Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-020-03656-9

CLINICAL STUDY

Awake surgery for right frontal lobe glioma can preserve visuospatial cognition and spatial working memory

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Received: 24 September 2020 / Accepted: 27 October 2020

Abstract

Purpose Awake surgery is the standard treatment to preserve motor and language functions. This longitudinal study aimed to evaluate the resection rate and preservation of neurocognitive functions in patients with right frontal lobe glioma who underwent awake surgery.

Methods Thirty-three patients (mean age, 48.0 years) with right frontal lobe glioma who underwent awake surgery at our hospital between 2013 and 2019 were included. Fourteen, thirteen, and six cases had WHO classification grades of II, III, and IV, respectively. We evaluated visuospatial cognition (VSC) and spatial working memory (SWM) before and three months after surgery. Relevant brain areas for VSC and SWM were intraoperatively mapped, whenever the task was successfully accomplished. Therefore, patients were divided into an intraoperative evaluation group and a non-evaluation group for each function, and the resection rate and functional outcomes were compared.

Results The removal rate in the evaluation group for VSC and SWM were similar to that in the non-evaluation group. Chronic impairment rate of VSC was significantly lower in the evaluation than in the non-evaluation group (5.6% vs. 33.3%, $p = 0.034$). No patient showed postoperative SWM impairment in the evaluation group as opposed to the non-evaluation group (16.7%, $p = 0.049$). The probability of resection of the deeper posterior part of the middle frontal gyrus, the relevant area of VSC, was higher in the non-evaluation group than in the evaluation group.

Conclusions We statistically verified that awake surgery for right frontal lobe glioma results in successful preservation of VSC and SWM with satisfying resection rates.

Keywords Awake surgery · Glioma · Frontal lobe · Working memory · Visuospatial cognition

Introduction

Awake craniotomy with intra-operative cortico-subcortical direct electrical stimulation (DES) is nowadays a well-established and recommended technique for low-grade and high-grade gliomas [1–8]. This surgical intervention is widely used for gliomas located in regions, such as motor and language-related regions, leading to broader resection and favorable neurological outcomes [6, 9]. In addition to motor and language functions, the neurocognitive function of the non-dominant hemisphere is also important in maintaining the patient's quality of life, and therefore should be preserved during awake surgery [5, 10–16].

Previously, awake surgery has been suggested to effectively preserve right frontal lobe (RFL) function [17–23]. Recently, we identified the crucial location in the RFL and the specific subcortical fibers serving visuospatial cognition

Electronic Supplementary Material The online version of this article (https://doi.org/10.1007/s11060-020-03656-9) contains supplementary material, which is available to authorized users.

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Published online: 02 November 2020

(VSC) and spatial working memory (SWM) with DES during awake surgery and neuroimaging analyses [22, 24]. Based on these findings, we tried to preserve the VSC and SWM in patients with an RFL glioma by means of awake surgery, as well as assess tumor resection rate. In particular, we evaluated the impact of an awake mapping on the functions of these regions. We hypothesized that awake surgery for RFL glioma could keep the tumor resection rate satisfactory and preserve VSC and SWM.

To the best of our knowledge, ours is the first study on VSC, SWM and oncological outcomes of awake surgery for RFL glioma.

Methods

Participants

A total of 139 patients with a brain tumor who underwent awake surgery in our hospital from August 2013 to December 2019 were recruited. The lesions were localized on the right side in 56 patients. Finally, 33 patients with an RFL lesion who met our inclusion criteria (lesion for right frontal lobe but excluding primary motor area and WHO grade I gliomas) were included (Supplementary Fig. 1). Serial neuropsychological examinations were completed until 3 months postoperatively in all 33 patients (mean age, 48.0 years; range, 23–72). A summary of patient demographics and clinical characteristics is shown in Supplementary Table 1. Written informed consent was obtained from all patients. This study was performed according to the guidelines of the Internal Review Board of our university and was approved by the Medical Ethics committee of our institution (approval number: 2593).

