



# Seed-Based Connectivity Analysis of Resting-State fMRI in Patients with Brain Tumors: A Feasibility Study

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■ **OBJECTIVE:** In this study, we present our experience using resting-state functional magnetic resonance imaging (rs-fMRI) in preoperative planning. We performed group analysis to demonstrate the effects of brain tumor on resting-state networks (RSNs).

■ **METHODS:** Thirty patients with supratentorial gliomas were included in the study. Preoperative rs-fMRI and structural magnetic resonance imaging were performed in all cases. The rs-fMRI was preprocessed (realignment, slice time correction, coregistration to structural images, normalization, and smoothing). The structural images were segmented and normalized. Band filtering and denoising were applied to the functional images. Connectivity analysis was performed using seed-based connectivity analysis (SCA) at single subject level and group level. Correlation algorithm has been used with  $r > 0.5$ .

■ **RESULTS:** RSNs could be detected in all patients. They showed similarity to the results of the task-based fMRI, when task-based fMRI was feasible. Detection of the networks was also possible in patients with neurologic deficits, in whom task-based fMRI was not possible. We could use SCA in patients under anesthesia. High-level networks (default mode, salience, and dorsal attention networks) were detectable but showed a wide spectrum of spatial alterations and component disconnections.

■ **CONCLUSIONS:** rs-fMRI is a feasible method for extended brain mapping. Diverse RSNs could be detected

in patients with brain tumors and could be applied in preoperative planning. SCA was a robust and direct approach for data analysis and could answer specific clinically relevant questions. However, further studies are needed to validate the technique and its clinical impact.

## INTRODUCTION

Detection of the blood oxygen level—dependent (BOLD) signal with functional magnetic resonance imaging (fMRI) has become a powerful tool for the in vivo analysis of a wide spectrum of brain functions. A large number of temporally coherent networks, that subserve different functions of the brain such as vision, audition, motor, and attention, could be detected at rest using resting-state fMRI (rs-fMRI). These networks show consistent, yet not identical, patterns of activation at rest.<sup>1-3</sup> Furthermore, resting-state networks (RSNs) show a high reproducibility.<sup>4</sup> Accordingly, it could be a robust method for examination of the intrinsic functional architecture, or “connectome,” of the human brain.<sup>5</sup>

rs-fMRI is an emerging method in preoperative diagnosis and planning in neuro-oncology and epilepsy surgeries.<sup>6-11</sup> Different eloquent functional networks, for instance motor, visual, or language networks, can be identified and spatially presented on coregistered high-resolution structural images (T1 or T2). In comparison with task-based fMRI, rs-fMRI has potential to identify the high order networks, which in contrast cannot be analyzed by conventional task-based fMRI. The subject is not required to perform any tasks; therefore, it could be suitable for

### Key words

- Brain mapping
- Functional connectivity
- Preoperative planning
- Resting-state fMRI
- Resting-state networks

### Abbreviations and Acronyms

- BOLD:** Blood oxygen level dependent
- DICOM:** Digital Imaging and Communications in Medicine
- DMN:** Default mode network
- fMRI:** Functional magnetic resonance imaging
- ICA:** Independent component analysis
- MNI:** Montreal Neurological Institute
- MRI:** Magnetic resonance imaging
- ROI:** Region of interest

