[16]. Therefore, glioma surgeons should increase the EOR for LGGs with the help of modern surgical tools and techniques, like iMRI[27], neuronavigation systems[32] and awake brain mapping techniques[4,24,27].

Duffau et al. reported that all sixteen patients that underwent supratotal resection using awake brain mapping for LGGs, after a mean postoperative follow-up of 11 years, are still alive without malignant transformation[17]. It has been suggested that extending resections beyond the abnormalities detected by T2-weighted MRI could convey an additional survival benefit, because tumor cells might have the potential to invade sites 10–20 mm far from the MRI-defined tumor boundaries[33]. Thus, we tried to achieve supratotal resection of the functional boundaries beyond the tumor margins visible by MRI, with the help of awake brain mapping.

Awake brain mapping could enable the safe resection of language dominant and nondominant diffuse frontal LGGs, while protecting cortical and subcortical functions. Regarding the tumors in the left language dominant frontal lobe, we were able to preserve oral and written language functions by using counting and picture-naming tasks (Table. 1, 2). Because of these intraoperative tasks, awake brain mapping can detect possible anatomo-functional associations, which have led to the ‘language connectivity’ of the brain. The language-associated subcortical fibers in the left frontal lobe include the inferior fronto-occipital fasciculus (IFOF), which construct a ventral pathway connecting orbitofrontal, prefrontal, and dorsolateral prefrontal areas to posterior temporo-occipitoparietal regions[34]. This ventral pathway is involved in semantic processing and IFOF stimulation during picture-naming tasks leads to semantic paraphasia[35]. Moreover, a dorsal pathway served by the superior longitudinal fasciculus (SLF), connecting the IFG and the ventral premotor cortex to the posterior temporal cortex, is also present in the left frontal lobe[36]. Phonemic paraphasia and articulatory disorders are elicited when stimulated. FAT is among the newly described frontal tracts that connect the supplementary motor complex in the medial frontal regions of the SFG, and the most posterior part of Broca's area[37]. FAT was considered to play a role in self-initiated speech, involving the pre-supplementary motor area and left IFG. In order to perform an extended resection of a margin beyond these MRI–defined abnormalities, in left frontal LGGs, we continued the resection until the functional boundaries, defined by the subcortical fibers IFOF, SLF and FAT (Table 2, Fig. 3).

On the other hand, although most of the right frontal lobe is believed to be a non-eloquent area, we sometimes observed that patients with right frontal tumors frequently presented with cognitive and behavioral deficits after postoperative neuropsychological assessment. Duffau et al. recently emphasized that awake brain mapping with cortical and subcortical stimulation should be performed for the removal of right side tumors in order to preserve movement execution and control, visual processes, spatial cognition, language and nonverbal semantic processing, executive functions, as well as social cognition[38,39]. Thus, in the present study, we performed awake functional mapping for frontal tumors in the right language non-dominant frontal lobe to preserve the functions of working memory (Table 2, Fig. 2). Moreover, we focused on the frontal lobe DLPFC that is associated with cognitive functions, such as working memory and selective attention. In particular, the right non dominant DLPFC plays a role in verbal and spatial reasoning in working memory, while the left DLPFC is necessary for manipulating verbal and spatial knowledge[40]. To examine the verbal working memory of patients with tumors in the right frontal lobe, we used the digit span test, where patients had to repeat increasing strings of numbers in forward and reverse order. We consider the digit span one of the most useful tasks for assessing verbal working memory, as it is easy to conduct even in a limited time window during awake surgery. N-back testing has been developed as a way to measure spatial working memory[29]. We used 1-back or 2-back tasks. As shown in Table 2, we were able to identify the functional boundaries while checking verbal and spatial working memory function through DLPFC stimulation with the digit span and visual N-back tasks in 100% of the right frontal tumor patients. Therefore, we managed to preserve the right frontal neurocognitive functions whilst performing supratotal resection for diffuse right frontal LGGs, with awake functional mapping.

