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Chronic spatial working memory deficit associated with the superior longitudinal fasciculus: a study using voxel-based lesion-symptom mapping and intraoperative direct stimulation in right prefrontal glioma surgery

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OBJECTIVE Although the right prefrontal region is regarded as a silent area, chronic deficits of the executive function, including working memory (WM), could occur after resection of a right prefrontal glioma. This may be overlooked by postoperative standard examinations, and the disabilities could affect the patient's professional life. The right prefrontal region is a part of the frontoparietal network and is subserved by the superior longitudinal fasciculus (SLF); however, the role of the SLF in spatial WM is unclear. This study investigated a persistent spatial WM deficit in patients who underwent right prefrontal glioma resection, and evaluated the relationship between the spatial WM deficit and the SLF.

METHODS Spatial WM was examined in 24 patients who underwent prefrontal glioma resection (right, n = 14; left, n = 10) and in 14 healthy volunteers using a spatial 2-back task during the long-term postoperative period. The neural correlates of spatial WM were evaluated using lesion mapping and voxel-based lesion-symptom mapping. In addition, the spatial 2-back task was performed during surgery under direct subcortical electrical stimulation in 2 patients with right prefrontal gliomas.

RESULTS Patients with a right prefrontal lesion had a significant chronic spatial WM deficit. Voxel-based lesion-symptom mapping analysis revealed a significant correlation between spatial WM deficit and the region that overlapped the first and second segments of the SLF (SLF I and SLF II). Two patients underwent awake surgery and had difficulties providing the correct responses in the spatial 2-back task with direct subcortical electrical stimulation on the SLF I, which was preserved and confirmed by postoperative diffusion tensor imaging tractography. These patients exhibited no spatial WM deficits during the postoperative immediate and long-term periods.

CONCLUSIONS Spatial WM deficits may persist in patients who undergo resection of the tumor located in the right prefrontal brain parenchyma. Injury to the dorsal frontoparietal subcortical white matter pathway, i.e., the SLF I or SLF I and II, could play a causal role in this chronic deficit. A persistent spatial WM deficit, without motor and language deficits, could affect the professional life of the patient. In such cases, awake surgery would be useful to detect the spatial WM network with appropriate task during tumor exploration.

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KEY WORDS direct electrical stimulation; right prefrontal glioma; spatial working memory; superior longitudinal fasciculus; voxel-based lesion-symptom mapping; oncology

ABBREVIATIONS DES = direct electrical stimulation; DTI = diffusion tensor imaging; DW = diffusion weighted; FDR = false discovery rate; MNI = Montreal Neurological Institute; SLF = superior longitudinal fasciculus; VLSM = voxel-based lesion-symptom mapping; VOI = volume of interest; WM = working memory.

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Spatial working memory (WM) is an essential executive function for goal-oriented behaviors.[2,14,16,21] It requires the ability to actively retain visuospatial information and is primarily localized in the right hemisphere.[26,33,41,44] Deficits in spatial WM are associated with behavioral disorders and affect social activities. Several studies have indicated that the prefrontal and parietal cortices are involved in spatial WM in both monkeys and humans.[11,12,22,28,31,41] White matter subcortical association fiber tracts connecting the prefrontal and parietal regions, including the superior longitudinal fasciculus (SLF), play an important role in spatial WM processing.[20,32,36,43] Although the dorsal attentional network, including the prefrontal cortex, is recruited to control the spatial orientation of attention and the second segment of the SLF (SLF II) is important in its processing,[4,37,40] few anatomical studies have focused on the relationship between spatial WM and specific dorsal subcortical pathway.

Right prefrontal brain tumors are regarded as noneloquent lesions. Therefore, little attention has been paid to deficits in higher cognitive functions, including spatial WM, without apparent motor and language deficits during the postoperative period. Nonetheless, many patients complain of a mild decline in their quality of life, which could be due to disturbance of cognitive functions, including spatial WM, after brain tumor resection.[1,19] Taken together, this suggests that resection of the tumor located in the prefrontal brain parenchyma (i.e., intrinsic tumor resection) may lead to persistent spatial WM deficits associated with a frontoparietal network disturbance during the long-term postoperative period.

The present study aimed to investigate whether chronic spatial WM deficits were present during the postoperative period in patients who underwent resection of the tumor located in the right prefrontal brain parenchyma. Furthermore, we assessed which pathway within the frontoparietal network, subserved by the SLF, could be implicated in spatial WM processing. Spatial WM was assessed using the spatial 2-back task. Affected brain regions were evaluated with lesion overlap and voxel-based lesion-symptom mapping (VLSM) analysis during the long-term postoperative period in patients who underwent right prefrontal glioma resection. Furthermore, responses to the spatial 2-back task were evaluated during awake surgery in 2 patients with right prefrontal low-grade gliomas during direct electrical stimulation (DES) of the area corresponding to the SLF. The stimulated region was confirmed by pre- and postoperative diffusion tensor imaging (DTI) tractography.

Methods

Patients and Healthy Volunteers

Twenty-four patients with a glioma localized to the frontal lobe participated in this study. They had all undergone craniotomies at Kanazawa University Hospital and were > 6 months postsurgery. Participants' demographic data are shown in Table 1. The study population consisted of 3 groups: 14 patients with right-hemisphere lesions (11 men and 3 women; mean age 46.8 ± 9.7 years), 10 patients with left-hemisphere lesions (7 men and 3 women; mean age 46.2 ± 9.8 years), and 14 healthy volunteers (9 men and 5 women; mean age 47.1 ± 6.5 years). Exclusion criteria included the following: the extraction cavity extending into other lobes, a Mini-Mental State Examination score < 23, and insufficient information obtained from the medical records. Five patients were excluded based on the last criterion. Two patients who were recruited underwent tumor resection under local anesthesia, and spatial WM was evaluated in each patient intraoperatively. In addition, pre- and postoperative DTI tractography was performed to determine the position of the SLF I. The profiles of the 2 patients who underwent awake surgery are shown in Table 2. Written informed consent for the use of the patient's images and neuropsychological data was obtained from all patients in the study, and all data were collected retrospectively from their medical records. The study was performed according to the guidelines of the institutional review board of Kanazawa University Hospital.