**rs-fMRI:** Resting-state functional magnetic resonance imaging

**RSNs:** Resting-state networks

**SCA:** Seed-based connectivity analysis

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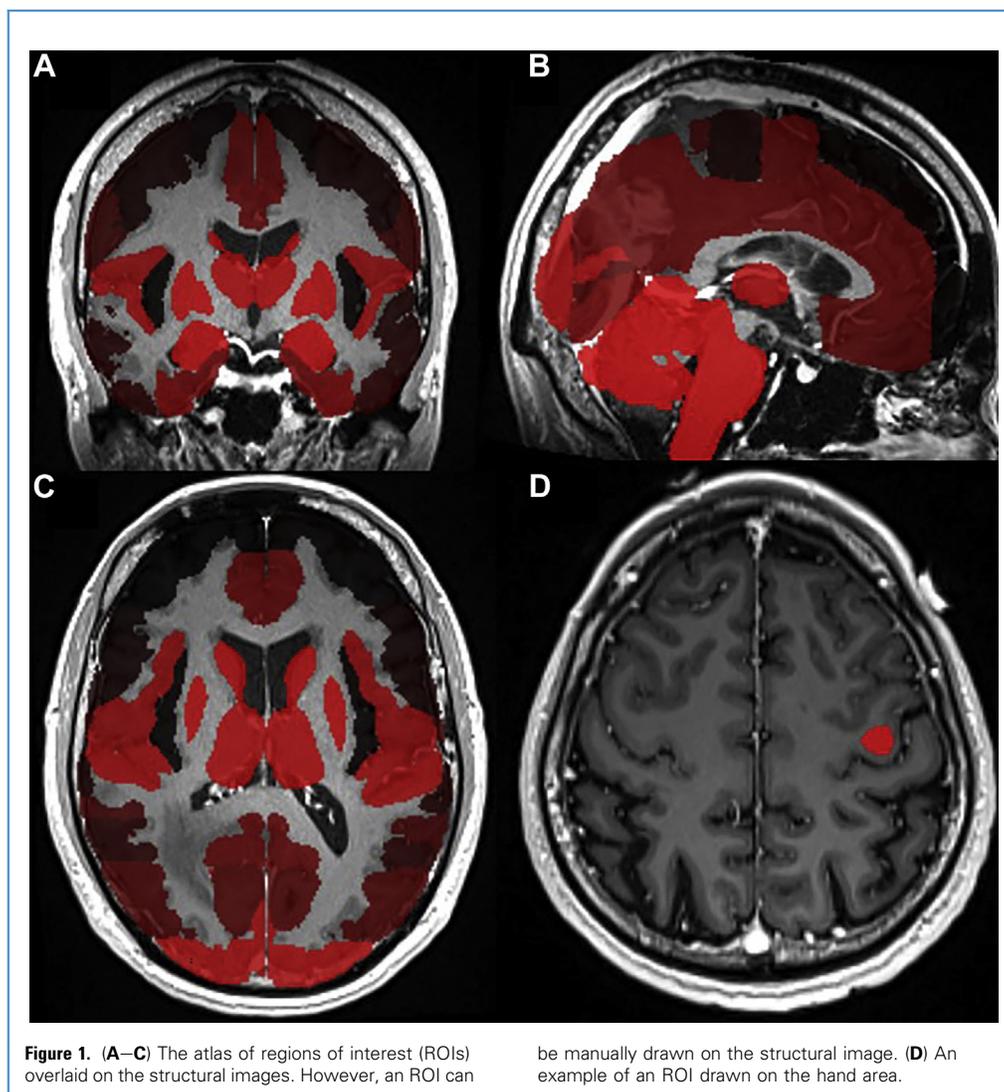
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**Table 1.** Patient Characteristics

Age	18–77 years (mean, 54 years)
Sex (M:F)	16:14
Eloquent cortex affected	Motor cortex: 22 patients Language: 7 patients Visual: 3 patients
Glioma grade	Grade I: 2 patients Grade II: 6 patients Grade III: 7 patients Grade VI: 15 patients
Recurrent tumor	3 patients
Previous radiation	3 patients

uncooperative patients or patients with impaired consciousness. Furthermore, only 1 MRI session is required to detect the desired RSNs, which could in turn be more convenient for some patients.<sup>1,3,12</sup>

The rs-fMRI data are commonly analyzed in clinical context using 2 approaches: independent component analysis (ICA)<sup>1,3,12</sup> and seed-based connectivity analysis (SCA).<sup>13,14</sup> ICA is a data-driven analysis, where the regions of the brain, which show coherent fluctuation in BOLD signals, reveal temporally coherent networks.<sup>3</sup> ICA provides higher dimensionality and robust statistical testing, but unfortunately at the cost of being potentially more complex to perform. SCA involves extracting a time series from a priori selected seed region of the brain (voxel, cluster, or region of interest [ROI] in atlas). It then correlates them to all other voxels in the brain to detect regions