We demonstrate here the conceptual overview of supratotal resection for right and left frontal LGGs with awake brain mapping (Fig. 4). For margin removal around the MRI-detected abnormalities in the dominant left frontal hemisphere, we recommend performing classical motor and/or language mapping throughout surgical resection. On the other hand, in order to achieve awake mapping for supratotal tumor resection in the non-dominant right frontal lobe, we propose using several tasks, to assess working memory and spatial cognition, by stimulating the fibers associated with higher brain functions.

Although this report provides novel information on supratotal resection for right and left frontal LGGs while maintaining brain functions, our results are limited when compared to those of prospective clinical trials, as retrospective studies might have been influenced by unrecognized bias.

Another limitation of our study is that it remains unclear whether a supratotal resection improved the clinical outcomes in our study because the postoperative follow-up duration of the current study was too short. Furthermore, this report is based on a small case number, thus, a larger cohort study is required to further establish the role of awake surgery with cortical and direct axonal electrical stimulation mapping in preserving neurocognitive functions, during resection of right lobe tumors. Additional evidence from awake functional mapping is crucial for our understanding of the objective neuropsychological assessments needed for the achievement of supratotal resection of diffuse dominant and non-dominant frontal LGGs.

Conclusions

Certain studies have reported that supratotal resection might improve the clinical outcomes of patients with LGGs by decreasing the risk of malignant transformation for a long period. In an attempt to achieve supratotal resection of right and left frontal LGGs, we performed awake functional mapping while preserving motor, language, and neurocognitive functions. In particular, we were able to preserve higher neurocognitive functions, including working memory and spatial cognition during awake brain mapping in patients with non-dominant right frontal tumors. Despite the small number of cases, our findings suggest the surgical outcomes of awake brain surgery for the supratotal resection of diffuse frontal lower-grade gliomas.

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Disclosure statement

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Figure legends

Fig. 1. Patient No 9: Preoperative sagittal T2-weighted MRI scan (A) showing a right frontal lower-grade glioma (right superior frontal gyrus) in a 29-year-old left-handed man with no previous medical history. He was transferred to our hospital with a convulsive attack, which was suspected to be a symptomatic tumor-associated epilepsy. Intraoperative photograph (B) obtained after tumor resection. Cortical mapping revealed the dorsolateral prefrontal cortex (DLPFC) on the lateral tumor side (number tags: 14), using a visual 2-back task to confirm functioning spatial working memory. We performed awake surgery with subcortical mapping to identify the frontal aslant tract (FAT) and the fronto-striatal tract (FST) as a safe resection margin for the functional boundaries (number tags: 33, 34, 41, and 42). Postoperative axial T2-weighted MRI scan (C) showing supratotal resection using awake brain mapping. The patient presented with no postoperative impairments concerning neuropsychological status, language processing, and motor control.

Three-dimensional tractography (D) indicating the tumor (orange) surrounded by FAT (red) and FST (blue). Red = FAT; blue = FST; yellow = corticospinal tract (bilateral); FAT, frontal aslant tract; FST, fronto-striatal tract.

Fig. 2. Patient No 3: Initial axial T2-weighted MRI (A) showing a right frontal lower-grade glioma located in the right superior frontal gyrus in a 39-year-old right-handed woman with no previous medical history that presented with episodic headache.

Intraoperative photograph (B) obtained after tumor resection. The letter tags indicate the tumor boundaries (tags: A-D). Cortical mapping revealed the dorsolateral prefrontal cortex (DLPFC) on the lateral tumor side (number tags: 1,3), using a 4-digit backward digit span task in order to confirm verbal working memory. DLPFC white matter stimulation along the tumor cavity wall also led to a positive response during the 4-digit backward span task (number tag: 31). In this case, pathological dignosis with tissues collected in the surgical margins was not glioma, healthy brain tissue, which indicated supratotal resection of the tumor.