TABLE 1. Demographic data of 34 study participants

Variable	Group		
	Rt Hemisphere	Lt Hemisphere	Control
Age in yrs, mean ± SD	46.8 ± 9.7	46.2 ± 9.8	47.1 ± 6.5
Sex			
M	11	7	9
F	3	3	5
Handedness			
Rt	13	9	14
Lt	1	1	0
Mos after surgery, mean ± SD	39.9 ± 32.0	31.3 ± 18.2	NA
WHO grade			
I	8	4	NA
II	4	5	NA
III	2	1	NA

NA = not applicable.

Spatial 2-Back Task for Assessing Spatial WM

The spatial 2-back task was performed pre-, intra-, and postoperatively using a 3 × 3 panel of circles (Fig. 1). Every 3 seconds, a closed circle stimulus appeared in 1 of 9 possible locations on a computer monitor. The patient

TABLE 2. Preoperative and postoperative spatial 2-back task responses for 2 patients with right prefrontal glioma*

Case No.	Age (yrs), Sex	Spatial 2-Back Task, % Correct Responses	
		Preop	7 Days Postop
1	37, F	96.9	100 (not worsened)
2	61, M	56.3	70.8 (improved)

* Both patients presented with seizure and had oligodendroglioma. SLF 1 was visualized in each patient pre- and postoperatively, and both patients had positive intraoperative responses during the spatial 2-back task.

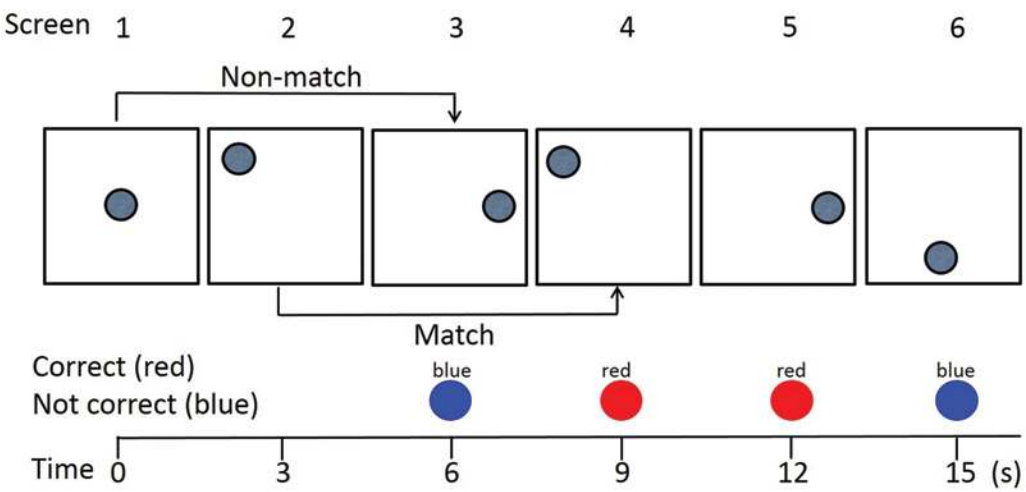

FIG. 1. A schematic representation of the spatial 2-back task. The locations of the *solid circles* are shown in the boxes. In this series, the locations of the first and third circles are different; therefore, the correct answer is "no" in the third screen and the blue button should be pushed. The second and fourth locations are the same; therefore, the correct answer is "yes" in the fourth screen and the red button should be used. Figure is available in color online only.

compared the location of the current stimulus with the location of the stimulus presented in the previous 2 trials and pressed a blue or a red button when a matched or a nonmatched location was presented, respectively. An occupational therapist evaluated whether the answer was correct or incorrect. There were 6 trials per set and each set was performed at least 3 times. The percentage of correct answers was recorded as a measure of spatial WM function. In 6 patients with right prefrontal lesions, spatial WM was evaluated preoperatively. In these instances, preoperative spatial WM was compared with postoperative spatial WM.

Intraoperative Spatial 2-Back Task

All surgical procedures were performed using an asleep-awake-asleep technique with direct stimulation mapping.[13,34] After the dural incision, the motor cortex was evaluated and preserved, with DES delivered via a bipolar probe with a 5-mm tip that delivered a biphasic current (pulse frequency, 60 Hz; single-pulse phase duration, 1 msec; amplitude, 1–4 mA). The posterior limiting border of the tumor resection was evaluated under continuous cortical and subcortical stimulation that evaluated the movement of the left upper and lower extremities. With the assistance of a neuronavigation system with integrated preoperative DTI tractography images and gross anatomical information in the surgical field, we evaluated the inferomedial proximity of the resection procedure to the SLF I. Spatial WM and awareness were evaluated with DES using the spatial 2-back task and the line bisection task, respectively. The intraoperative spatial 2-back task was performed with a 3 × 3 panel of circles, as described above (Fig. 1). There were 6 trials per set and each set was performed 3 times. Incorrect responses observed in 2 or all 3 sets (66% or 100% incorrect responses) were evaluated as positive intraoperative responses. The intraoperative line bisection task was performed as described previously.[38]

Postoperative Evaluations

The postoperative assessment was performed 1 month after surgery to avoid mistakenly assessing very early postoperative surgical damages, including edema. Postoperative MRI, including DTI tractography, was performed within 48 hours after surgery. In the 2 patients who underwent awake surgery and did not present with an intraoperative spatial WM deficit, postoperative assessment was performed only approximately 7 days after surgery to confirm preserved spatial WM function during, and shortly after, the surgical procedure.

