Resting-State Functional Connectome in Patients with Brain Tumors Before and After Surgical Resection

Gianvincenzo Sparacia[1,3], Giuseppe Parla[3], Vincenzina Lo Re[4], Roberto Cannella[1], Giuseppe Mamone[3], Vincenzo Carollo[3], Massimo Midiri[1], Giovanni Grasso[2]

■ PURPOSE: **High-grade glioma surgery has evolved around the principal belief that a safe maximal tumor resection improves symptoms, quality of life, and survival. Mapping brain function has been recently improved by resting-state functional magnetic resonance imaging (rest-fMRI), a novel imaging technique that explores networks connectivity at "rest."**

■ METHODS: **This prospective study analyzed 10 patients with high-grade glioma in whom rest-fMRI connectivity was assessed both in single-subject and in group analysis before and after surgery. Seed-based functional connectivity analysis was performed with CONN toolbox. Network identification focused on 8 major functional connectivity networks. A voxel-wise region of interest (ROI) to ROI correlation map to assess functional connectivity throughout the whole brain was computed from a priori seeds ROI in specific resting-state networks before and after surgical resection in each patient.**

■ RESULTS: **Reliable topography of all 8 resting-state networks was successfully identified in each participant before surgical resection. Single-subject functional connectivity analysis showed functional disconnection for dorsal attention and salience networks, whereas the language network demonstrated functional connection either in the case of left temporal glioblastoma. Functional connectivity in group analysis showed wide variations of functional connectivity in the default mode, salience, and sensorimotor networks. However, salience and language networks, salience and default mode networks, and salience and sensorimotor networks showed a significant correlation (*P* uncorrected <0.0025; *P* false discovery rate <0.077) in comparison before and after surgery confirming non-disconnection of these networks.**

■ CONCLUSIONS: **Resting-state fMRI can reliably detect common functional connectivity networks in patients with glioma and has the potential to anticipate network alterations after surgical resection.**

INTRODUCTION

Surgical resection of focal brain tumors aims to maximize the resection while preserving brain function. Mapping brain function was recently improved by a novel imaging technique that explores distributed connectivity networks at "rest," which requires minimal participant collaboration. Resting-state functional magnetic resonance imaging (rest-fMRI) represents a novel tool to study brain functional network connectivity associated with both normal and pathologic neurologic function. This novel imaging technique is based on the quantification of

Key words
- Brain mapping
- Brain tumors
- Functional connectivity
- Resting-state fMRI

Abbreviations and Acronyms
BOLD: Blood oxygen level dependent
DMN: Default mode network
EOR: Extent of resection
FDR: False discovery rate
fMRI: Functional magnetic resonance imaging
KPS: Karnofsky performance status
MR: Magnetic resonance
rest-fMRI: Resting-state functional magnetic resonance imaging
ROI: Region of interest
RSNs: Resting-state networks

From the [1]Radiology Service and [2]Neurosurgical Unit, Department of Biomedicine, Neurosciences and Advanced Diagnostics (BiND), University of Palermo, Palermo; and [3]Radiology Service, Department of Diagnostic and Therapeutic Services, and [4]Neurology Service, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (IRCCS-ISMETT), Palermo, Italy

To whom correspondence should be addressed: Gianvincenzo Sparacia, M.D.
[E-mail: gianvincenzo.sparacia@unipa.it]

Citation: World Neurosurg. (2020).
https://doi.org/10.1016/j.wneu.2020.05.054

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

hemodynamic changes following the activation of brain areas. Neuronal activity creates a hemodynamic response that locally alters local brain concentrations of oxyhemoglobin and deoxyhemoglobin. This process produces time-dependent alterations in T2- and T2*-relaxation times, forming the basis of the blood oxygen level-dependent (BOLD) contrast imaging.[1]

As opposed to task-driven fMRI, the resting-state fMRI is acquired in the absence of any stimulus or task. The result is a map reflecting the spontaneous BOLD signal fluctuation, and therefore activation of a distinct patterns of cerebral areas during the resting state that may reflect the underlying cerebral connectivity. This connectivity patterns are represented as "networks" between active regions of the brain and are called resting-state networks (RSNs).[2,3]

Temporally coherent networks can be reliable assessed by rest-fMRI and are well recognized in the literature based on the different functions of the brain that they accomplish, such as vision, language, motor, and attention.[1,4,5] Assessment of RSNs by rest-fMRI shows a high reproducibility; thus, this technique became a valid method for examination of the intrinsic functional architecture, or "connectome," of the human brain.[4-7]

With this method, several RSNs have been identified; the main ones are the default mode network (DMN), the sensorimotor network, the visual network, the auditory network, the executive control network, the lateralized frontoparietal network, and the temporoparietal network.[4-7] The most significant proof of their existence lies in the reproducibility of the networks in the single subject, in the consistency of the networks between different subjects, and in the correspondence of the cortical areas identified with different methods of study.[8,9]

Although serval recent studies have explored the potential applications of resting-state fMRI in various neurologic diseases,[10-13] the value of this technique in the neurosurgical planning of patients with brain tumors was not fully defined.[2,3,14-19] Therefore, further validation is necessary to prove the clinical value of rest-fMRI for neurosurgical planning of brain tumors. Moreover, rest-fMRI potentially could allow evaluating functional reorganization in patients after neurosurgical resection of brain tumors.[2,14,19] There is a limited report in the literature of the changes in intersubject and intrasubject variability of the RSNs in patients with brain tumors undergoing surgery using intraoperative rest-fMRI.[19] The aim of this study, therefore, was to map the functional connectome of known RSNs in single subjects and in group analysis before and after surgical resection of brain tumors in a routine clinical setting and to assess changes in neuronal networks related to the surgery.

METHODS

Data for this study were prospectively collected as part of a larger ongoing follow-up study in patients with brain glioma who undergo resective surgery at our institution. The study was reviewed and approved by the institutional research review board of our institution, and informed consent form was waived. However, informed written consent to magnetic resonance (MR) and the surgical procedure was obtained in all the patients.

From August 2018 to December 2019, patients with a neuroradiologic diagnosis of brain glioma were enrolled. Patients underwent neurologic examination along with Karnofsky performance status (KPS) assessment. Neuropsychologic evaluation by using standardized tests for cognitive, perceptual, motor, and psychological functions was performed.[20]

The topography and the size of the tumor were accurately analyzed on a preoperative MRI, with T1-weighted images obtained before and after gadolinium enhancement in the 3 orthogonal planes, T2-weighted coronal images, and fluid-attenuated inversion recovery axial images. Resting-state fMRI was performed in all the patients before and 1 month after surgery.

MR Data Acquisition

MR examinations were acquired with a 3T MR scanner (Discovery 750w; General Electric Healthcare, Milwaukee, Wisconsin, USA) with a 32-channel dedicated head coil before surgery and 1 month following the tumor resection. Volumetric high-resolution isotropic anatomical MR imaging T1-weighted tri-dimensional spoiled gradient recalled acquisition in steady state MR images (1 × 1 × 1 mm voxels, repetition time 8.6 milliseconds, echo time 3.2 milliseconds, field of view 240 mm, matrix size 256 × 256, flip angle 12°) were acquired in the axial plane before and after paramagnetic contrast media administration (Gadovist; Bayer AG, Leverkusen, Germany). Anatomical images were used for coregistration with rest-fMRI images. For the rest-fMRI acquisition, the patient was instructed to stay still with eyes closed while relaxing. Resting-state fMRI was acquired with echo-planar imaging sequence (repetition time 2000 milliseconds, echo time 30 milliseconds, voxel size 3 × 3 × 3 mm, slice thickness 3 mm, number of slices 39, number of volumes 210).