Postoperative axial T2-weighted MRI (C) showing supratotal mass resection by using awake brain mapping. The patient had no post-operative impairment of neurological functions, including working memory, as determined by forward and backward digit span tasks. The patient's visual span of 7 digits (which was higher than the average adult cutoff of 5 digits) was perfectly preserved after surgery. Instead, a slight improvement in working memory was observed after the surgery with 4-digit “memory updating task” results improving from a preoperative 87.5% (which was much higher than the average adult score of 63%) to 93.8% after surgery.

Three-dimensional tractography (D) indicating the tumor (orange) surrounded by FAT (red). Green = IFOF; blue = SLF; yellow = corticospinal tract (bilateral); IFOF, fronto-occipital fasciculus; FAT, frontal aslant tract; SLF, superior longitudinal fasciculus

Fig. 3. Patient No 1: Preoperative sagittal T2-weighted MRI (A) showing a left frontal lower-grade

glioma (left superior frontal gyrus) in a 29-year-old right-handed woman, with no previous medical history, who presented with headache and transient difficulty in using her right hand. Transient right hand disability was probably caused by symptomatic tumor-associated epilepsy.

We performed awake surgery with cortical and subcortical mapping to identify the inferior fronto-occipital fasciculus (IFOF) and frontal aslant tract (FAT) and safely resect the tumor with IFOF and FAT as the functional boundaries. Intraoperative photograph (B) obtained after the resection, showing letter tags that indicate the angioma boundaries (tags: A-E). Precentral gyrus stimulation induced speech arrest (number tag: 1). IFOF stimulation generated semantic paraphasia (number tags: 42, 43, 44), and FAT stimulation elicited anomia (number tags: 40, 41, 45, 46). Error with the pyramids and palm tree test (PPTT) was induced by stimulation of the anterior-inferior tumor cavity side (number tags 42, 43, 44), which corresponded to the IFOF. These positive mappings determined the limits of the tumor resection. The tumor was resected up to the interhemispheric fissure medially and the cingulate gyrus inferiorly. Consequently, the tumor was completely resected up to the functional boundaries. IFOF: white arrowhead, FAT: yellow arrowhead; arrow: sylvian fissure. Tissues collected in the surgical margins did not include glioma cells, only normal brain cells.

Postoperative axial T2-weighted MRI (C) showing supratotal mass resection using awake brain mapping. The patient presented with no postoperative impairments of neuropsychological status, language function or motor paralysis. Supratotal resection with functional preservation was achieved.

Three-dimensional tractography (D) indicating the tumor (orange) surrounded by FAT (red) and IFOF (green). blue = SLF; yellow = corticospinal tract (bilateral); IFOF, fronto-occipital fasciculus; FAT, frontal aslant tract; SLF, superior longitudinal fasciculus

Fig. 4. Conceptual diagram of supratotal resection for diffuse frontal lower-grade gliomas with awake functional mapping

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Table 1. Preferred testing paradigms for bilateral frontal areas

Frontal lobes	Tasks performed intraoperatively
Language non-dominant hemisphere (right)	▪Motor function: Movement of the upper and lower limb ▪Working memory: Verbal working memory: digit span test Spatial working memory: N-back Test Double task ▪Spatial awareness: line bisection task
Language dominant hemisphere (left)	▪Motor function: Movement of the upper and lower limb ▪Language function: Picture naming task Counting task ▪Working memory: Double task, digit span test