Awake surgery and intraoperative evaluation

Awake surgery was performed using the 'asleep-awake-asleep' technique, where cortical and subcortical brain mapping was accomplished through DES [25]. General anesthesia is maintained during positioning, skull pinning, craniotomy, and dural opening. We prefer to use total intravenous anesthesia with propofol and remifentanil, and to set up the patient on a lateral position. Once dura is open, all drugs were stopped, and the patient progressively awakened. Direct electrical stimulation for the cortical and subcortical mapping was delivered via a bipolar probe with a 5-mm space between the tips that delivered a biphasic current (pulse frequency 60 Hz, single-pulse phase duration 0.2 ms and amplitude 2–6 mA). To determine the stimulation thresholds, the stimulation intensity should be increased stepwise from 1.5 mA by 0.5 mA until inhibition of counting and upper limb movement are observed by the stimulation at the negative motor area (inferior frontal gyrus, just anterior to the primary facial motor area). This stimulation intensity should be used for further mapping. The maximum stimulation intensity is 6 mA as previously described [26]. Main complication during the awake surgery is seizure. In this study, intraoperative stimulation-induced seizures were observed in 6 case (18.2%), but it could be rapidly terminated by the local irrigation of cortical surface with cold sterile iced saline [27].

In the current study, we focused on VSC and SWM for intraoperative evaluations, performed as previously reported [24, 28]. Most importantly, to achieve appropriate onco-functional balance for all patients, we first resected the central part of the tumor, namely the enhanced lesion if existing, and then we performed an intraoperative evaluation with brain mapping for extended resection [29]. For lesions without enhancement, the T2/FLAIR hyper lesion was resected as long as negative mapping was confirmed.

Line bisection test

The line bisection test is the most common evaluation for VSC [28, 30, 31]. In this test, patients are asked to point to the midpoint of a 20-cm line while the cortical or subcortical region is stimulated (Supplementary Fig.2a, Supplementary video 1).

Spatial 2-back test

The N-back test is a common and reliable assessment for working memory [32], and is advantageous for assessing the temporal retentive capacity of visual information and management ability. In it, visual stimuli (e.g., symbol, dot pattern, and matrix figures) appear automatically every few seconds (usually 2 or 3s) on a computer monitor. Patients are asked to perform two tasks simultaneously, e.g., to remember the current stimulus and compare it with the ones presented in the previous N trials (Supplementary Fig. 2b, Supplementary video 2).

Patients were divided into two groups for each function: an intraoperative evaluation group (EG) and a non-evaluation group (NEG). The NEG includes cases in which the task could not be successfully accomplished because of patients' conditions such as fatigue, insufficient motivation, or low awakening.

Pre- and post-operative evaluation of frontal lobe function

A neuropsychological examination was performed to assess changes over time for all patients both pre-surgery and 3 months postoperatively as standard care. We used the line bisection test and 2-back test to assess VSC and SWM, respectively.

Neuroimaging acquisition and identification of positive mapping sites

Structural magnetic resonance (MR) imaging scans were acquired during the postoperative 3 months. Scans were acquired using conventional high-resolution three-dimensional T1-weighted sequences on a 3.0 Tesla MR imaging scanner (Signa™ Excite HDx 3.0T; GE Healthcare, Little Chalfont, UK). Each MR image conformed to the MNI template using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), implemented in MATLAB (https://www.mathworks.com/products/matlab/). Resection cavities were manually reconstructed via MRIcron software (https://people.cas.sc.edu/rorden/mricron/index.html). Each reconstruction was achieved initially by R.N. and then systematically checked by a neurosurgeon (M.K.). We calculated the extent of resection by using the hyperintense areas on T2-weighted images for grade II/III tumors and the contrast enhanced area for grade IV tumors. Extent of resection was defined as follows: partial resection, < 85%; subtotal resection, ≥ 85%, < 95%; gross total resection, ≥ 95%, < 100%; total resection, = 100%.

Positive mapping sites during awake surgery were plotted on the corresponding normalized MR images using operative reports and intraoperative video records. The locations of the intraoperative cortical and subcortical stimulation sites were determined according to their spatial relationship to various anatomical landmarks (gyri, sulci, the midline, deep gray nuclei, and/or lateral ventricles). The spatial topography of stimulation points was plotted on the 3D MNI template using MRIcroGL software (https://www.cabiatl.com/mricrogl/).

Statistical analysis

First, to compare the extent of resection between EG and NEG, the Wilcoxon test was used. As for behavioral data, all row-scores were converted to Z-scores using the mean and standard deviations of age-matched controls. A deficit was recorded if the Z-score was ≤ − 1.65 than age matched controls [33]. The likelihood-ratio chi-squared test with Bonferroni correction was used to analyze functional outcomes, that is whether patients could maintain preoperative function. All statistical analyses were performed using statistical analysis software (JMP, version 14.3.0; SAS Institute, Inc.).

Voxel-based lesion-symptom (VLSM) analyses were performed to investigate the relationship between the resected region and postoperative RFL function. The dependent variable was the standard residual from a multiple regression analysis where age and educational level were entered as predictors. ROIs, which were damaged in at least 10% of the patients, were automatically selected. Parametric *t*-tests were used to generate statistical maps. Significant differences between the frontal lobe functional test score and voxels with and without lesions were identified and presented as *Z*-scores at MNI coordinates.