Resting-State fMRI Analysis

One of the most critical processes of rest-fMRI is the identification of the resting-state brain functional networks. This can be achieved by several methods: an automatic or semiautomatic procedure with independent component analysis or through a spatial matching with respect to network templates[16,21] or manually with a seed-based approach, where predefined regions of interest (ROIs) are selected based on a-priori hypothesis using the Brodmann atlas coordinates.[1-3] Novel alternative methods, such as machine-learning approaches,[17,22] cortical parcellating approach,[8,23] or graph analyses,[7] are also used for easier-to-use methods in the clinical practice.

We adopted the seed-based method[3] with a cortical parcellation approach.[8] Seed-based functional connectivity analysis was performed with CONN toolbox version 18[24] running under SPM12 (Statistical Parametric Mapping 12; Wellcome Centre for Human Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk) and MATLAB (The MathWorks Inc., Natick, Massachusetts, USA). The CONN toolbox provides predefined 164 ROIs, which compose an atlas of cortical and subcortical areas from the FSL Harvard-Oxford atlas,[19,24] as well as cerebellar areas from the automated anatomical labeling atlas.[24] The atlas is normalized in Montreal Neurological Institute space and could be applied to the normalized images of the subject(s) (**Figure 1**).

Resting-state preprocessing was performed by compensation for slice-dependent time shifts, correction of systematic odd—even slice intensities due to interleaved acquisition, head spatial registration to correct head movement within sequences, and

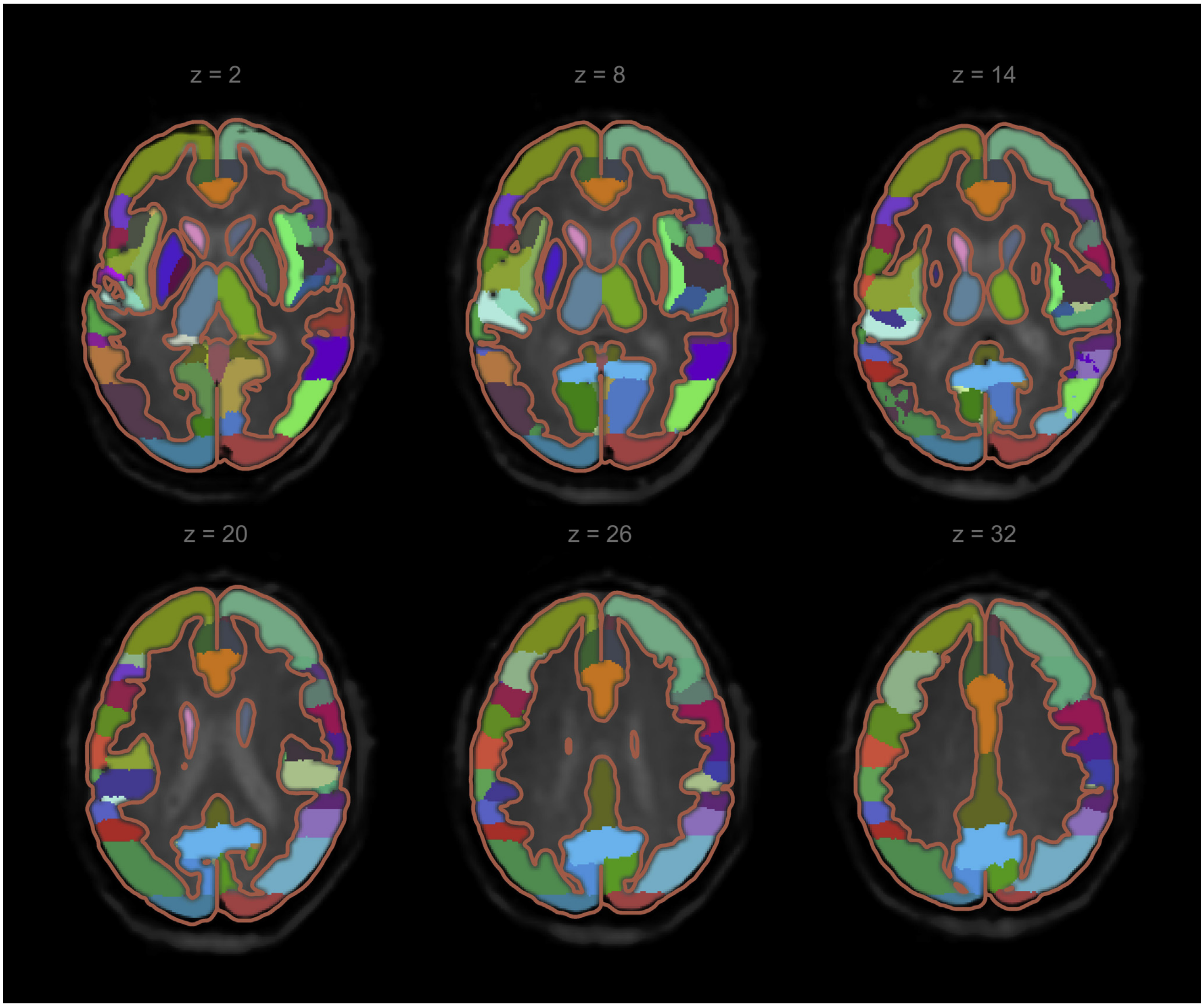

Figure 1. Example of predefined region of interest map composing an atlas of cortical and subcortical areas from the FSL Harvard-Oxford atlas used by CONN toolbox.

spatial smoothing using a Gaussian kernel. Voxel-wise nuisance-signal suppression is obtained by removing signals related to cerebrospinal fluid, white matter, and the global signal, as well as movement-related artifacts. The signal is low-pass filtered at 0.1 Hz. After time series realignment, rest-fMRI raw data are normalized to Montreal Neurological Institute space [1] at 2-mm voxel resolution and are coregistered to structural 3D T1-weighted spoiled gradient recalled acquisition in steady state MR images. The transformed structural images are then segmented into gray matter, white matter, and cerebrospinal fluid.

Network identification based on 32 seed-based ROIs correlation analysis of the functional connectivity focused on the sensorimotor network, language network, visual network, executive control network, lateralized frontoparietal network, salience network, dorsal attention network, and DMN.[25,26] (Table 1). Seed-based analysis, in general, necessitates a priori knowledge of presumed brain networks. Having selected a ROI as the seed, whole-brain correlations of rest-fMRI BOLD time courses can be computed, generating spatial maps of the network of interest.[3,20,27]

We used a 32 seed-based correlation matrix to associate BOLD correlation maps corresponding to predefined seeds with specific RSNs identities (Figure 2). A voxel-wise ROI to ROI correlation maps to produce estimates of RSNs membership throughout the

Table 1. Network Identification Based on Seed-Based Correlation Analysis Using the CONN Toolbox

Network	Seed Location
Sensorimotor network (SMN)	Central sulcus
Language network (LAN)	Broca's region
Visual network	Calcarine sulcus
Executive control network (ECN)	Medial prefrontal regions
Lateralized frontoparietal network (FPN)	Anterior prefrontal cortex
Salience network (SN)	Anterior cingulate cortex
Dorsal attention network	Posterior and lateral parietal regions
Default mode network (DMN)	Precuneus

Functional connectivity focused on the sensorimotor network (SMN), language network (LAN), visual network, executive control network (ECN), lateralized frontoparietal network (FPN), salience network (SN), dorsal attention network, and default mode network (DMN).

whole brain was computed to assess functional connectivity from a priori seeds ROI in specific RSNs before and after surgical resection in each patient, and the results were analyzed by using the graph theory to compare functional connectivity before and after surgical resection in single participants.