Parameters for DTI Tractography

Diffusion-weighted (DW) MR images were acquired both pre- and postoperatively using a 3.0-T MRI scanner (Signa Excite HDx 3.0T, General Electric Medical Systems). A series of axial DW images with (b-value = 1000 sec/mm^2) and without (b-value = 0) a diffusion-sensitizing gradient along 30 directions was obtained. The other diffusion parameters were as follows: TR 14,000 msec, TE 69.6 msec, number of excitations 2, 60 axial slices and slice thickness 2.5 mm with no interslice gap, and field of view 220 × 220 mm with a matrix 88 × 88 resulting in an effective resolution of 2.5-mm^3 isotropic voxels. The DW MR images were transferred to a PC workstation using iPlan Stereotaxy 3.0 software (BrainLab), which generated qualitative maps. Regions of interest targeting the SLF I were chosen manually by referring to the DTI tractography atlas and previous studies. The multiple regions of interest approach, including dorsal prefrontal, superior parietal, and regions parallel to the cingulum, was used to identify the targeted fiber tract.[7,18,23]

Lesion Mapping

Structural MR images were also acquired during the 6-month postoperative period. The lesion resection cavity in 14 patients with right frontal glioma was reconstructed in standardized Montreal Neurological Institute (MNI) space (resolution of 1 × 1 × 1 mm) by M.K. using SPM 8 implemented in a MATLAB environment (R2010a, version 7.10; The MathWorks, Inc.) with cost function masking[6] and MRIcron software (Chris Rorden, MRIcron 2013, http://www.mccauslandcenter.sc.edu/mricro/mricron/install.html). The reconstructed volume of interest (VOI) was compared with the non-normalized image and operative record.

Voxel-Based Lesion-Symptom Mapping

To demonstrate the putative relationship between the spatial 2-back task scores and location of the resection cavity, VLSM was performed using NPM software[30] provided in the MRIcron package. A parametric t-test was chosen to compare the resulting statistical maps. A false discovery rate (FDR) correction, which corrects for multiple comparisons and spatial dependence, with a threshold of $q = 0.05$, was systematically applied to avoid false-positive results (Type I error). The software automatically computed this correction. The identified significant relationships were presented as Z scores at MNI coordinates, with and without the lesion resection volume. To demonstrate the potential roles of SLFs I, II, and III, a standardized white matter atlas was used.[35] The VOI of the VLSM analysis was overlapped with the regions encompassing more than 50% of SLF I (blue), II (green), and III (yellow) on an MNI template.

Statistical Analysis

Data are presented as the mean percentage of correct responses ± SD for the spatial 2-back task. One-way ANOVA with a post hoc Tukey-Kramer test was used to compare groups. Differences were considered significant when $p < 0.05$. All data were analyzed using the statistical analysis software JMP (Version 10.0.0; SAS Institute, Inc.).

Results

Use of the Spatial 2-Back Task to Evaluate a Chronic Spatial WM Deficit

Although there was no significant difference between patients and the healthy control group preoperatively, a significant decline was observed postoperatively in the patients who did not undergo awake surgery ($p = 0.013$; preoperative, 93.8 ± 6.5; postoperative, 88.5 ± 12.3; control, 98.7 ± 3.3) (Fig. 2). The mean percentage of correct responses was significantly lower in the patients with right-hemisphere lesions when compared with the healthy control group ($p = 0.02$; right, 90.0 ± 6.5; left, 91.7 ± 5.0; control, 98.7 ± 3.3) (Fig. 3).

Intraoperative Spatial 2-Back Task and DTI Tractography in 2 Patients

Figure 4 shows neuroradiological images and an intraoperative photograph from Case 1. When the stimulation probe was located at a deep medial site of the resection cavity, intraoperative DES reproducibly caused difficulty in providing the correct responses in the spatial 2-back task.

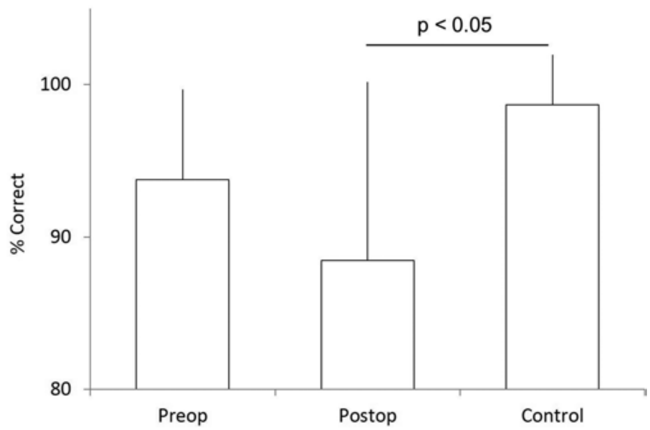

FIG. 2. Results of spatial 2-back task in patients with right prefrontal lesions. The comparison is between the pre- and postoperative periods.

However, the patient provided the correct responses without DES. No reproducible deviations were observed in the line bisection task during intraoperative DES of the same site. The surgical procedure was terminated when a positive response in the spatial 2-back task was elicited. Postoperative MRI and DTI tractography revealed gross-total resection of the tumor lesion and preservation of the SLF I, respectively. Postoperative spatial WM did not worsen.