Results

Anatomical, demographic, and clinical data

The overlap maps of all resection cavities (n = 33) demonstrated the greatest overlap in the posterior deep part of the RFL (Supplementary Fig. 3). The independence level (Karnofsky Performance Statues [KPS]) at pre-operation and 3 months were 93.0 ± 8.5 (range, 70–100) and 86.1 ± 15.4 (range, 50–100) respectively, demonstrating that KPS at the chronic phase was almost preserved compared with the pre-operative condition. Progression-free survival (median) by malignant grades was as follows: 65 months for grade II, 35 months for grade III, and 34 months for grade IV. The total EG and NEG numbers were as follows: line bisection test, 18 and 15, respectively; spatial 2-back test, 15 and 18, respectively. Neither intra-operative line bisection test nor spatial 2-back test were performed in 11 patients. The two groups consisted of homogenous populations with respect to age, WHO grade, biomolecular pattern, tumor volume, and preoperative test score (Table 1). Moreover, all patients received the same treatments (tumor removal without post-operative radio- and chemotherapy for grade II, complete resection of enhanced areas with post-operative radio- and chemotherapy for grade III/IV). Preoperatively, no significant differences for each test score between the two groups were observed: the percentage of impaired patients was 0% and 6.7% for VSC, and 20.0% and 27.8% for SWM in the EG and NEG, respectively (Table 1).

Lesion study on RFL function

We performed VLSM analyses to identify the responsible region for VSC and SWM, and found that patients with the following resected regions showed a high possibility of damage to each function: the deep white matter of the posterior part of the middle frontal gyrus involving the dorsal superior longitudinal fasciculus (SLF) for VSC (Fig. 1a), and deep white matter of the posterior part of the superior to middle frontal gyri involving the cingulum for SWM (Fig. 1b). These results were mostly consistent with our previous reports [22, 24]. As shown in Fig. 2, the spatial location for positive mapping sites obtained from intraoperative DES corresponded to the results of VLSM analyses: the posterior part of the middle frontal gyrus and its subcortical region for

Table 1 Demographic and clinical characteristic of participants in each group

Factors	Evaluation group: Non-evaluation group		Statistical analysis
	Line bisection test 18:15	Spatial 2-back test 15:18	
Age	43.9 ± 11.2: 52.9 ± 15.0	45.6 ± 13.2: 50.0 ± 14.0	NS
Handedness; right/left	16/2: 13/2	13/2: 16/2	NS
WHO grade; II/III/IV	8/8/2: 6/5/4	8/6/1: 6/7/5	NS
IDH-1; mutant/wild/ND	15/1/2: 12/3/0	13/1/1: 14/3/1	NS
1p19q; codeletion/intact/ND	11/6/1: 5/8/2	10/3/2: 6/11/1	NS
Pre-op tumor volume (cc)	35.4 ± 37.6: 54.5 ± 47.8	32.7 ± 33.3: 53.6 ± 48.4	NS
Post-op treatment; yes/non	10/8: 9/6	7/8: 12/6	NS
Pre-op Line bisection test; Impaired/unimpaired	0/18: 1/14	–	NS
Pre-op spatial 2-back test; Impaired/unimpaired	–	3/12: 5/13	NS

Wilcoxon test or chi-squares test were utilized

ND not detected, *NS* not significant ($p > 0.05$)

VSC (8 points), and the posterior medial part of the prefrontal deep white matter for SWM (5 points).

Surgical and functional outcome

The percentage of tumor resection was comparable between NEG (patients not monitored for neither SWM nor VSC) and EG for SWM and VSC. The extent of resection did not decrease in EG for SWM and VSC compared with that of NEG (Fig. 3). Rather, the extent of tumor removal seems better in EG for VSC than NEG, despite not being significantly different.

Next, functional outcomes were compared between the EG and NEG. The number of patients with disturbed VSC was significantly lower for those assessed with the intraoperative line bisection test than those without (5.6% vs 33.3%; $p = 0.034$, Fig. 4a). One-third of patients in NEG had impaired VSC postoperatively, although preoperatively only one patient presented with an impairment in VSC ($p = 0.0044$, Fig. 4a). Regarding SWM, though 24.2% of patients were damaged preoperatively, the number of damaged patients decreased postoperatively in both groups, statistically significant in EG ($p = 0.0096$, Fig. 4b). The remaining deficit at the chronic phase in patients assessed with the intraoperative 2-back test was 0%, a significantly lower probability compared to that of patients without intraoperative monitoring (16.7%, $p = 0.049$).