Table 2. Clinical characteristics

Patient No.	Age (years)	Sex	Handedness	WHO grade	Pathology	IDH1 mutation	First symptom	Tumor side R/L	Tumor location	Cortical and/or subcortical functional boundaries	Tumor volume (cm^3)
1	30	F	R	II	diffuse astrocytoma	+	seizure	L	SFG, MFG	FAT, IFOF	18.8
2	40	F	R	II	oligodendroglioma	+	seizure	R	SFG	DLPFC	18.7
3	39	F	R	II	diffuse astrocytoma	+	incidental	R	SFG	DLPFC	7.8
4	29	M	R	III	anaplastic astrocytoma	+	seizure	L	MFG	PT, IFOF, FAT	10.6
5	49	M	R	II	diffuse astrocytoma	+	incidental	R	SFG	DLPFC, FST	32.3
6	40	F	R	II	oligodendroglioma	+	incidental	L	IFG	DLPFC	8.7
7	33	F	R	II	diffuse astrocytoma	+	incidental	L	SFG	FAT	20.5
8	17	M	R	II	diffuse astrocytoma	+	incidental	L	SFG	DLPFC, FAT	17.8
9	29	M	L	II	oligodendroglioma	+	seizure	R	SFG	DLPFC, FAT, FST	55.2

Abbreviation: DNT: Dysembryoplastic neuroepithelial tumor, SFG: superior frontal gyrus, MFG: middle frontal gyrus, IFG: inferior frontal gyrus, PC: premotor cortex, FAST: frontal aslant tract, IFOF: inferior fronto-occipital fasciculus, SMA: supplementary motor area, CST: corticospinal tract, DLPFC: dorsolateral prefrontal cortex, PT: pars triangularis, FST: fronto-striatal tract

Table 3. Neuropsychological testing data for 9 patients with lower grade gliomas in right or left frontal lobe

Neuropsychological test		Preop Mean (SD)	Postop Mean (SD)	Postop-preop (Z, p value)
WAIS-III	Verbal IQ (VIQ)	97.4 (18.1)	104.8 (15.0)	-2.03, **0.04**
	Performance IQ (PIQ)	102.9 (17.6)	112.8 (11.3)	-0.73, 0.46
	Full IQ (FIQ)	100.1(18.8)	109.2 (13.6)	-1.21, 0.23
	Verbal comprehension (VC)	95.6 (18.2)	104.3 (16.4)	-2.21, **0.03**
	Perceptual organization (PO)	102.4 (17.8)	106.2 (9.1)	-0.32, 0.75
	Working memory (WM)	96.9 (14.5)	101.2 (18.1)	-0.63, 0.53
	Performance speed (PS)	101.9 (15.9)	109.3 (8.1)	-1.08, 0.28
WMS-R	Verbal memory (VeM)	98.0 (21.0)	114.5 (12.8)	-1.78, 0.08
	Visual memory (ViM)	104.3 (17.5)	116.5 (5.3)	-1.48, 0.14
	Generalized memory (GM)	100.6 (19.5)	116.8 (12.6)	-1.89, **0.04**
	Attention/concentration (A/C)	102.1 (17.3)	112.7 (7.3)	-1.36, 0.17
	Delayed recall (DR)	101.2 (21.6)	119.8 (10.9)	-2.02, **0.04**
FAB	Similarities	2.7 (0.5)	2.5 (0.5)	-1.00, 0.32
	Lexical fluency	2.8 (0.7)	2.5 (0.8)	-1.41, 0.16
	Motor series	2.9 (0.3)	3.0 (0.0)	-1.00, 0.32
	Conflicting instructions	3.0 (0.0)	2.9 (0.4)	-1.00, 0.32
	Go-No-Go	3.0 (0.0)	2.5 (0.8)	-1.63, 0.10
	Prehension behavior	3.0 (0.0)	3.0 (0.0)	0.00, 1.00

Abbreviation: SD; standard deviations, WAIS-III; the third version of Wechsler adult intelligence score, WMS-R; Wechsler memory scale revised, FAB;