Correlation Analysis

Single-subject and group analyses of the relevant network in each subject, along with a group analysis of the commonly used functional network, were performed and graphically displayed as a circular connectome (connectogram) using the CONN toolbox via seed region connectivity analysis.[24] Pearson correlations were calculated between the mean time series of each ROI resulting in a 32 × 32 correlation matrix for each subject preoperatively and postoperatively. The correlation coefficients were Fisher Z-transformed to z scores to allow a group ROI-voxel analysis to detect the average effect of the tumor resection on the functional connectivity across subjects. The Fischer Z-transformation is used to transform the voxel-wise correlation values to a range of numbers because correlation values range from −1 to +1, whereas Z values are not bounded by upper or lower limits. Z-transformation of the values is useful for subsequent statistical group comparisons. The seed-based functional connectivity maps

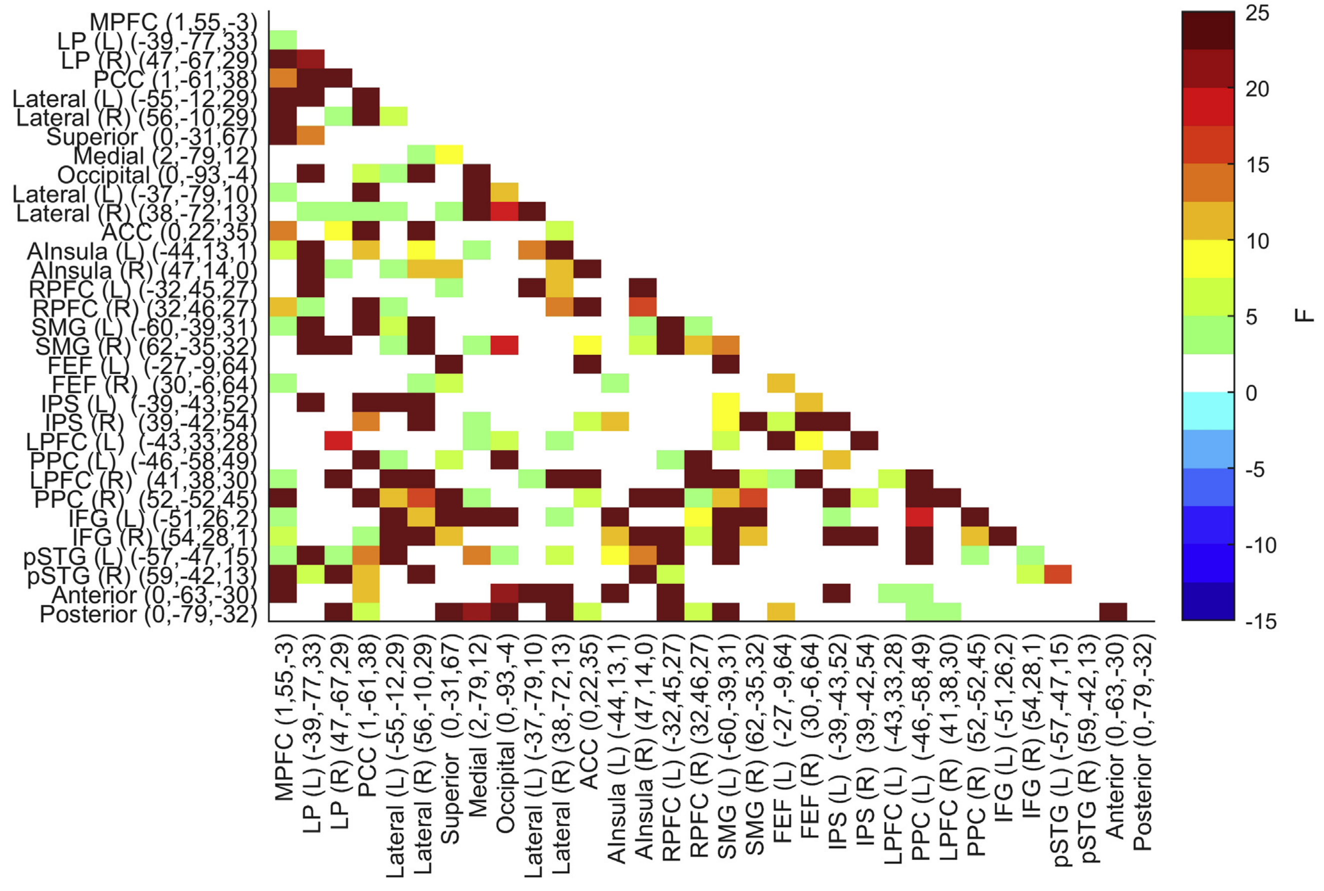

Figure 2. Connectivity matrix between 32 regions of interest corresponding to predefined seeds with specific resting-state network identities.

Table 2. Patient Characteristics

No.	Age, years	Sex	Tumor Type	WHO Grade	Tumor Location	EA Affected	Handedness	Tumor Volume, mL	Preoperative KPS Score	Preoperative Symptoms	Surgery	EOR, %	Postoperative KPS Score	Postoperative Symptoms
1	25	M	AA	III	Left frontal	Motor	Right	98	90	Seizure	GA	90	95	Improved
2	46	M	AA	III	Left frontal	Motor	Right	144	90	Focal weakness	GA	95	95	Improved
3	48	M	AA	III	Right parietal and frontal	Motor	Right	182	100	Seizure	GA	96	100	Improved
4	67	M	GBM	IV	Left temporal	Language	Right	405	95	Mild aphasia	A	95	95	Unchanged
5	60	M	GBM	IV	Left temporal	Language	Right	325	95	Mild aphasia	GA	90	95	Unchanged
6	52	M	AA	III	Right temporal	Language	Right	250	100	Headache	GA	90	100	Improved
7	51	M	AA	III	Left temporal	Language	Right	190	95	Moderate aphasia	GA	95	95	Unchanged
8	60	F	GBM	IV	Left temporal	Language	Right	178	90	Mild aphasia	GA	90	90	Unchanged
9	49	F	AA	III	Right temporal	Language	Right	186	80	Moderate aphasia	GA	80	75	Worsened
10	52	F	AOD	III	Right Occipital	Visual	Left	215	100	Right superior QDA	GA	95	90	Worsened

WHO, World Health Organization; EA, eloquent area; KPS, Karnofsky performance status; EOR, extent of resection; M, male; AA, anaplastic astrocytoma; GA, General anesthesia; GBM, glioblastoma multiforme; A, awake; AOD, anaplastic oligodendroglioma; QDA, quadrantanopia.