To investigate the cause of the high probability of the remaining VSC deficit in patients without intraoperative monitoring, resected areas were compared between the EG and NEG for VSC. We found that the posterior part of the superior to middle frontal gyrus and its deep white matter were resected with high probability in patients who did not undergo the intraoperative line bisection test (Fig. 5a, black to green region. Color closer to green indicates higher probability of resection), and partially overlapped with a VSC-related region identified by VLSM analysis (Fig. 5b, see also Fig. 1a). This result suggests that the VSC-related region was resected with statistically high probability in patients without intraoperative monitoring by line bisection test.

Discussion

It remains unclear whether awake craniotomy and intraoperative mapping for tumor resection can be effective for RFL glioma. Hence, we divided 33 patients who underwent awake surgery into two groups based on the successful intraoperative mapping of VSC and SWM. In order to avoid possible conceptual and statistical biases, we confirmed that the groups consisted of homogenous populations. Further, they did not differ in cognitive performance before surgery. In this study, we demonstrate for the first time that intraoperative evaluation of VSC and SWM in patients with RFL glioma tended to prevent permanent functional deficits without deterioration of tumor resection.

The complication of VSC impairment after surgery is unexpectedly prevalent [34, 35]. VSC deterioration can result in limitations to the patients' social lives [34]. Our VLSM analyses demonstrated that the region related to VSC was the posterior deep part of the middle frontal gyrus, involving a pathway in the dorsal SLF. This is in accordance with our previous study and others [17, 22, 36–39]. Our results show that the positive mapping site found by line bisection test was close to the related VSC region obtained by neuroimaging analyses, suggesting that this test is a useful task to identify the VSC related region. These results are consistent with previous findings demonstrating that an impairment of VSC can be avoided by mapping with line