Figure 5 shows neuroradiological images and an intraoperative photograph from Case 2. When the stimulation probe was located at a lower anterior region of the resection cavity, intraoperative DES reproducibly caused difficulty in providing the correct responses in the spatial 2-back task. This site did not elicit a positive response in the line bisection task. The surgical procedure was terminated when a positive response in the spatial 2-back task was elicited. This patient had a mild deficit in spatial WM preoperatively (43.7% incorrect responses on the spatial 2-back task) but had reproducible 100% incorrect responses with stimulation intraoperatively. In addition, the patient reproducibly provided the correct responses without DES in the positive response area. Postoperative MRI and DTI tractography revealed partial resection of the lesion

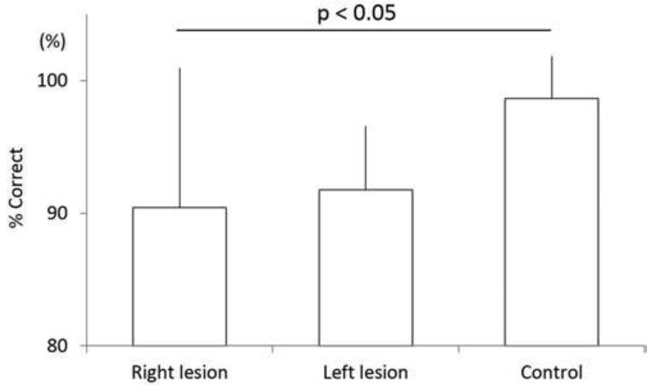

FIG. 3. Results of spatial 2-back task. The comparison is between the right prefrontal and left prefrontal lesions.

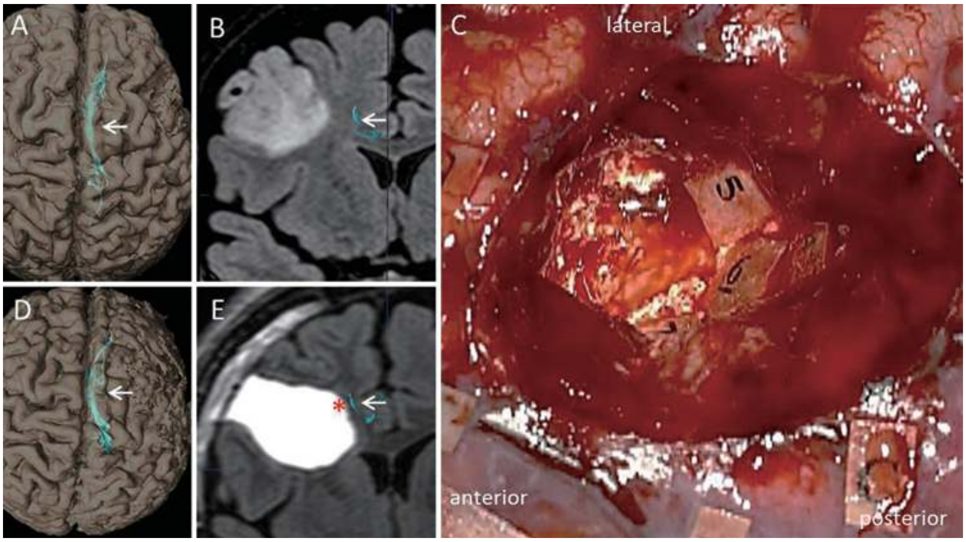

FIG. 4. Neuroradiological images and an intraoperative photograph from Case 1 are shown. **A:** Preoperative tractography (3D image) showing the SLF I (blue tract indicated by a *white arrow*). **B:** Preoperative tractography (coronal image) showing the SLF I (blue section indicated by a *white arrow*). **C:** Intraoperative photograph showing positive site mapping during the intraoperative spatial 2-back task (tag numbers *6* and *7*). **D:** Postoperative tractography (3D image) showing the preserved SLF I (blue tract indicated by a *white arrow*). **E:** Postoperative tractography (coronal image) showing the SLF I (blue section indicated by a *white arrow*). The *red asterisk* indicates the site of DES over the SLF I, corresponding to the tags in panel C. Figure is available in color online only.

(tumor remnant in the motor area) and preservation of the SLF I, respectively. Spatial WM improved postoperatively.

Lesion Mapping

The overall distribution of the resection cavity in all patients with right prefrontal glioma is shown in Fig. 6. The overlap results indicated that the maximal resection cavity overlap falls in the prefrontal white matter, where several intrahemispheric association fiber tracts are present. We then performed a VLSM analysis to evaluate the anatomical correlates of the spatial WM deficits and specific association fibers.

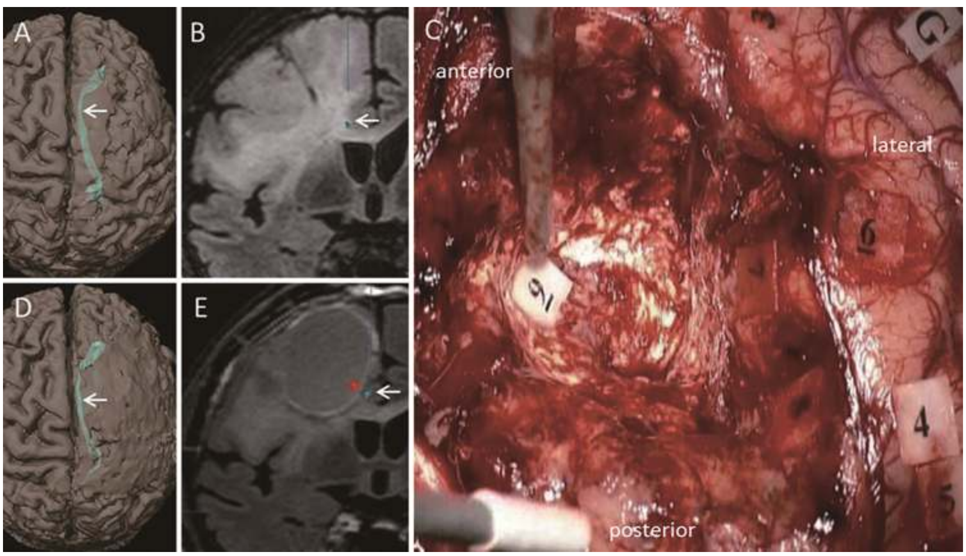

FIG. 5. Neuroradiological images and an intraoperative photograph from Case 2 are shown. **A:** Preoperative tractography (3D image) showing the SLF I (blue tract indicated by a *white arrow*). **B:** Preoperative tractography (coronal image) showing the SLF I (blue section indicated by a *white arrow*). **C:** Intraoperative photograph showing a positive mapping site during the intraoperative spatial 2-back task (tag number *9*). **D:** Postoperative tractography (3D image) showing the preserved SLF I (blue tract indicated by a *white arrow*). **E:** Postoperative tractography (coronal image) showing the SLF I (blue section indicated by a *white arrow*). The *red asterisk* indicates the site of DES over the SLF I, corresponding to the tag in panel C. Figure is available in color online only.