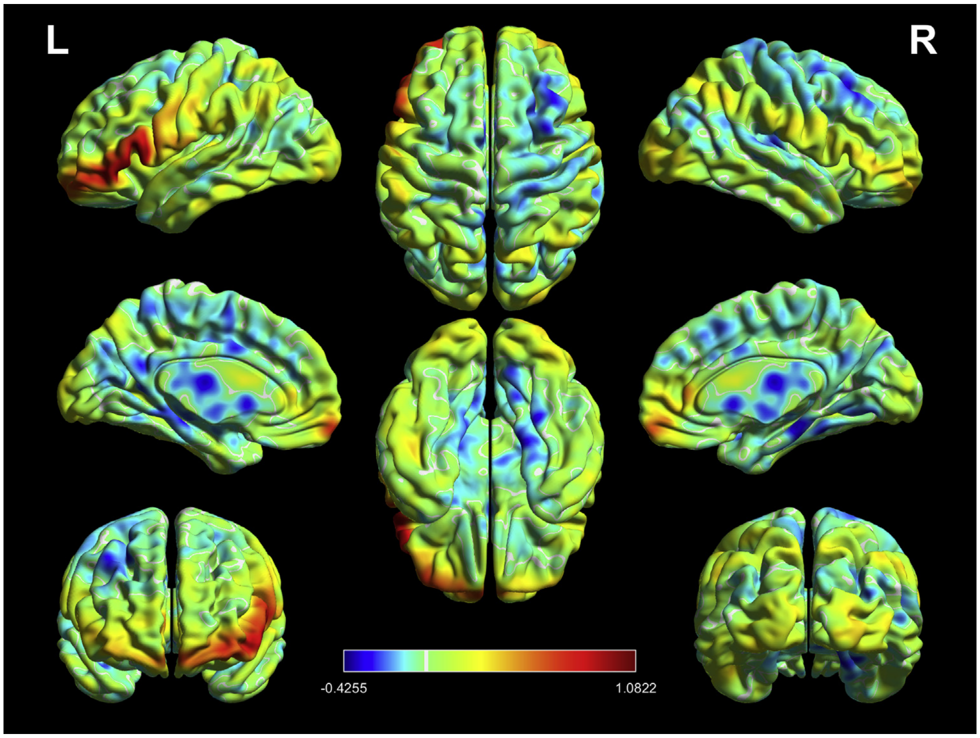

Figure 3. Brain surface mapping of single-subject functional connectivity before and after surgery. The tri-dimensional images show significantly reduced connectivity (*P*-uncorrected <0.0025; *P*-false discovery rate <0.077) in dorsal attention and salience networks (*blue areas*) with preservation of functional connectivity of the language network (*red areas*) after surgical resection of a left temporal lobe glioblastoma.

(correlation r values or Z-statistics) that are estimated for each individual subject is then used for group-level analysis. The difference in the overall functional connectivity between preoperative and postoperative rest-fMRI examinations was calculated. The paired t test was used to test the significance of the changes between rest-fMRI examinations for each subject and within the group in each rest-fMRI examination.

A P-uncorrected <0.0025 was used to threshold connectomes for voxel-wise paired statistical analysis to take in account the lateralization effect (i.e., the left region is involved and the right is not involved as it occurs for the language network). Due to the lateralization effect, it is possible that the right region shows essentially the same effect, but the effect is marginally weaker and, therefore, the left side just survived statistical thresholding and the right side did not. To address this potentially issue that can either mean that there was no effect, or it could mean that it was just under the standard fixed threshold $P < 0.001$, commonly used in most fMRI analysis software packages including SPM, it is necessary to adopt a P-uncorrected value to slight adjust the threshold to take in account the lateralization effect. In detail, a P value refers to the probability of falsely rejecting a particular null hypothesis, i.e., the probability of making a type I error. The uncorrected P value refers to the null hypothesis for a single voxel, so uncorrected P values only have a useful meaning if the regional hypothesis refers to only one voxel. More commonly, we have a hypothesis about a particular brain region that contains more than one voxel. In such cases, nonparametric statistics are recommended with a greater (i.e., more liberal) voxel-wise height thresholds P-uncorrected <0.0025 that give unquantified error control, because the actual error rate for a particular uncorrected P value depends on the size and shape of the hypothesized region and the smoothness of the statistic image.[28] Thus, data are presented at P-uncorrected <0.0025 and with a multiple comparisons correction using the false discovery rate (FDR) P-FDR <0.077. FDR correction is a more stringent technique than P-uncorrected results as the threshold is calculated directly from the uncorrected P values and depends on the data. Specifically, the FDR threshold is heavily influenced by the amount and strength of the activations that are present in the whole brain map.[29] To estimate FDR for multiple hypothesis testing, we used the method described in the literature[30] using the MatLab function “mafdr” for P-uncorrected <0.0025 obtaining the P-FDR <0.077.

RESULTS

Patient Characteristics and Surgical Findings

This series included 10 patients (7 male and 3 female) ranging in age from 25 to 67 years (median 51 years) and affected by supratentorial glioma. Nine patients were right-handed and one left-

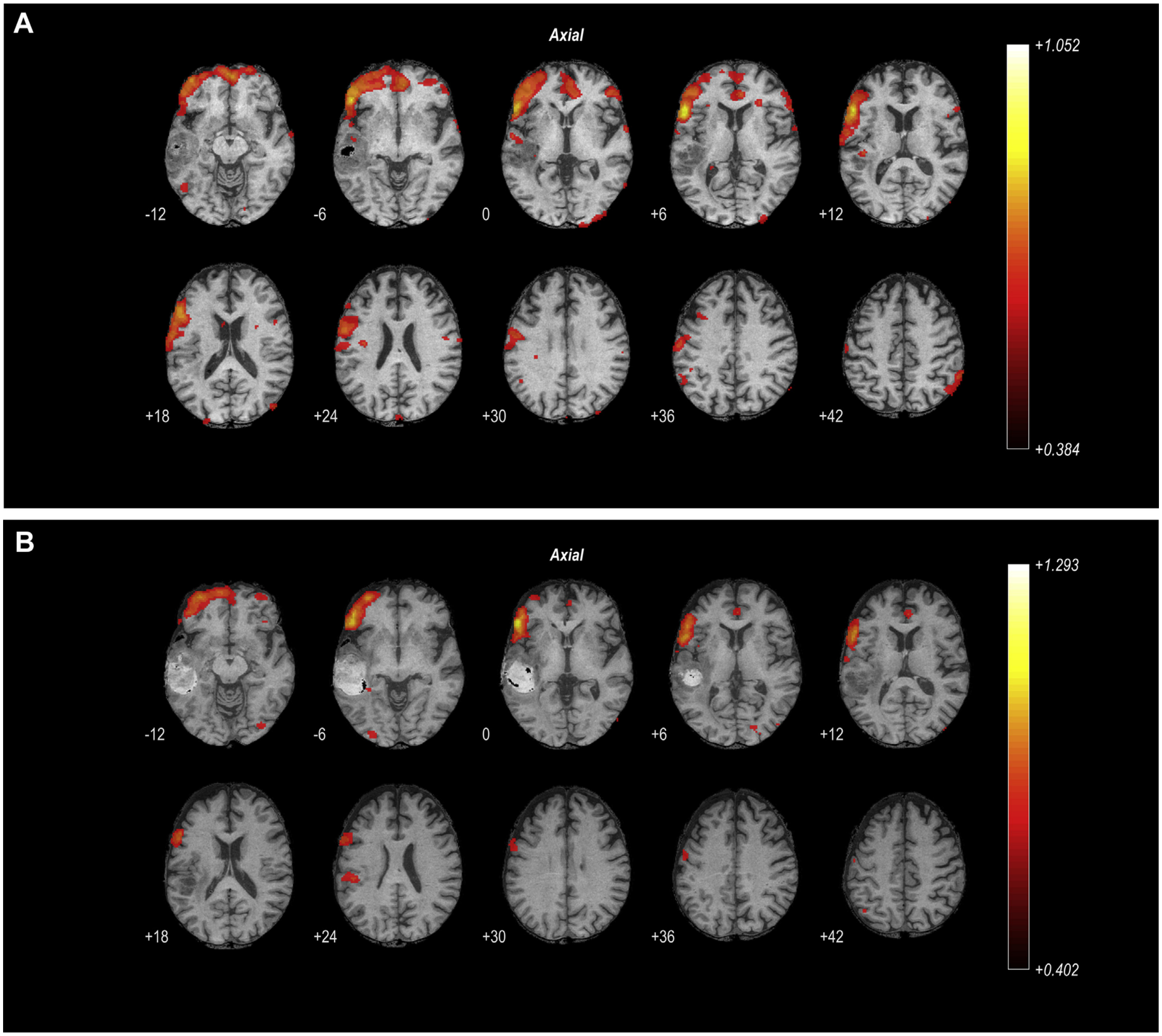

Figure 4. Single-subject resting-state functional connectivity using a seed region on Broca's area (**A**) before and after (**B**) surgical resection of a left temporal lobe glioblastoma. The tumor was resected with preservation of the eloquent cortex as demonstrated at follow-up resting functional magnetic resonance imaging.