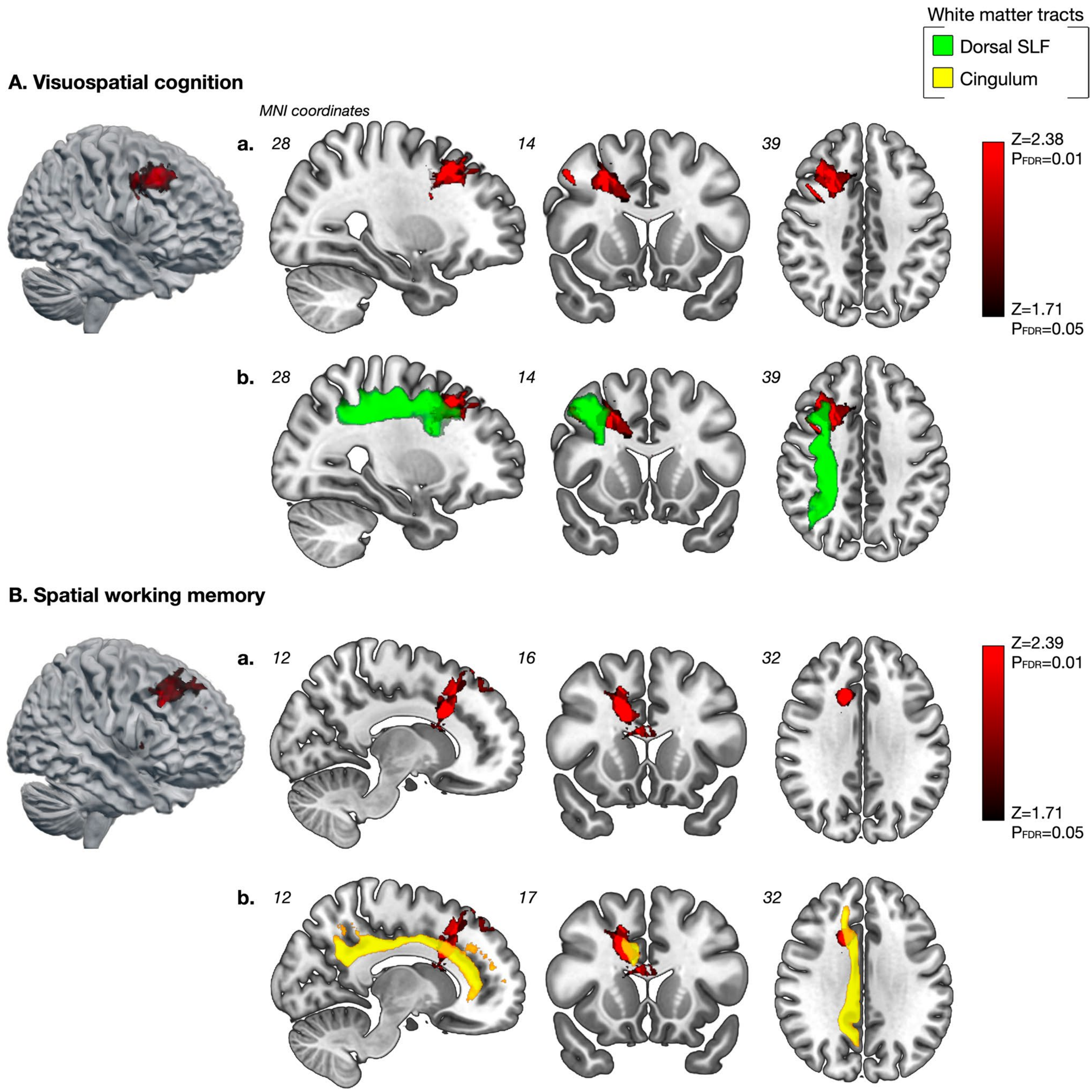

Fig. 1 Voxel-based lesion symptom analyses were performed to identify the responsible lesion for visuospatial cognition and working memory. The largest significant clusters were located in the posterior and deep part of the middle frontal gyrus for visuospatial cognition (**a**), and the deep part of the superior and middle frontal gyrus for spatial working memory (**b**). To clarify the spatial location of the white matter tract running through each region, the dorsal superior longitudinal fasciculus (SLF, green) and cingulum (yellow) were overlaid. Numbers at the upper left of slice images indicate coordinates of the MNI template.

bisection test [22, 28, 40, 41]. Our data indicated that suitable identification of the VSC region with the line bisection test could effectively preserve VSC. Moreover, one-third of non-mapping cases resulted in VSC deficits attributed to the removal of VSC-related regions. Taken together, intraoperative mapping with line bisection test for RFL glioma is highly recommended for VSC preservation.

Previous studies indicated right hemispheric lateralization for SWM [42]. An impairment in working memory can have a negative influence on a patient's social life including work, housework, and schoolwork [24, 43, 44]. Recently, it has been reported that SWM disturbance hardly recovers once it is impaired by surgery [22, 24]. Hence, SWM preservation should be a high priority during surgery. The