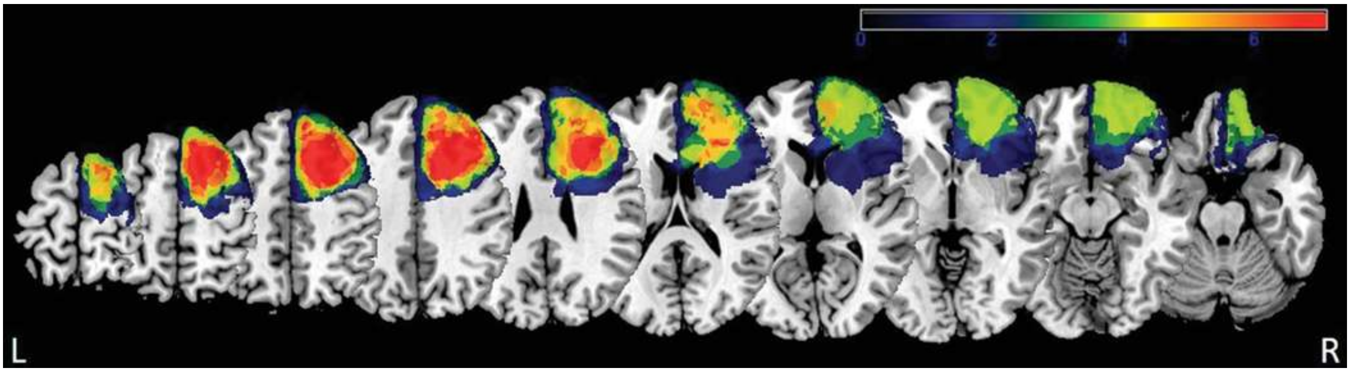

FIG. 6. Overlay map of the resection cavities of patients with a right frontal lobe lesion (n = 14). The *red color* shows the region where the resection cavities overlap by more than 50%. L = left; R = right. Figure is available in color online only.

The VLSM and Its Relation to the SLF

Figure 7A shows the statistical map from the VLSM analysis performed with the spatial 2-back task scores. The largest cluster of significant voxels was located in the deep white matter region of the right frontal lobe (Z max = 1.74; p = 0.05 FDR corrected; cluster size = 35 voxels; and MNI coordinates of center [x = 22, y = 0, z = 39]). Following this, the VOI of significant voxels was overlaid with the VOIs of SLFs I, II, and III on an MNI template (Fig. 7B). The result showed that the statistically significant ($p < 0.05$) cluster from the VLSM was localized in a region that overlapped the middle of SLFs I and II.

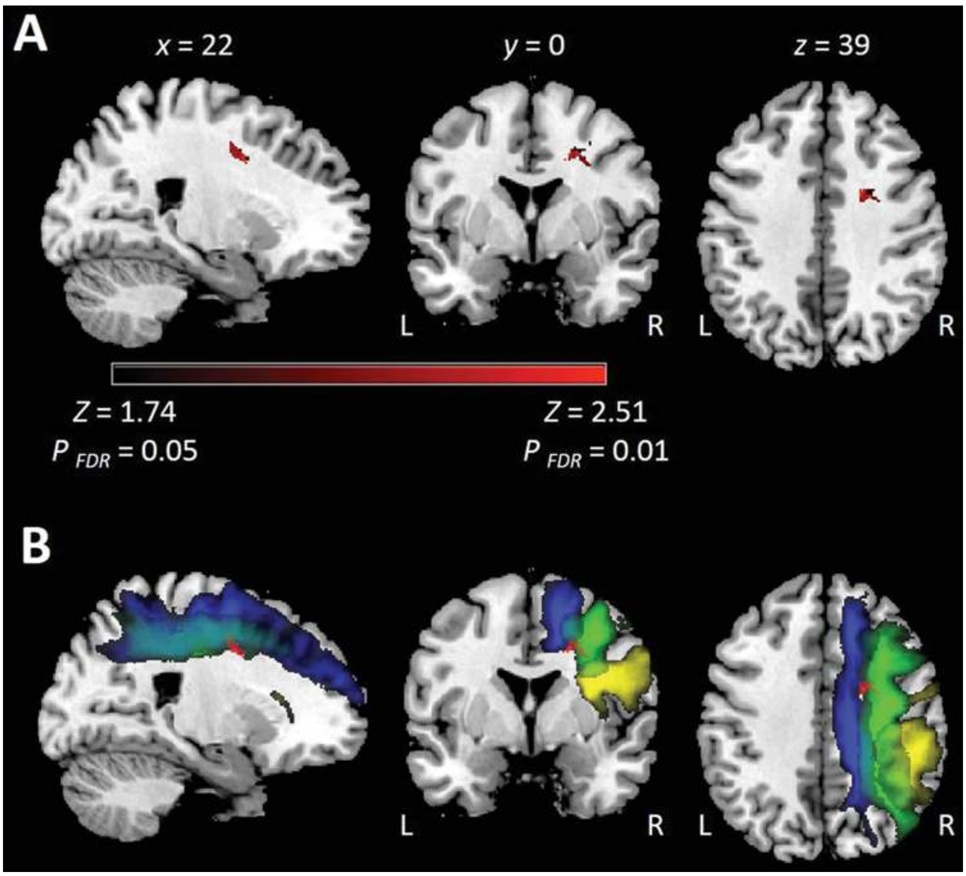

FIG. 7. The results of the VLSM. A statistically significant cluster (*red voxels*) of the resection cavity analyzed with the spatial 2-back task scores (**A**) was overlapped with SLFs I (*blue*), II (*green*), and III (*yellow*) (**B**). The statistical map shows only significant voxels with an FDR-controlled threshold (p = 0.05; z = 1.74). The MNI coordinates of each section are shown (x = sagittal, y = coronal, z = axial). Figure is available in color online only.