**Table 2.** ROIs Used for SCA to Identify Commonly Investigated Networks

Network	ROIs
Motor network	Precentral gyrus
Visual network	Intracalcarine cortex
Language network	Superior temporal gyrus, anterior division left, Angular supramarginal gyri, pars triangularis
Saliency network	Anterior cingulate cortex
Default mode network	Posterior cingulate gyrus
Attention (dorsal)	Posterior and lateral parietal regions
Executive	Medial prefrontal regions

ROIs, regions of interest; SCA, seed-based connectivity analysis.

of the brain that have coherent time courses, and which subsequently constitute a network, with this region.<sup>15</sup> This could be helpful in the clinical setup to address explicit relevant questions. This straightforward interpretability, in comparison with other methods, also makes SCA an attractive approach in clinical practice. A recent assessment of the test-retest reliability of these methods has indicated that resting-state connectivity relationships, which are identified by SCA, showed moderate-to-high reliability.<sup>16</sup> Accordingly, it would be more practical in surgical planning, saves time, is easily interpreted, and reliable.

The current work aims to provide a reproducible feasible pipeline for rs-fMRI preprocessing and analysis in patients with brain tumors. This method can suit both fast analysis for the identification of certain networks of clinical interest and in-depth analysis of the functional connectivity. The steps of preprocessing as well as network identification and their overlay on structural images are described. Although the main aim of the study was to provide a guideline for spatial identification of different networks to be used in preoperative planning, we describe, in addition, a method for first-level analysis (single-subject analysis) and second-level analysis (group analysis across subjects). We added selective case examples to clarify the technique and its usability.

## METHODS

The study has been approved from the local ethical committee.

### Patients Characteristics

From May 2016 till December 2018, rs-fMRI has been performed for 30 patients with gliomas near to eloquent cortex. A summary of patient characteristics is presented in **Table 1**. The rs-fMRI did not add extra cost and was performed during the preoperative MRI analysis.

### Software and Hardware Configuration

For the analysis, CONN<sup>17</sup> and SPM (Statistical Parametric Mapping 12, Wellcome Centre for Human Neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk>) software, which runs based on Matlab (The MathWorks, Inc., Natick, Massachusetts, USA),

**Table 3.** The Time Cost of Each Job in the Analysis

Job		Time Cost
Preprocessing	Realign (estimate and reslice)	30 seconds
	Slice time correction	9 seconds
	Coregister (estimate)	47 seconds
	Segment of structural image	125 seconds
	Normalization (write) of structural image	35 seconds
	Normalization (write) of functional images	45 seconds
	Smooth	25 seconds
	Total	270 seconds = 4.5 minutes
	First-level analysis	Denoising, filtering, and detrending, ROI-ROI analysis

ROI, regions of interest.

were used. The analysis was performed on a Microsoft Windows 10-based computer powered by a quadcore processor (Intel Core i7-8650U) and installed with 16 GB RAM with activated parallel computing (Matlab function). For the inspection of the images and overlay of the resulting components on the structural images, we used MRICron software.<sup>18</sup>