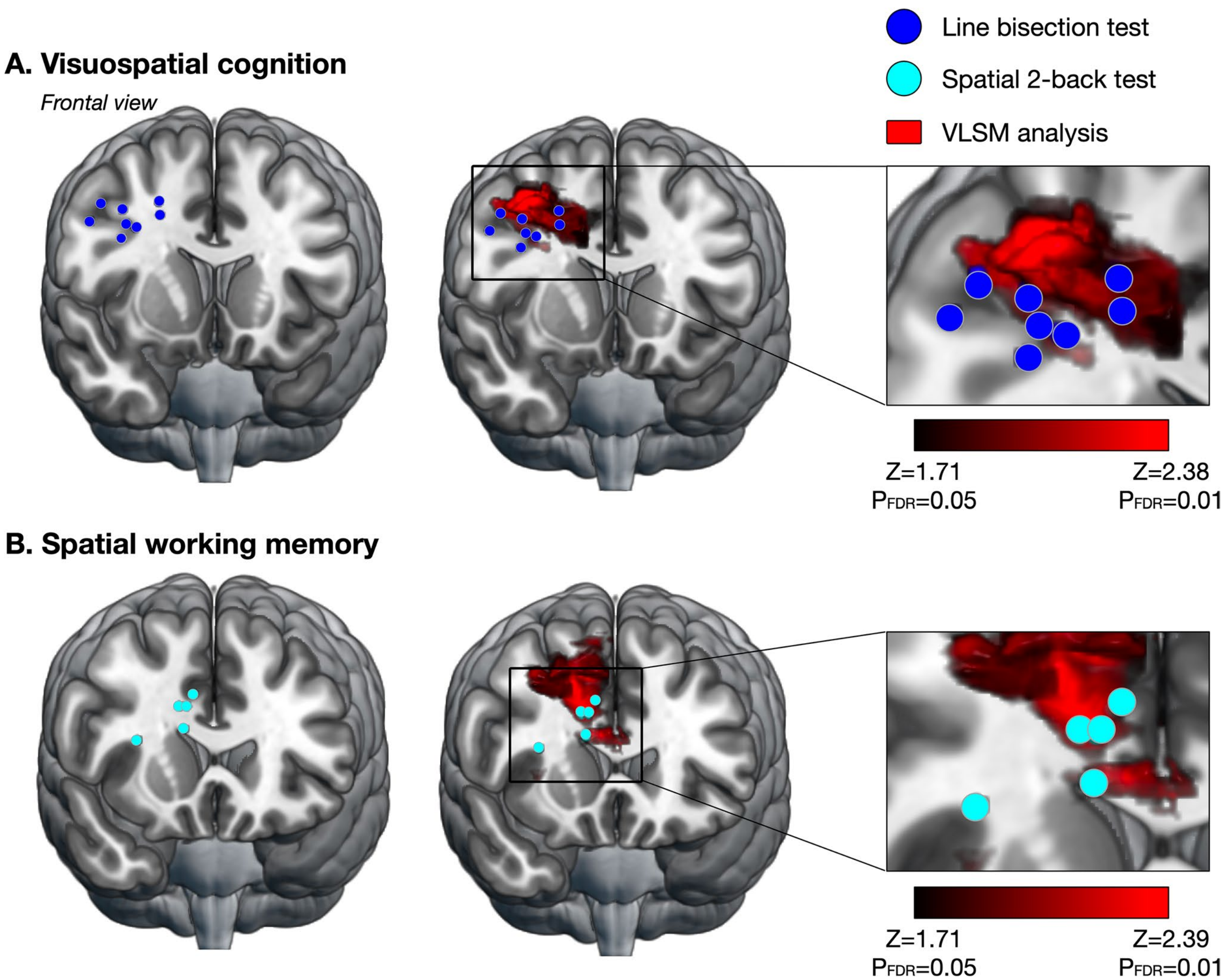

Fig. 2 Spatial relationship between positive mapping sites of each right frontal lobe function and results of voxel-based lesion-symptom (VLSM) analysis. Visuospatial cognition (**a**) and spatial working memory (**b**) were assessed via intraoperative line bisection test and spatial 2-back test, respectively. The statistical map obtained from VLSM analysis shows only significant voxels with a false discovery rate–controlled threshold. Obtained data from direct electrical stimulation mostly corresponds to results of VLSM analysis (See also Fig. 1).

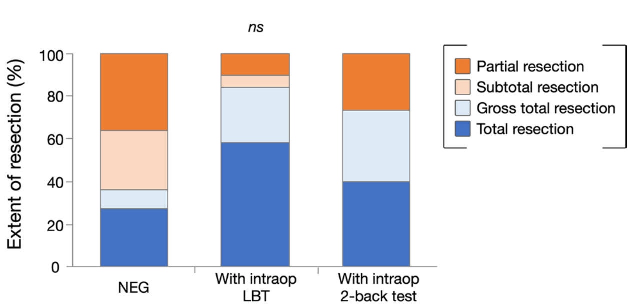

Fig. 3 Extent of resection compared among three groups, i.e., non-evaluation group (NEG; neither visuospatial cognition (VSC) nor spatial working memory (SWM)), and with intraoperative monitoring for VSC with line bisection test (LBT) and SWM with 2-back test. We used the likelihood-ratio chi-squared test and could not find significant difference among the groups. *ns* not significant.

SWM-related region was demonstrated to be the posterior deep area of the superior-middle frontal gyri including a part of cingulate gyrus, also consistent with our previous data [24]. In this study, a positive mapping site was matched to the SWM-related region in our data. Surprisingly, the SWM impairment rate for the chronic phase was 0% in the EG, whereas it was 16.7% in the NEG. We speculate the significant improvement of SWM in the EG resulted from the intraoperative preservation of cingulum without preoperative irreversible impairment. Therefore, we highly recommend the 2-back test during awake surgery for patients with RFL glioma.

Generally, an RFL glioma would be extensively removed without awake mapping. Therefore, awake mapping is supposed to possibly interrupt extensive resection.