Discussion

Spatial WM is part of a central executive storage system that requires the ability to actively represent visuospatial information.[2,16] Deficits in spatial WM can significantly interfere with daily life activities. In the present study, we found that a chronic spatial WM deficit, without motor and language deficits, could persist postoperatively in patients following a prefrontal intrinsic glioma resection. Classically, a right prefrontal lesion is regarded as noneloquent because apparent motor and language deficits usually do not occur following tumor resection. Nonetheless, a persistent spatial WM deficit after right prefrontal intrinsic tumor resection could affect a patient's professional life. Therefore, patients with right prefrontal intrinsic tumors should be informed about the possibility of a chronic spatial WM deficit.

In such cases, awake surgery with an appropriate task to detect the spatial WM network during tumor exploration could be used for tumor resection in this region. Although a chronic spatial WM deficit could often occur after right prefrontal intrinsic tumor resection, it is not clear from the present study how this deficit actually affects the quality of life of each patient. A study that evaluates the relationship between spatial WM deficits and a patient's quality of life should be performed in the future.

Frontoparietal connections of the human and nonhuman primate brain are similarly organized. The SLF, a major intrahemispheric fiber tract, is composed of 4 components. Among these, SLFs I, II, and III connect frontal and parietal regions.[18,23,25] The SLF I connects the superior parietal and superior frontal regions in humans and extends to the dorsal premotor and dorsolateral prefrontal regions. The SLF II is located in the central core of the white matter above the insula and extends from the angular gyrus to the caudal dorsolateral prefrontal regions. The SLF III occupies the ventral frontoparietal pathway and extends from the supramarginal gyrus to ventral prefrontal regions.

Based on these anatomical features, the potential functional roles of the frontoparietal networks of the SLF can be hypothesized as follows: the SLF I is activated during voluntary orienting of spatial attention and is related to top-down spatial attention processing; the SLF II provides a pathway for direct communication between the dorsal and ventral networks; and the SLF III overlaps the ventral pathway, which is activated during the automatic capture of spatial attention.[3,21,35] Therefore, spatial WM, which is associated with top-down attention processing, can be modulated by the SLF I or II, or by both.

In contrast, visuospatial awareness, which is related to automatic spatial attention and spatial neglect, can be modulated by the SLF II or III, or by both. Several recent reports have indicated that visuospatial neglect occurs with lesions located in the SLF II.[4,37,40,42] In the present study, lesion-symptom analysis indicated that a region overlapping SLFs I and II contained the main subcortical white matter lesion that caused the spatial WM deficit in our patients. These findings are supported by recent studies that indicate that a region associated with spatial WM has been identified around the superior frontal sulcus in humans.[10,39] This may be the same region as the one that we found overlapping SLFs I and II in the human brain. It is possible that cortical lesions are responsible for a spatial WM deficit; i.e., both frontal and parietal terminations of the SLFI and II, including the dorsolateral prefrontal cortex (which is connected by the subcortical pathway), could be more specifically associated with spatial WM.[11,22,28,41]

Nonetheless, taking into account the brain plasticity potential in cortical lesions and the crucial role of the white matter pathway as the "minimal common brain" (which has reduced potential for plasticity and is more important for preservation of function), white matter pathway injuries are likely to lead to long-standing functional deficits without compensation.[4,17] Elucidating which cortical or subcortical region is more specifically associated with chronic spatial WM deficits is beyond the scope of this study and could not be evaluated with the specific methods used. Future studies designed to compare cortical and subcortical functions would be necessary.

We found that intraoperative DES on the SLF I led to incorrect responses in the spatial 2-back task. To the best of our knowledge, this is the first report to provide direct evidence that the SLF I subserves spatial WM processing in humans. We were able to visually confirm the presence of the SLF with DTI tractography in these patients, and postoperative spatial WM was preserved or improved. In contrast, DES at a deep lateral site of the resection cavity, most likely corresponding to the SLF II, did not elicit a positive response in the spatial 2-back task.

These findings indicated that spatial WM processing is mediated by a more dorsal SLF pathway, such as the SLF I—not the SLF II. However, we could not evaluate the SLF II in these patients because the tumors were located in the dorsolateral prefrontal region, within which the SLF II is located. Therefore, we were unable to visualize the SLF II with DTI tractography. Several recent studies, which have included an intraoperative line bisection task, have indicated that the SLF II is the main pathway associated with the spatial neglect found in spatial awareness disturbances.[4,37,38,40,42] In addition, spatial WM may have a close interaction with spatial awareness.[24]

Interestingly, several patients who were recruited in this study revealed spatial neglect on the line bisection test (data not shown). The region associated with chronic spatial WM deficit in patients with right prefrontal glioma resection was located in a region overlapping SLFs I and II. However, we could not reproducibly elicit a positive response in an intraoperative line bisection task during DES to the SLF I and other sites. These results could be due to the following reasons: 1) The tumor invaded the SLF II and its function was being compensated for by other regions; 2) spatial WM and spatial awareness information are processed independently by different pathways (as found in intraoperative DES, a more dorsal pathway of the SLF, such as the SLF I, could be a causative pathway for the postoperative chronic spatial WM deficit); and 3) the line bisection task is inappropriate for intraoperative detection of spatial neglect in some cases. It is beyond the scope of this study to elucidate the relationship between spatial WM deficit and spatial neglect. Future intraoperative evaluation of the SLF II in humans using DES, as well as the 2-back task and other appropriate tasks for detecting spatial neglect, is necessary to elucidate its functional roles in spatial WM and awareness.