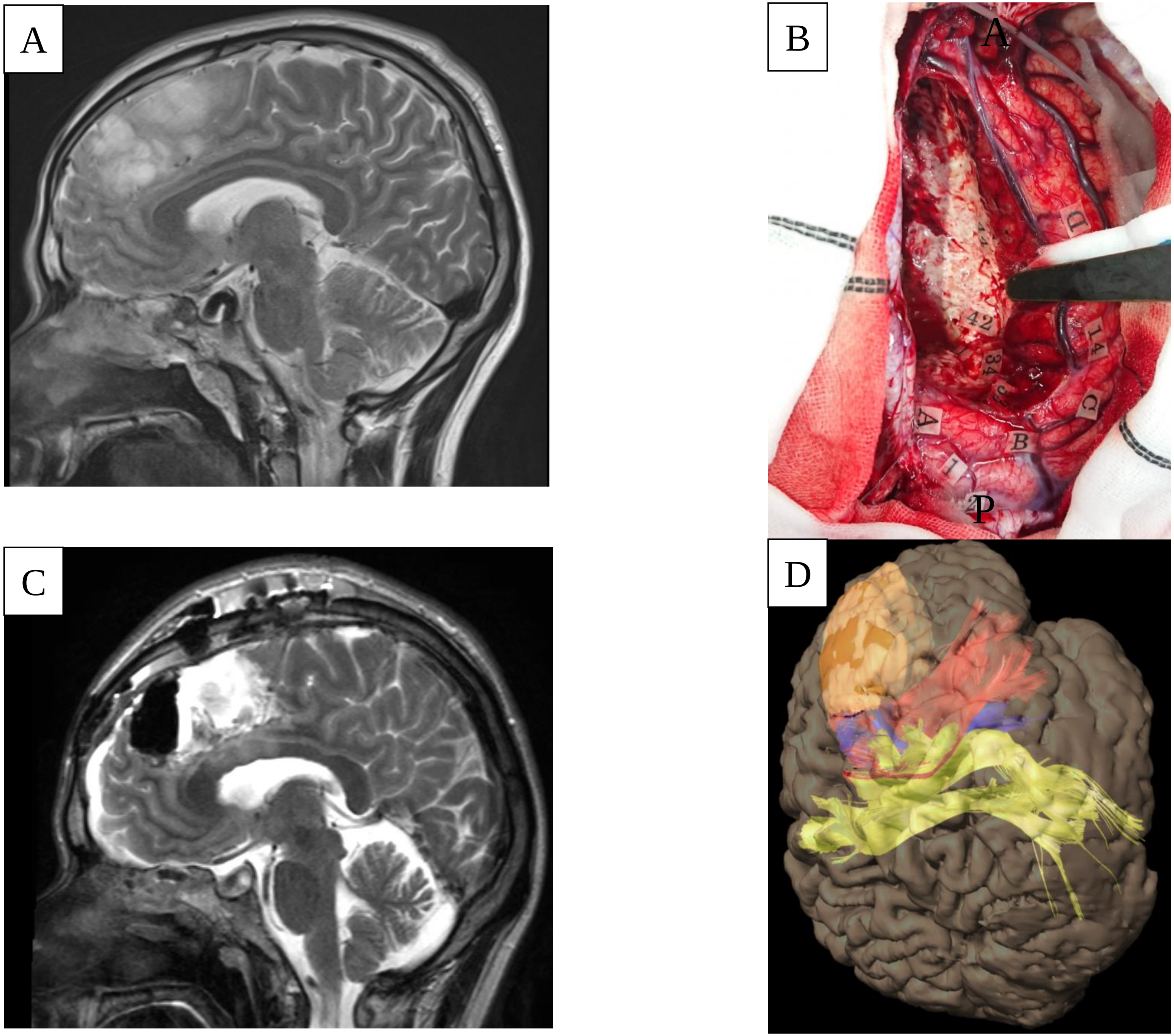


Figure 1. Motomura et al.