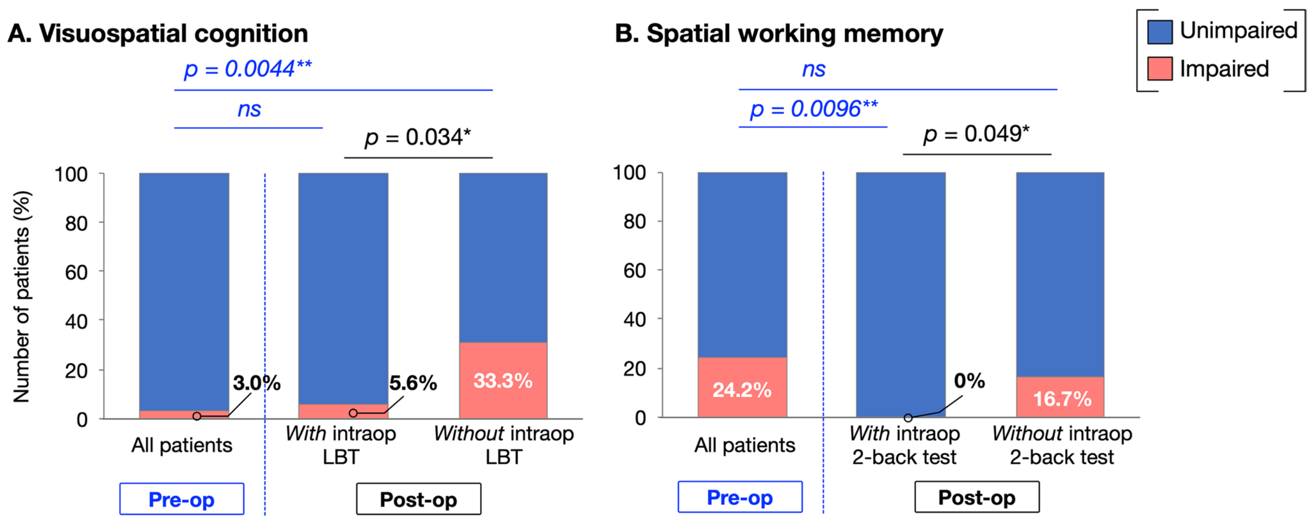

Fig. 4 Visuospatial cognition (VSC) and spatial working memory (SWM) assessed with line bisection test (LBT) and spatial 2-back test, respectively before and after surgery. When comparing the functional outcomes between groups, patients who underwent intraoperative assessment of VSC (**a**) and SWM (**b**) showed significantly better outcome than patients who did not (likelihood-ratio chi-squared test). Additionally, patients who did not undergo intraoperative monitoring for VSC had significantly higher remaining deficits than preoperatively (blue letter). Patients who underwent intraoperative monitoring for SWM significantly improved SWM compared with their preoperative condition (blue letter). ns, not significant. Red, impaired patients; blue, unimpaired patients.

Nevertheless, our data indicated that the extent of resection did not decrease in EG compared to NEG. The greatest overlap of all resection cavities laid in the posterior deep part of the RFL, suggesting tumor locations tend to include relating lesions of VSC and SWM. We speculate that we might hesitate removing posterior part of superior and middle frontal gyrus and its deep part without successful awake mapping because of worrying about the impairment of VSC and SWM, and also damage to the pyramidal tract. In contrast, we can remove the tumor as much as possible confirming the boundaries of function with mapping.

The main limitations of this study are its sample size and the retrospective design. Therefore, the results should be considered with caution. Nevertheless, the neuropsychological follow-up data at postoperative 3 months is valuable, since awake surgery aiming to preserve function of the RFL function is still challenging in glioma surgery. Another limitation was the divided criteria to determine whether the patient would undergo an intraoperative evaluation. We did not include age, WHO grade, or tumor volume in the selection criteria. However, we included grade II without postoperative therapy, as well as grade III and IV gliomas with/without postoperative chemoradiation. This may influence functional outcomes. However, impaired VSC and SWM ratios are similar between grade II and grade III/IV (Supplementary Fig. 4). Considering that patients had similar VSC and SWM impairments preoperatively, the main selection criterion was the objective and subjective ability of patients to cooperate and accomplish tasks for mapping during surgery. Although a randomized study is ideal to evaluate the effects of intraoperative mapping, that is difficult from an ethical point of view. Further research with a large number of participants is required to validate the advantages of awake surgery for RFL glioma. Then, the results should be analyzed from multidimensional aspects, such as functional and oncological outcome including survival, and quality of life.

Conclusions

To the best of our knowledge, this is the first study to show the advantages of awake surgery for RFL gliomas of grades II, III, and IV on VSC and SWM preservation. Our data suggest that intraoperative mapping by awake surgery seems to result in better cognitive outcomes and similar resection rates to surgery without mapping. Therefore, awake surgery with line bisection test and 2-back test can be good options for the treatment of RFL glioma.