handed. The presenting symptoms were language disturbance in 5 cases, seizure in 2 cases, headache in 1 patient, and motor and visual impartment in 2 cases, respectively. The mean tumoral volume was 217 mL (range: 98–405 mL).

Tumor resection was performed with the patients under general anesthesia, except for 1 patient (patient no. 4), in whom awake surgery was performed, since almost all patients refused such a treatment. Tumor removal was performed with the aid of neuronavigation and 5-aminolevulinic acid fluorescence. Furthermore, the intraoperative monitoring neurologic findings were obtained in all the cases by using motor-evoked potentials, sensory-evoked potentials, and visual-evoked potentials.

In each case, early postoperative MRI was obtained between days 1 and 5 after surgery. Overall, there was no enhancement in 80% of patients with an extent of resection (EOR) estimate ranging from 80% to 95%. Overall, the postoperative KPS and symptoms improved in the majority of the cases, except in 2 patients (patients no. 9 and 10). Table 2 shows the main patient characteristics.

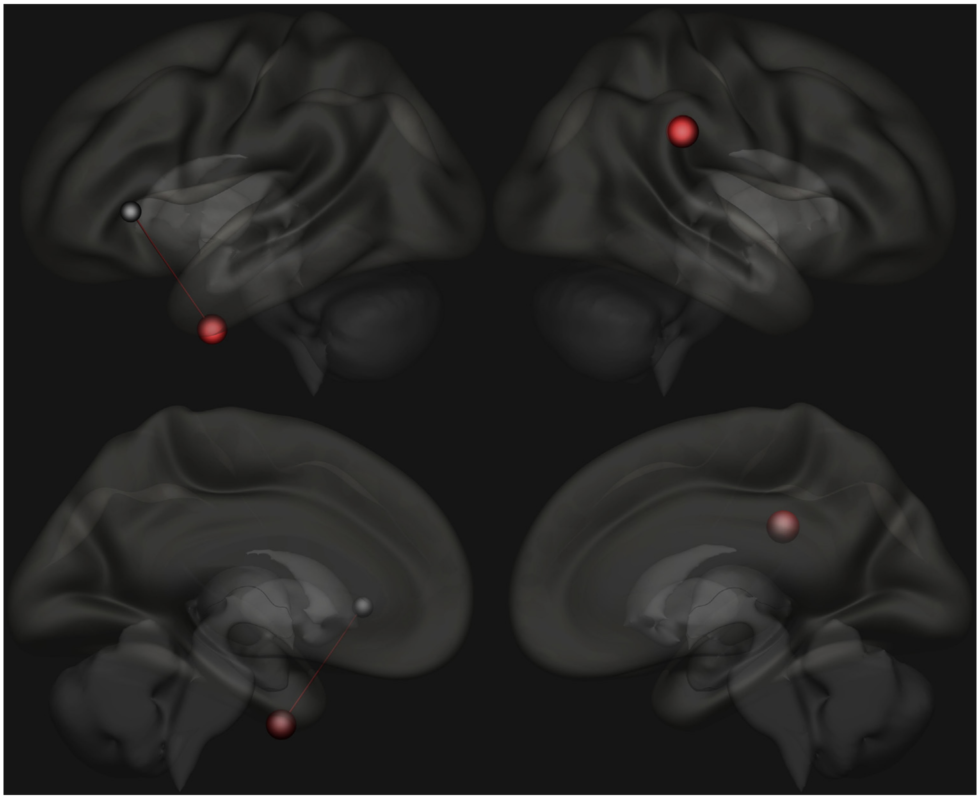

Figure 5. Brain surface overlap of single-subject functional connectivity comparison before and after surgical resection of a left temporal lobe glioblastoma demonstrating the preservation of the language inferior frontal gyrus network.

Rest-fMRI Features

Sensorimotor, visual, salience, language, and default mode networks were correctly identified in all patients at rest-fMRI before and after surgical resection despite some networks showing spatial deformations due to tumor mass effect and edema and due to surgery. In general, the functional connectivity tended to decrease in postoperative rest-fMRI examination for the default mode, dorsal attention, and salience networks. The most evident reduction in functional connectivity in single-subject analysis was seen for dorsal attention and salience networks, representing functional disconnection of these networks (Figure 3), whereas the language network demonstrated functional connection after surgery either in case of left temporal glioblastoma (Figures 4 and 5).

In the group analysis, the default mode, salience, and sensorimotor networks showed wide variations of functional connectivity before and after surgery (Figure 6). However, salience and language networks, salience and default mode networks, and salience and sensorimotor networks showed a significant correlation (P-uncorrected <0.0025; P-FDR <0.077) in comparison before and after surgery, confirming the connection of these networks. Results are summarized in Table 3 and Figure 7. These results were not correlated to a specific tumor location.

DISCUSSION

Functional connectivity assessment with rest-fMRI has been demonstrated to be useful in the preoperative localization of the eloquent cortex aimed to reduce the risk of surgery-induced neurologic deficits.[1,2,14,19] The main advantage of rest-fMRI is that it does not require any patient activity and thus can be used in young children and in patients who are aphasic, paretic, or under anesthesia. Multiple function networks can be identified with rest-fMRI also in patients who may not be fully cooperative. An additional advantage of rest-fMRI is that does not require additional personnel or equipment commonly used for task-based fMRI. The main limitation for the clinical implementation of a rest-fMRI is the lack of standardization for data processing, which requires trained personnel and a high level of expertise.[6,7]

Although in the literature preliminary results of the clinical feasibility of rest-fMRI in surgical planning of brain tumor have been described,[14,16-19,23,27] assessment of rest-fMRI functional connectivity pre- and postsurgical resection of brain tumors has not been fully investigated. Metwali and Samii[3] reported their preliminary results in intraoperative resting-state functional connectivity assessment in patients with intracerebral lesions. However, intraoperative resting-state functional connectivity