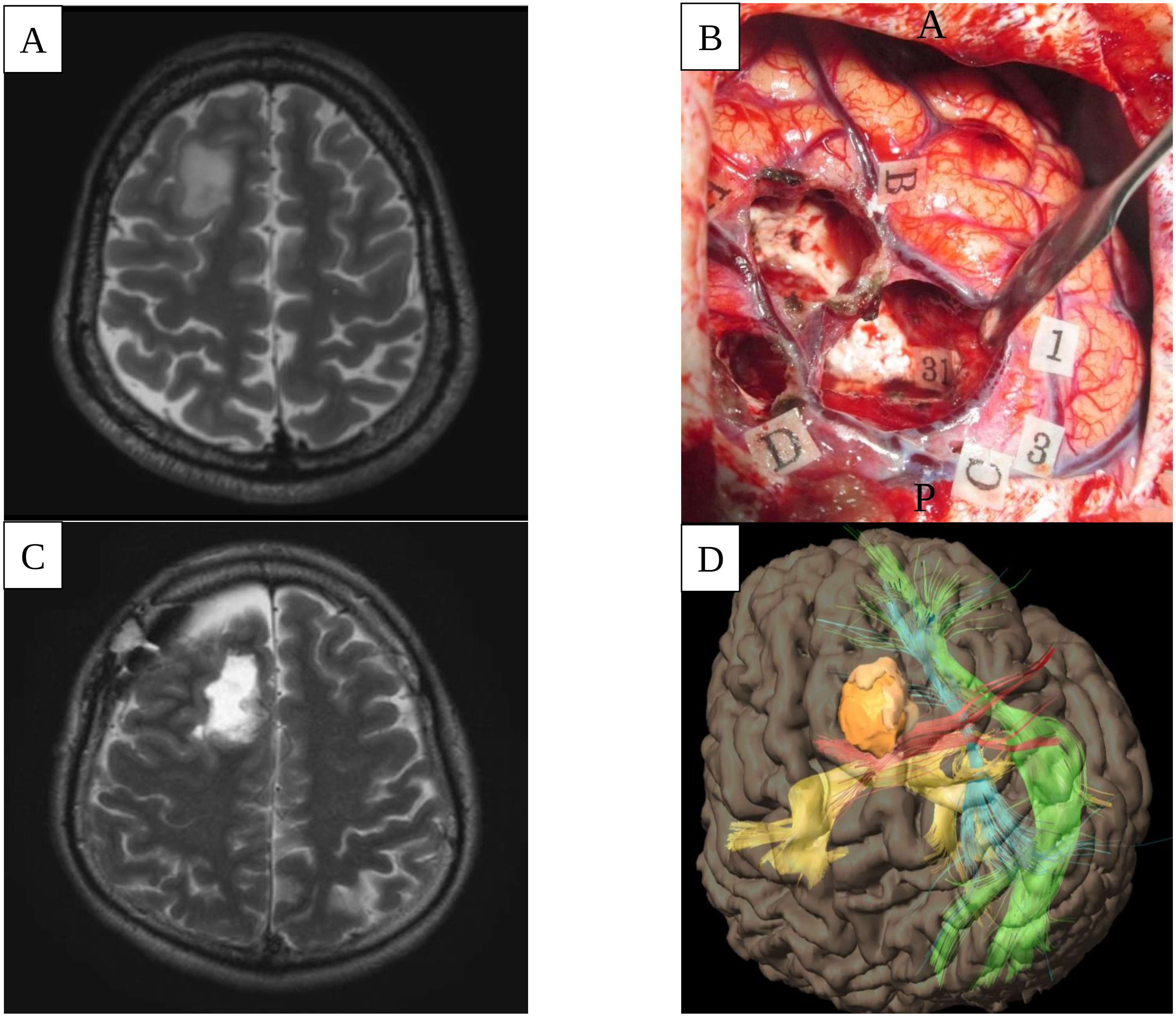


Figure 2. Motomura et al.