No significant difference was found on the spatial 2-back task between patients with left prefrontal lesions and healthy volunteers. However, patients with a left prefrontal lesion showed a tendency to carry a small spatial WM deficit when compared with healthy volunteers ($p = 0.10$). Although the possibility that brain tumor pathology or its treatment may influence these results could not be ruled out, we speculate that these results indicated that both hemispheres are implicated in spatial WM processing with right lateralization. This result is supported by right lateralization theories in spatial cognitive processing. The first theory is related to the competence of the 2 hemispheres to deal with the left and right sides of space. According to this theory, the left hemisphere can represent only the right space, whereas the right hemisphere is able to represent both right and left space.[15,27] Therefore, the right hemisphere can deal with the entire horizontal space in a left-hemisphere injury, but not vice versa.

The second theory is based on a multiple-region network that is lateralized to the right hemisphere.[8,9] This spatial processing network includes the inferior parietal, posterior superior temporal, inferior and middle frontal, and frontal operculum regions. In contrast to simple attentional processes, WM processing is a higher cognitive function; therefore, it is associated with a functional network that includes multiple regions connected by association fiber tracts. This theory may explain the right lateralization of the chronic spatial WM deficit in our study.

Finally, despite the small number of patients recruited in the present study and the heterogeneity of tumor pathology (including different tumor grades), our findings showed that resection of a right prefrontal glioma (i.e., glioma diagnosed postoperatively) caused a postoperative chronic spatial WM deficit. The n-back tasks, including the spatial 2-back task, are representative tests used to detect WM disturbances. Nonetheless, another task may be more sensitive and suitable for use intra- and postoperatively. In addition, the relationship between the spatial WM deficit and spatial neglect is yet to be elucidated. Furthermore, VLSM during the long-term period has its own methodological limitations: the damage to a particular voxel is independent of damage to other voxels, plasticity in brain functional networks would make it difficult to infer the original function of the healthy brain, and so on.[5,29] We acknowledge these limitations. However, to the best of our knowledge, we have demonstrated for the first time that dorsal frontoparietal pathway injuries subserved by the SLF may play an important role in the occurrence of postoperative chronic spatial WM deficits in patients with right prefrontal glioma.

Conclusions

Right prefrontal lesions are regarded as noneloquent, and postoperative deficits of the higher cognitive function have been overlooked by standard motor and language examinations. Nonetheless, we demonstrated that right prefrontal glioma resection could result in a chronic spatial WM deficit. One of the causative factors for the deficit could be an impairment of the dorsal frontoparietal subcortical white matter pathway subserved by the SLF. An analysis performed using VLSM revealed that among the segments of the SLF, SLFs I and II could be candidates. Furthermore, intraoperative DES of the SLF I elicited transient disturbance of the spatial WM processing.

To the best of our knowledge, this is the first direct evidence indicating the relationship between the spatial WM and the SLF in humans. Even in the absence of motor and language deficits, chronic spatial WM deficit could lead to an impediment to continuation of a patient's professional activities. Awake surgery with DES to detect the pathway during the tumor exploration would be useful in such patients. To confirm the usefulness of intraoperative mapping for spatial WM preservation, more surgical cases with spatial WM tasks will be necessary in the future. Finally, some patients with prefrontal lesions may choose to undergo a more limited resection under awake surgery, aimed at the preservation of normal functioning at the known risk of a shorter lifespan. Alternatively, patients may choose the more radical tumor resection, aimed at the preservation of life with the potential cost of lost neural function, which could affect the patient's lifestyle. Customized surgical strategies should be developed according to the patient's wishes.

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References

1. Aaronson NK, Taphoorn MJB, Heimans JJ, Postma TJ, Gundy CM, Beute GN, et al: Compromised health-related quality of life in patients with low-grade glioma. **J Clin Oncol 29:**4430–4435, 2011
2. Baddeley A: Working memory: looking back and looking forward. **Nat Rev Neurosci 4:**829–839, 2003
3. Bartolomeo P, Thiebaut de Schotten M, Chica AB: Brain networks of visuospatial attention and their disruption in visual neglect. **Front Hum Neurosci 6:**110, 2012
4. Bartolomeo P, Thiebaut de Schotten M, Doricchi F: Left unilateral neglect as a disconnection syndrome. **Cereb Cortex 17:**2479–2490, 2007
5. Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, et al: Voxel-based lesion-symptom mapping. **Nat Neurosci 6:**448–450, 2003
6. Brett M, Leff AP, Rorden C, Ashburner J: Spatial normalization of brain images with focal lesions using cost function masking. **Neuroimage 14:**486–500, 2001
7. Catani M, Thiebaut de Schotten M: **Atlas of Human Brain Connections.** New York: Oxford University Press, 2012
8. Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A: Neural basis and recovery of spatial attention deficits in spatial neglect. **Nat Neurosci 8:**1603–1610, 2005
9. Corbetta M, Shulman GL: Control of goal-directed and stimulus-driven attention in the brain. **Nat Rev Neurosci 3:**201–215, 2002
10. Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV: An area specialized for spatial working memory in human frontal cortex. **Science 279:**1347–1351, 1998
11. Curtis CE: Prefrontal and parietal contributions to spatial working memory. **Neuroscience 139:**173–180, 2006
12. du Boisgueheneuc F, Levy R, Volle E, Seassau M, Duffau H,