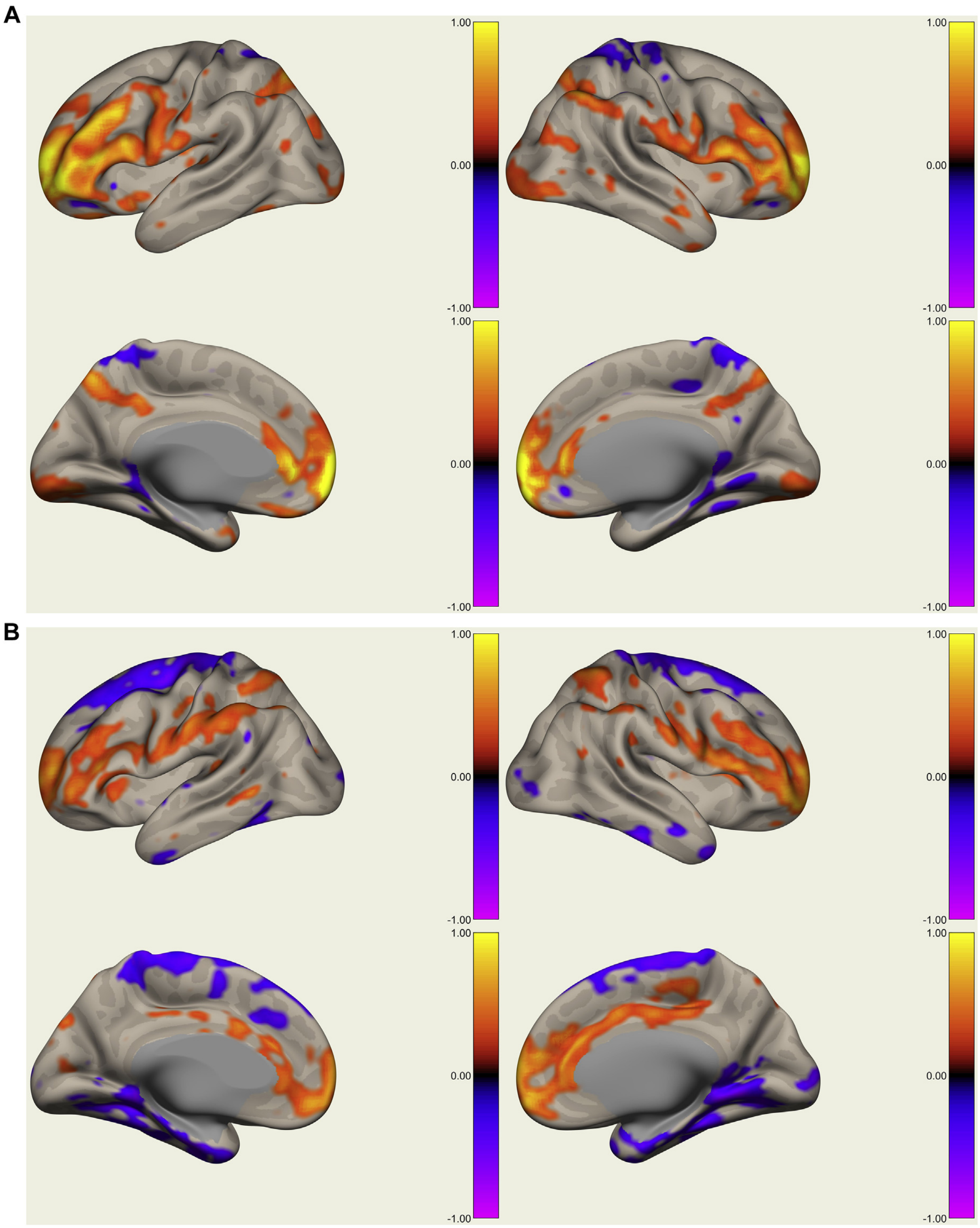

Figure 6. Brain surface mapping of group analysis showing wide variations of functional connectivity (**A**) before and (**B**) after surgery of the default mode, salience, sensorimotor, and language networks.

Table 3. Group Analysis Result of Significantly Connected Resting-State Networks (P-Uncorrected < 0.0025; P-FDR <0.077) Before and After Surgical Resection of Brain Gliomas

Analysis Unit	*P*-Unccorrected <0.0025	*P*-FDR <0.077
Salience.SMG—Language.IFG	0.0011	0.0343
Language.IFG—Salience.SMG	0.0011	0.0343
DefaultMode.LP (L) —Salience.AInsula (R)	0.0012	0.0364
Salience.AInsula (R) —DefaultMode.LP (L)	0.0012	0.0364
Salience.SMG—SensoriMotor.Lateral (R)	0.002	0.0382
Salience.SMG—Salience.RPFC (L)	0.0025	0.0382
SensoriMotor.Lateral (R) —Salience.SMG	0.002	0.0634
Salience.RPFC (L) —Salience.SMG	0.0025	0.0764

FDR, false discovery rate; SMG, supramarginal gyrus; IFG, inferior frontal gyrus; L, left; AInsula, anterior insula; R, right; LP, lateral parietal cortex; RPFC, rostral prefrontal cortex.

assessment in neurosurgical practice presents some limitations due to the limited availability of the intraoperative MRI and the confounding effect of the and anesthesia.

In this study, we assessed alterations of specific networks analyzed in single-subject analysis and in group analysis similarly as reported intraoperatively at 1.5T[3] using a routine clinical 3T MR unit. Functional connectivity assessed by rest-fMRI in patients with brain tumors in the adult and pediatric population demonstrated the feasibility to recognize different RSNs.[16-21,23,26,27,31-35] Recently, alterations of specific networks were analyzed at the level of the single subject and in group analysis by intraoperative rest-fMRI in the presurgical planning of brain lesions.[3] The literature reports[34] that several key functional networks could be identified in patients with brain tumors using rest-fMRI. Zhang et al.[36] demonstrated the feasibility of sensorimotor cortex mapping in patients with brain tumors using rest-fMRI, and its localization showed good correspondence with cortical stimulation mapping. The language-associated cortex also can be identified using rest-fMRI in patients with brain tumors.[37]

In this study, we present our experience with routine clinical rest-fMRI acquired before and after surgical resection of supratentorial gliomas to assess functional connectivity in patients with brain tumors. The results of this study add evidence that rest-fMRI is capable of identifying the functional network distribution and connection or disconnection in patients with brain tumors even when task-based fMRI is not feasible. In clinical practice, rest-fMRI may be successfully performed in addition to regular anatomic imaging and intraoperative mapping, replacing the preoperative task-driven fMRI that is not feasible in patients without appropriate collaboration. The postoperative evaluation may be useful to evaluate potential alterations in functional connectivity due to surgical resection. Particularly, in our study, single-subject functional connectivity analysis showed functional disconnection for dorsal attention and salience networks. Group analysis showed wide variations of functional connectivity before and after surgery in the default mode, salience, sensorimotor, and language networks; however, salience and language networks, salience and default mode networks, and salience and sensorimotor networks showed significant connection when we compared the results before and after surgery (Figure 7).

Although surgical resection was achieved in all the cases with a satisfactory EOR and without substantial clinical worsening, as shown by results from neurologic and neuropsychologic evaluations and KPS score assessment, the rest-fMRI showed impairment of selected functional connectivity. Taken collectively, our data suggest that rest-fMRI can provide information on functional networks that are difficult to disclose clinically, at least in the early follow-up. The exact influence of these networks in damaging quality of life is a demanding issue, considering its scarce identification by neuropsychological tests. From clinical practice, it is known that patients who experience cognitive complaints do not necessarily show lower scores on neuropsychologic tests. In addition, on the contrary, if patients show a lower test performance, they do not always experience cognitive problems in their daily life. However, during the subsequent clinical follow-up a progressive impairment in the executive functions was observed (data not shown). Executive functions include several higher-order cognitive processes that allow people to control and regulate their own behavior.[38] Key executive functions are inhibition, cognitive flexibility, and working memory which, all together, comprise self-decision-making.[38] Accordingly, rest-fMRI can anticipate information about impairment in executive functions following surgery and is useful as outcome measure. Also, it can be of help in identifying behavioral changes and guiding services for the patient and family. The need for neural-network preservation should be considered when facing with the concept of EOR.[39-41] In this scenario, the information gained by rest-fMRI will contribute in tailoring a personalized glioma surgery augmenting the surgeon's ability to increase the EOR and simultaneously minimize the risk to damage eloquent brain structures and critical neuronal networks responsible for executive function integrity.