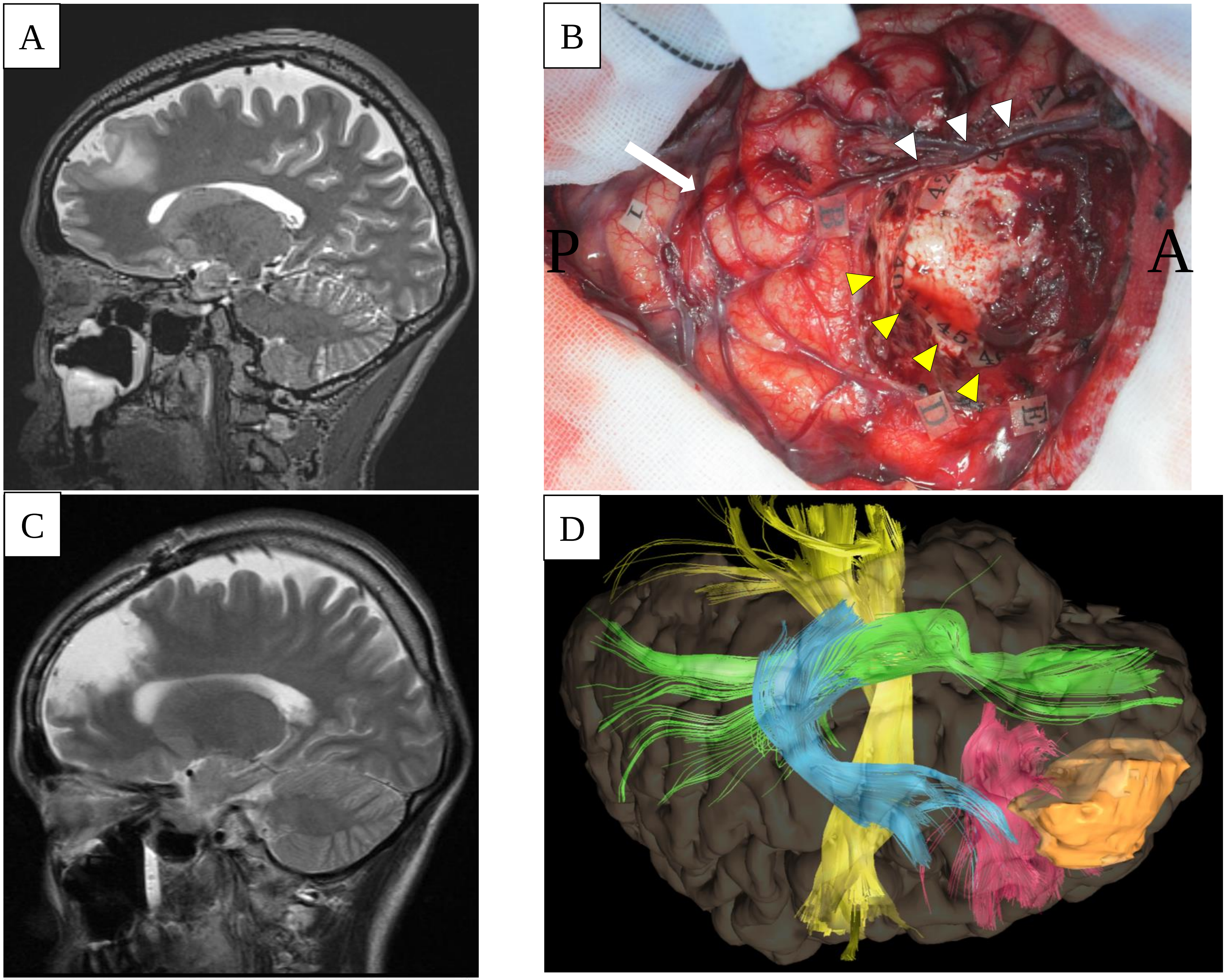
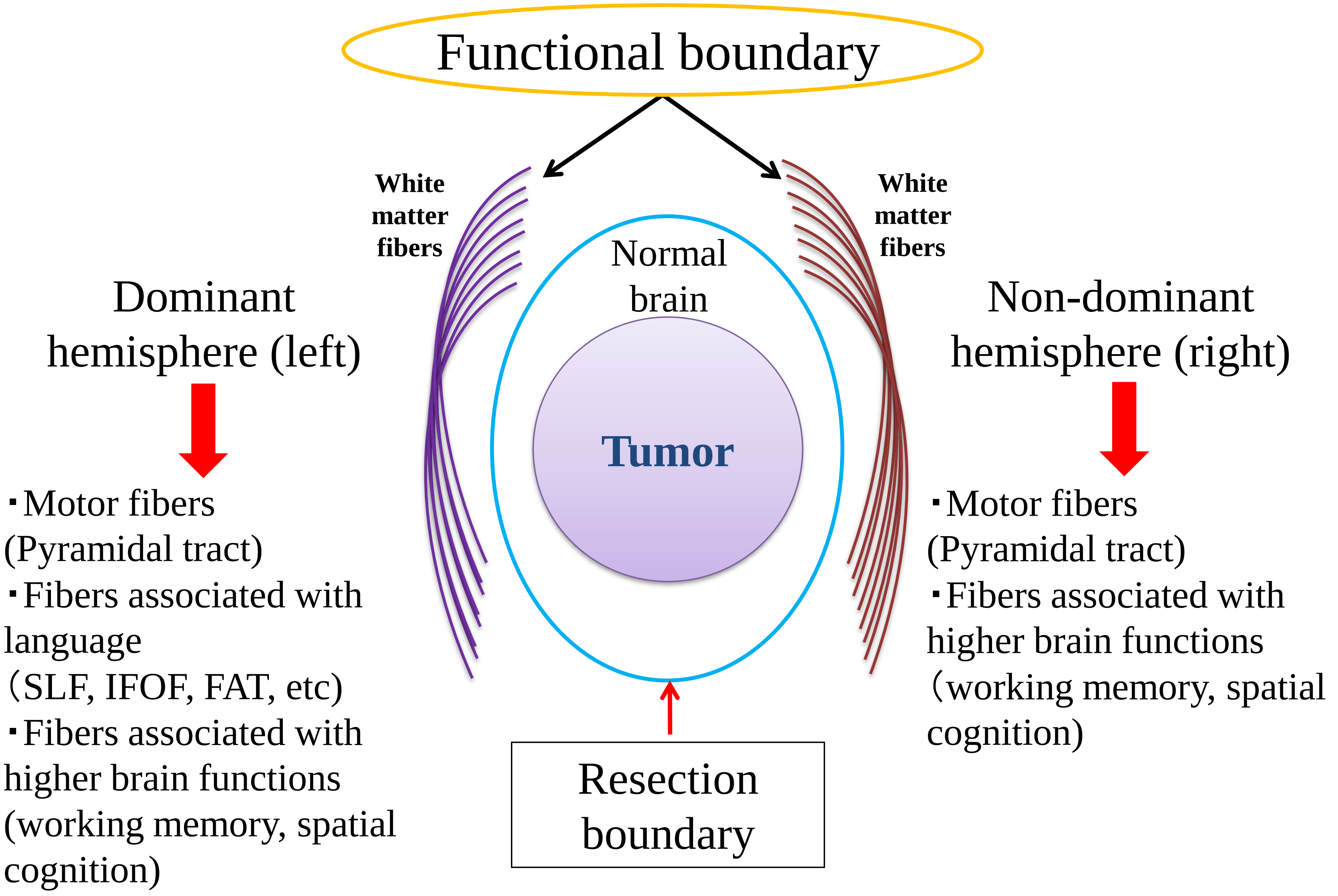


Figure 3. Motomura et al.



Functional boundary

White matter fibers

White matter fibers

Normal brain

Tumor

Resection boundary

Dominant hemisphere (left)

▪Motor fibers (Pyramidal tract)

▪Fibers associated with language （SLF, IFOF, FAT, etc)

▪Fibers associated with higher brain functions (working memory, spatial cognition)

Non-dominant hemisphere (right)

▪Motor fibers (Pyramidal tract)

▪Fibers associated with higher brain functions （working memory, spatial cognition)

Figure 4. Motomura et al.