Kinkingnehun S, et al: Functions of the left superior frontal gyrus in humans: a lesion study. **Brain 129:**3315–3328, 2006
13. Duffau H, Peggy Gatignol ST, Mandonnet E, Capelle L, Taillandier L: Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere. **J Neurosurg 109:**461–471, 2008
14. Gazzaley A, Nobre AC: Top-down modulation: bridging selective attention and working memory. **Trends Cogn Sci 16:**129–135, 2012
15. Heilman K, Watson R, Valenstein E: Neglect and related disorders, in Heilman K, Valenstein E (eds): **Clinical Neuropsychology, ed 3.** New York: Oxford University Press, 1993, pp 279–336
16. Hofmann W, Schmeichel BJ, Baddeley AD: Executive functions and self-regulation. **Trends Cogn Sci 16:**174–180, 2012
17. Ius T, Angelini E, Thiebaut de Schotten M, Mandonnet E, Duffau H: Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: towards a “minimal common brain”. **Neuroimage 56:**992–1000, 2011
18. Kamali A, Flanders AE, Brody J, Hunter JV, Hasan KM: Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. **Brain Struct Funct 219:**269–281, 2014
19. Klein M, Duffau H, De Witt Hamer PC: Cognition and resective surgery for diffuse infiltrative glioma: an overview. **J Neurooncol 108:**309–318, 2012
20. Klingberg T: Development of a superior frontal-intraparietal network for visuo-spatial working memory. **Neuropsychologia 44:**2171–2177, 2006
21. Kravitz DJ, Saleem KS, Baker CI, Mishkin M: A new neural framework for visuospatial processing. **Nat Rev Neurosci 12:**217–230, 2011
22. Levy R, Goldman-Rakic PS: Segregation of working memory functions within the dorsolateral prefrontal cortex. **Exp Brain Res 133:**23–32, 2000
23. Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, et al: Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. **Cereb Cortex 15:**854–869, 2005
24. Malhotra P, Jäger HR, Parton A, Greenwood R, Playford ED, Brown MM, et al: Spatial working memory capacity in unilateral neglect. **Brain 128:**424–435, 2005
25. Martino J, De Witt Hamer PC, Berger MS, Lawton MT, Arnold CM, de Lucas EM, et al: Analysis of the subcomponents and cortical terminations of the perisylvian superior longitudinal fasciculus: a fiber dissection and DTI tractography study. **Brain Struct Funct 218:**105–121, 2013
26. Mayer JS, Bittner RA, Nikolić D, Bledowski C, Goebel R, Linden DE: Common neural substrates for visual working memory and attention. **Neuroimage 36:**441–453, 2007
27. Mesulam MM: Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. **Philos Trans R Soc Lond B Biol Sci 354:**1325–1346, 1999
28. Müller NG, Knight RT: The functional neuroanatomy of working memory: contributions of human brain lesion studies. **Neuroscience 139:**51–58, 2006
29. Rorden C, Karnath HO: Using human brain lesions to infer function: a relic from a past era in the fMRI age? **Nat Rev Neurosci 5:**813–819, 2004
30. Rorden C, Karnath HO, Bonilha L: Improving lesion-symptom mapping. **J Cogn Neurosci 19:**1081–1088, 2007
31. Salazar RF, Dotson NM, Bressler SL, Gray CM: Content-specific fronto-parietal synchronization during visual working memory. **Science 338:**1097–1100, 2012
32. Schmahmann JD, Pandya DN: **Fiber Pathways of the Brain.** New York: Oxford University Press, 2006
33. Smith EE, Jonides J, Koeppe RA: Dissociating verbal and spatial working memory using PET. **Cereb Cortex 6:**11–20, 1996
34. Szelényi A, Bello L, Duffau H, Fava E, Feigl GC, Galanda M, et al: Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. **Neurosurg Focus 28(2):**E7, 2010
35. Thiebaut de Schotten M, Dell’Acqua F, Forkel SJ, Simmons A, Vergani F, Murphy DG, et al: A lateralized brain network for visuospatial attention. **Nat Neurosci 14:**1245–1246, 2011
36. Thiebaut de Schotten M, Dell’Acqua F, Valabregue R, Catani M: Monkey to human comparative anatomy of the frontal lobe association tracts. **Cortex 48:**82–96, 2012
37. Thiebaut de Schotten M, Tomaiuolo F, Aiello M, Merola S, Silvetti M, Lecce F, et al: Damage to white matter pathways in subacute and chronic spatial neglect: a group study and 2 single-case studies with complete virtual “in vivo” tractography dissection. **Cereb Cortex 24:**691–706, 2014
38. Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Lévy R, Dubois B, et al: Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. **Science 309:**2226–2228, 2005
39. Ungerleider LG, Courtney SM, Haxby JV: A neural system for human visual working memory. **Proc Natl Acad Sci U S A 95:**883–890, 1998
40. Vallar G, Bello L, Bricolo E, Castellano A, Casarotti A, Falini A, et al: Cerebral correlates of visuospatial neglect: a direct cerebral stimulation study. **Hum Brain Mapp 35:**1334–1350, 2014
41. van Asselen M, Kessels RP, Neggers SF, Kappelle LJ, Frijns CJ, Postma A: Brain areas involved in spatial working memory. **Neuropsychologia 44:**1185–1194, 2006
42. Verdon V, Schwartz S, Lovblad KO, Hauert CA, Vuilleumier P: Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. **Brain 133:**880–894, 2010
43. Vestergaard M, Madsen KS, Baaré WF, Skimminge A, Ejersbo LR, Ramsøy TZ, et al: White matter microstructure in superior longitudinal fasciculus associated with spatial working memory performance in children. **J Cogn Neurosci 23:**2135–2146, 2011
44. Walter H, Bretschneider V, Grön G, Zurowski B, Wunderlich AP, Tomczak R, et al: Evidence for quantitative domain dominance for verbal and spatial working memory in frontal and parietal cortex. **Cortex 39:**897–911, 2003

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Hayashi, Kinoshita, Nakajima. Acquisition of data: Hayashi, Kinoshita, Nakajima, Okita. Analysis and interpretation of data: Hayashi, Kinoshita, Nakajima. Drafting the article: Hayashi, Kinoshita, Nakajima. Critically revising the article: all authors. Reviewed submitted version of manuscript: Hayashi, Kinoshita, Nakajima. Approved the final version of the manuscript on behalf of all authors: Hayashi. Statistical analysis: Kinoshita, Nakajima. Administrative/technical/material support: Hayashi, Shinohara, Miyashita, Tanaka, Okita, Nakada. Study supervision: Hayashi.

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