Our results confirm that the presence of a tumor can affect the connectivity of diverse networks, particularly the dorsal attention, salience, and DMNs. Reduction in DMN connectivity in patients with gliomas compared with a control group was demonstrated in the literature[31]; our study confirms this report in the single-subject analysis and in the group analysis in patients with gliomas. Disconnections of the DMN, salience, and dorsal attention networks have been also observed in the pediatric population.[23]

Limitations

This study presents some limitations. First, the sample size is small, second further rest-fMRIs in the subsequent follow-ups would have been of help in providing additional information on neural network changes and plasticity over time. However, the lack of information in this field and the prospective design of the study make the current study a necessary first step in an area deserving much more work. Another drawback of this study lies in the fact that we did not correlate the postoperative rest-fMRI changes in neural network with EOR and patients' long-term

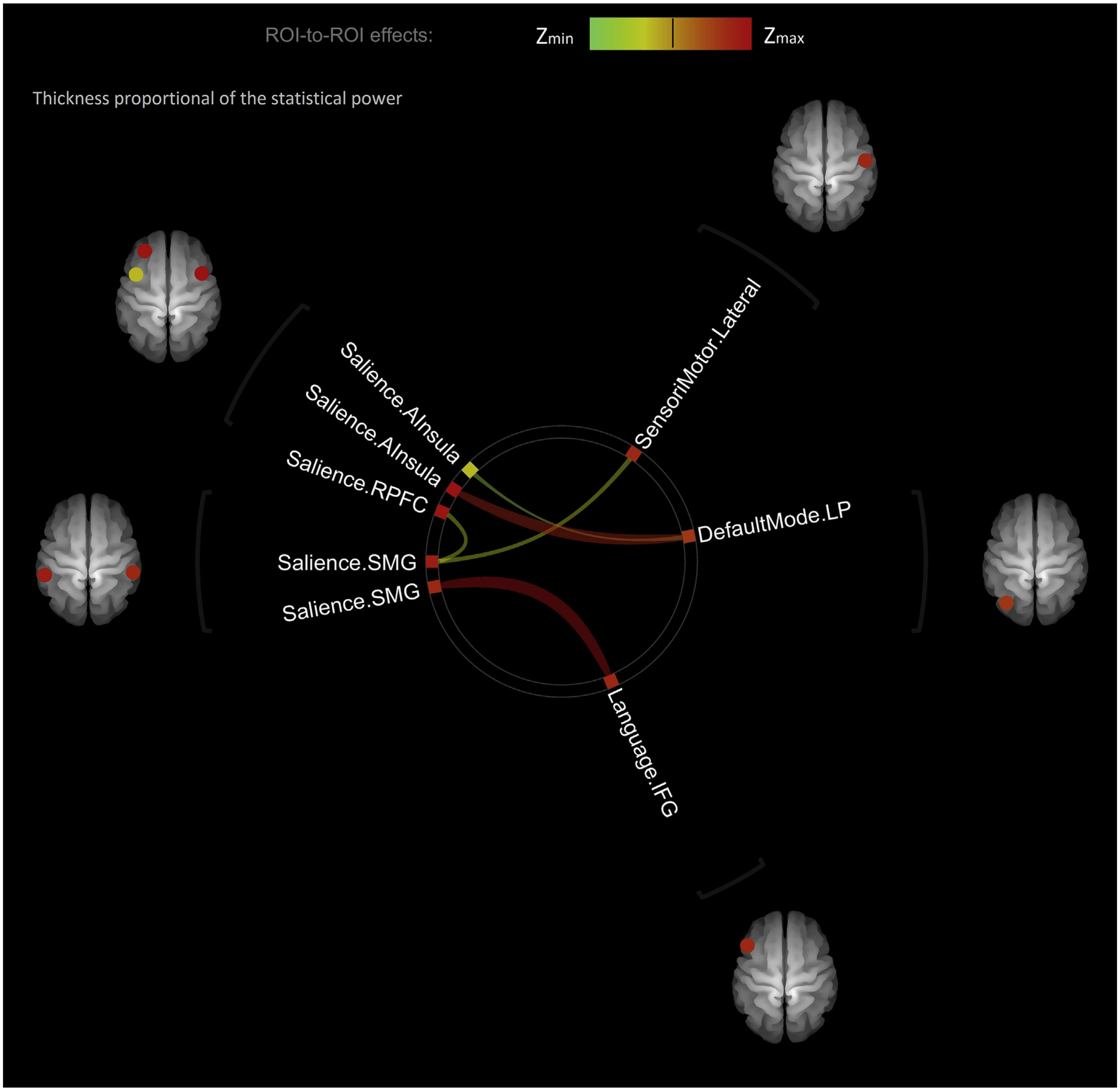

Figure 7. Functional connectome representing group analysis result before and after surgical resection of brain gliomas. The circular connectome shows the significant correlation of the salience and language networks, salience and default mode networks, and salience and sensorimotor networks, confirming the connection of these networks (*P*-uncorrected <0.0025; *P*-false discovery rate <0.077). SMG, supramarginal gyrus; RPFC, rostral prefrontal cortex; LP, lateral parietal cortex; IFG, inferior frontal gyrus.

prognosis after surgery. Future studies with a larger population are needed to validate the clinical relevance of the rest-fMRI for long-term risk stratification of neurologic deficits and prognosis. In addition, a comparison of results for single-subject and group analysis between patients and healthy volunteers would be useful to better define the role of rest-fMRI in surgical planning of brain gliomas.

Although rest-fMRI has been validated in neurologic and psychiatric settings, in patients presenting with brain tumors, the ROI placement can be affected by possible mass effect of the tumor, which can cause a structural shift and mismatch between the atlas and the local cortical topography and between functional and structural images that can lead to false results. Furthermore, the tumor has a metabolic effect that can affect the BOLD signals, thus causing the phenomenon of neurovascular uncoupling, which leads to false-negative results.[3]

CONCLUSIONS

Although task-based fMRI is commonly used in presurgical planning,[3] rest-fMRI has proven to be reliable in providing useful information about different networks of the brain, which could be used for preoperative brain mapping. In this initial experience with 10 patients affected by brain gliomas, rest-fMRI was able to provide valuable information for the detection of glioma-related functional brain network alterations. In the future, rest-fMRI could be used in the routine clinical preoperative setting not only to map eloquent areas but also to assess changes in neuronal networks related to the tumor and surgery, providing an assessment for diagnosis, prognosis, and personalized treatment.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Gianvincenzo Sparacia: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft. **Giuseppe Parla:** Data curation, Formal analysis, Software, Writing - review & editing. **Vincenzina Lo Re:** Data curation, Writing - review & editing. **Roberto Cannella:** Methodology, Writing - original draft, Writing - review & editing. **Giuseppe Mamone:** Conceptualization, Visualization, Writing - review & editing. **Vincenzo Carollo:** Conceptualization, Visualization, Writing - review & editing. **Massimo Midiri:** Resources, Writing - review & editing. **Giovanni Grasso:** Conceptualization, Data curation, Resources, Writing - review & editing.