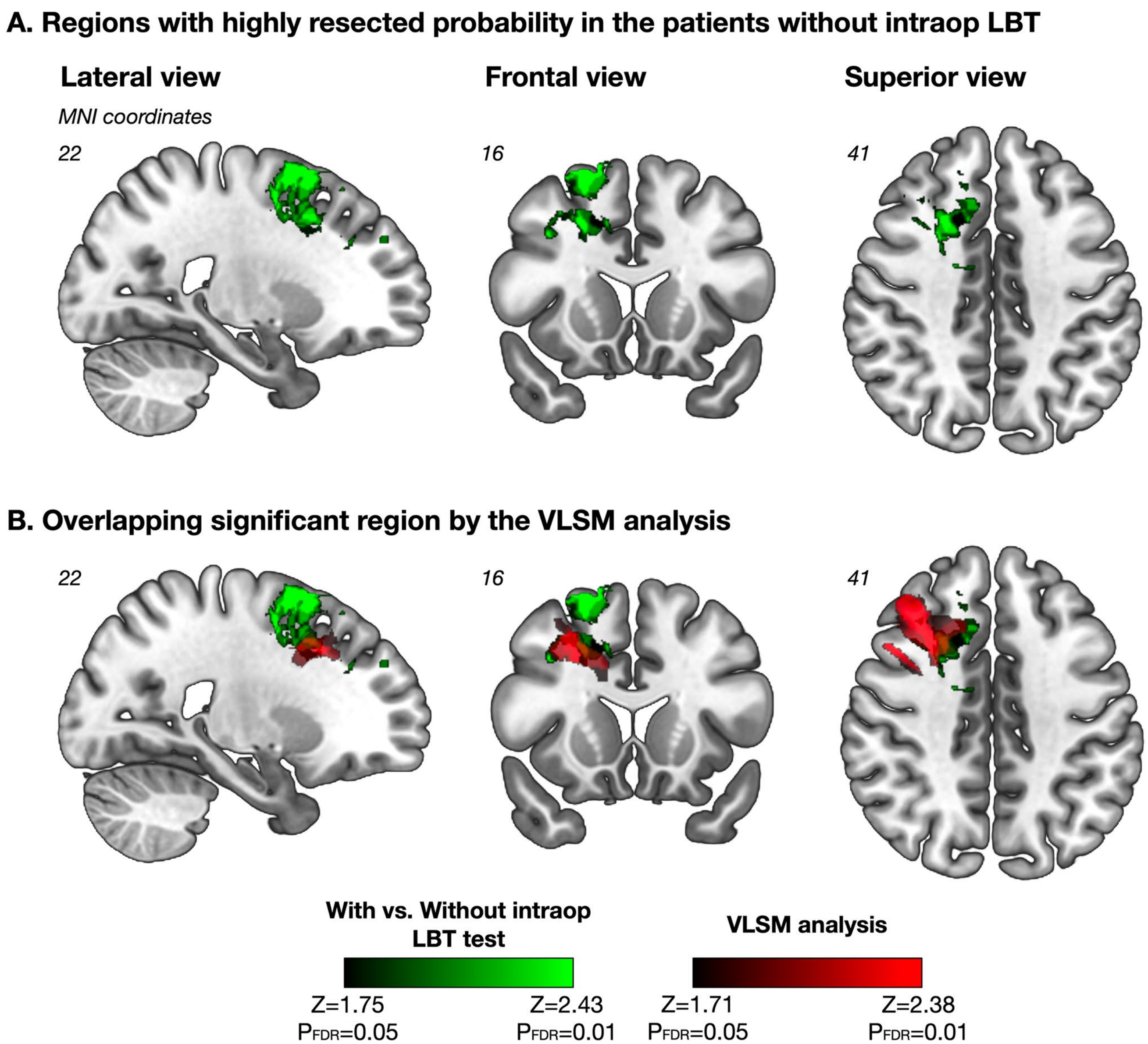

Fig. 5 **a** The resected area was compared between the evaluation group (EG) with line bisection test (LBT) and the non-evaluation group (NEG) using voxel-based lesion-symptom (VLSM) analysis (black, p = 0.05, Z = 1.75; green, p = 0.01, Z = 2.43; cluster size, 18,152; Z_{max} = 3.80). The extent of resection in the posterior parts of the superior and middle frontal gyrus and its deep white matter were significantly higher in the NEG (green) than the EG. **b** When the responsible region for visuospatial cognition by the VLSM analysis was overlaid (red, see also Supplementary Fig. 4), it partially overlapped with the green regions. The statistical map obtained from VLSM analysis shows only significant voxels with a false discovery rate–controlled threshold (green, p = 0.05, Z = 1.75; red, p = 0.05, Z = 1.71)

Author contributions Conception and design: MN. Acquisition of data: MK, HO, YN, TY, ST, RN. Analysis and interpretation of data: MN, RN. Drafting article: MN, RN. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: MN.

Funding This work was supported by JSPS KAKENHI Grant Number 18K19606, 19K22801 and 20K21649.

Compliance with ethical standards

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

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