REFERENCES

1. Lv H, Wang Z, Tong E, Williams LM, et al. Resting-state functional MRI: everything that nonexperts have always wanted to know. *AJNR Am J Neuroradiol*. 2018;39:1390-1399.
2. Sparacia G, Parla G, Cannella R, et al. Resting-state functional magnetic resonance imaging for brain tumor surgical planning: feasibility in clinical setting. *World Neurosurg*. 2019;131:356-363.
3. Metwali H, Samii A. Seed-based connectivity analysis of resting-state fMRI in patients with brain tumors: a feasibility study. *World Neurosurg*. 2019;128:e165-e176.
4. Duyn J. Spontaneous fMRI activity during resting wakefulness and sleep. *Prog Brain Res*. 2011;193:295-305.
5. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995;34:537-541.
6. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. *AJNR Am J Neuroradiol*. 2013;34:1866-1872.
7. Barkhof F, Haller S, Rombouts SA. Resting-state functional MR imaging: a new window to the brain. *Radiology*. 2014;272:29-49.
8. Wang D, Buckner RL, Fox MD, et al. Parcellating cortical functional networks in individuals. *Nat Neurosci*. 2015;18:1853-1860.
9. Shirer WR, Ryali S, Rykhlevskaia E, et al. Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb Cortex*. 2012;22:158-165.
10. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007;27:2349-2356.
11. Koch W, Teipel S, Mueller S, et al. Diagnostic power of default mode network resting state fMRI in the detection of Alzheimer's disease. *Neurobiol Aging*. 2012;33:466-478.
12. Barnett A, Audrain S, McAndrews MP. Applications of resting-state functional MR imaging to epilepsy. *Neuroimaging Clin N Am*. 2017;27:697-708.
13. O'Neill TJ, Davenport EM, Murugesan G, et al. Applications of resting state functional MR imaging to traumatic brain injury. *Neuroimaging Clin N Am*. 2017;27:685-696.
14. Zacà D, Jovicich J, Corsini F, et al. ReStNeuMap: a tool for automatic extraction of resting-state functional MRI networks in neurosurgical practice. *J Neurosurg*. 2018;131:764-771.
15. Shurtleff H, Warner M, Poliakov A, et al. Functional magnetic resonance imaging for presurgical evaluation of very young pediatric patients with epilepsy. *J Neurosurg Pediatr*. 2010;5:500-506.
16. Lu J, Zhang H, Hameed NUF, et al. An automated method for identifying an independent component analysis-based language-related resting-state network in brain tumor subjects for surgical planning. *Sci Rep*. 2017;7:13769.
17. Dierker D, Roland JL, Kamran M, et al. Resting-state functional magnetic resonance imaging in presurgical functional mapping: sensorimotor localization. *Neuroimaging Clin N Am*. 2017;27:621-633.
18. Lang S, Duncan N, Northoff G. Resting-state functional magnetic resonance imaging: review of neurosurgical applications. *Neurosurgery*. 2014;74:453-464.
19. Metwali H, Raemaekers M, Kniese K, Samii A. Intraoperative resting-state functional connectivity and resting-state networks in patients with intracerebral lesions: detectability and variations between sessions. *World Neurosurg*. 2020;133:e197-e204.
20. Benedict W, Primeau M, Blodgett-Dycus C, Thulborn KR, Prabhu VC. Cortical mapping in the resection of cerebral gliomas—preoperative planning. *Contemp Neurosurg*. 2006;28:1-6.
21. Sair HI, Yahyavi-Firouz-Abadi N, Calhoun VD, et al. Presurgical brain mapping of the language network in patients with brain tumors using resting-state fMRI: comparison with task fMRI. *Hum Brain Mapp*. 2016;37:913-923.
22. Vergun S, Gaggl W, Nair VA, et al. Classification and extraction of resting state networks using healthy and epilepsy fMRI data. *Front Neurosci*. 2016;10:440.
23. Rosazza C, Aquino D, D'Incerti L, et al. Preoperative mapping of the sensorimotor cortex: comparative assessment of task-based and resting-state FMRI. *PLoS One*. 2014;9:e98860.
24. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect*. 2012;2:125-141.
25. Hart MG, Price SJ, Suckling J. Functional connectivity networks for preoperative brain mapping in neurosurgery. *J Neurosurg*. 2017;126:1941-1950.
26. Lin HY, Tseng WY, Lai MC, et al. Altered resting-state frontoparietal control network in children with attention-deficit/hyperactivity disorder. *J Int Neuropsychol Soc*. 2015;21:271-284.
27. Sair HI, Agarwal S, Pillai JJ. Application of resting state functional MR imaging to presurgical mapping: language mapping. *Neuroimaging Clin N Am*. 2017;27:635-644.
28. Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci USA*. 2016;113:7900-7905.
29. Bijsterbosh J, Smith SM, Beckmann CF. *Introduction to Resting State fMRI Functional Connectivity*. Oxford, UK: Oxford University Press; 2017.
30. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Roy Stat Soc Ser B*. 1995;57:289-300.
31. Esposito R, Mattei PA, Briganti C, et al. Modifications of default mode network connectivity in patients with cerebral glioma. *PLoS One*. 2012;7.
32. Roland JL, Griffin N, Hacker CD, et al. Resting state functional magnetic resonance imaging for surgical planning in pediatric patients: a

preliminary experience. *J Neurosurg Pediatr*. 2017;20:583-590.

33. Harris RJ, Bookheimer SY, Cloughesy TF, et al. Altered functional connectivity of the default mode network in diffuse gliomas measured with pseudo-resting state fMRI. *J Neurooncol*. 2014;116:373-379.

34. Quigley M, Cordes D, Wendt G, et al. Effect of focal and nonfocal cerebral lesions on functional connectivity studied with MR imaging. *AJNR Am J Neuroradiol*. 2001;22:294-300.

35. Shimony JS, Zhang D, Johnston JM, Fox MD, Roy A, Leuthardt EC. Resting-state spontaneous fluctuations in brain activity: a new paradigm for presurgical planning using fMRI. *Acad Radiol*. 2009;16:578-583.

36. Zhang D, Johnston JM, Fox MD, et al. Preoperative sensorimotor mapping in brain tumor patients using spontaneous fluctuations in neuronal activity imaged with functional magnetic resonance imaging: initial experience. *Neurosurgery*. 2009;65(suppl):226-236.

37. Tie Y, Rigolo L, Norton IH, et al. Defining language networks from resting-state fMRI for surgical planning—a feasibility study. *Hum Brain Mapp*. 2014;35:1018-1030.

38. Karr JE, Areshenkoff CN, Rast P, Hofer SM, Iverson GL, Garcia-Barrera MA. The unity and diversity of executive functions: a systematic review and re-analysis of latent variable studies. *Psychol Bull*. 2018;144:1147-1185.

39. Rossi M, Nibali MC, Torregrossa F, Bello L, Grasso G. Innovation in neurosurgery: the concept of cognitive mapping. *World Neurosurg*. 2019;131:364-370.

40. Grasso G, Torregrossa F, Leone L. Maximizing the extent of resection in high-grade glioma. *World Neurosurg*. 2019;123:256-258.

41. Grasso G. Extent of resection and survival in glioblastoma multiforme. *JAMA Oncol*. 2016;2:1508-1509.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 3 March 2020; accepted 6 May 2020

Citation: World Neurosurg. (2020).
https://doi.org/10.1016/j.wneu.2020.05.054

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***