### Data Acquisition

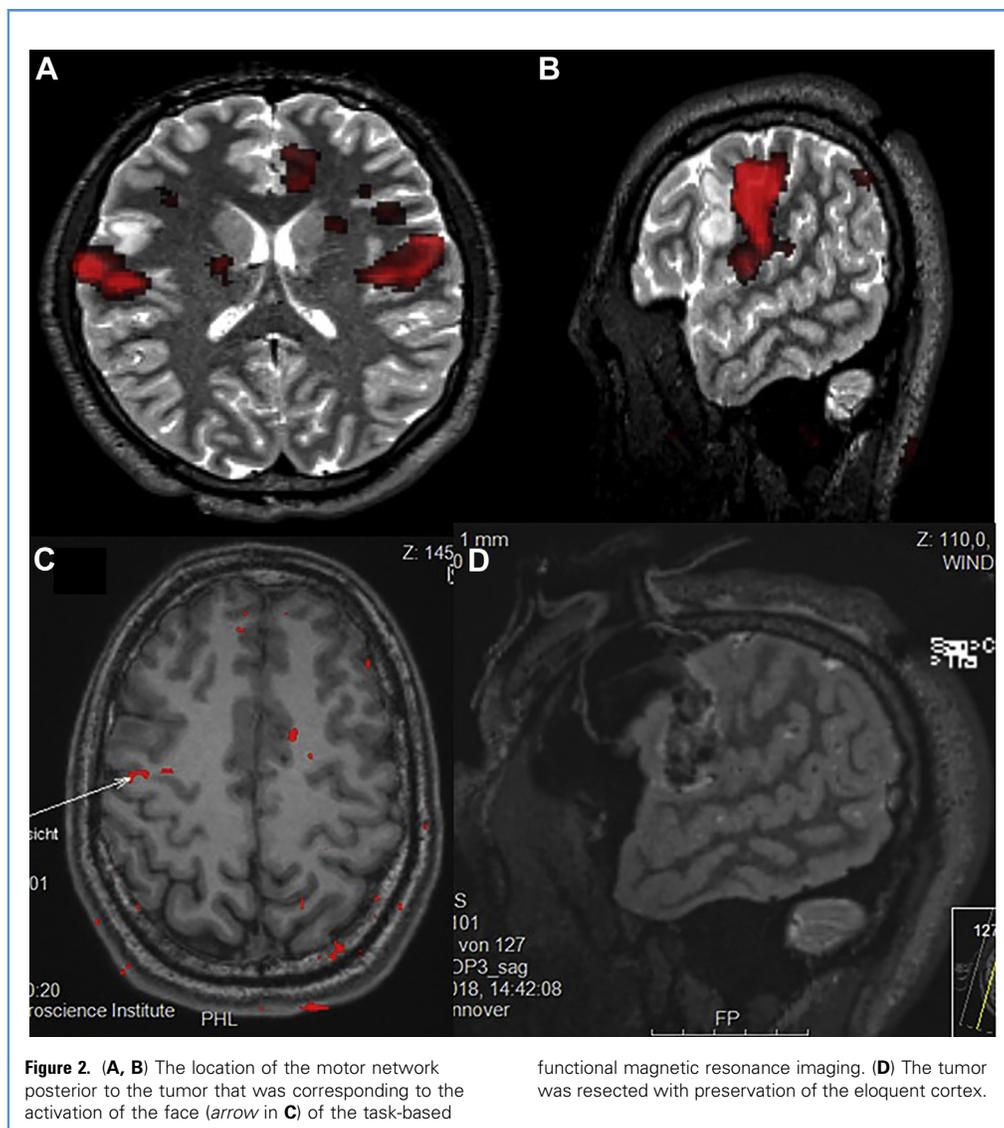
All the patients underwent MRI examination using a 3 Tesla Scanner (Skyra Siemens AG Medical Solution, Munich, Germany). The MRI included volumetric high-resolution anatomical imaging (T1 or T2), as well as rs-fMRI echo-planar imaging sequences (TR 2000 milliseconds, TE 30 milliseconds, voxel size  $3 \times 3 \times 3$  mm, slice thickness 3 mm, number of slices 36, number of volumes 178).

### Images Conversion

The Digital Imaging and Communications in Medicine (DICOM) data of the functional and the structural images acquired from the scanner was transferred to the working computer using a universal storage bus drive. The DICOM data of the functional images was converted into a 4-dimensional Neuroimaging Informatics Technology Initiative file, which includes the bitmap, the affine transformation matrix, and the time series of all volumes, using dcm2nigui incorporated in MRICron software.<sup>18</sup> The DICOM data of the structural images was converted into a 3-dimensional Neuroimaging Informatics Technology Initiative file, which includes the bitmap and the affine transformation matrix using the same software package as for the functional images.

### Preprocessing

The preprocessing was performed using Statistical Parametric Mapping (SPM 12, <http://www.fil.ion.ucl.ac.uk>) running in MATLAB 2016a (The MathWorks Inc.) after activation of parallel computing.



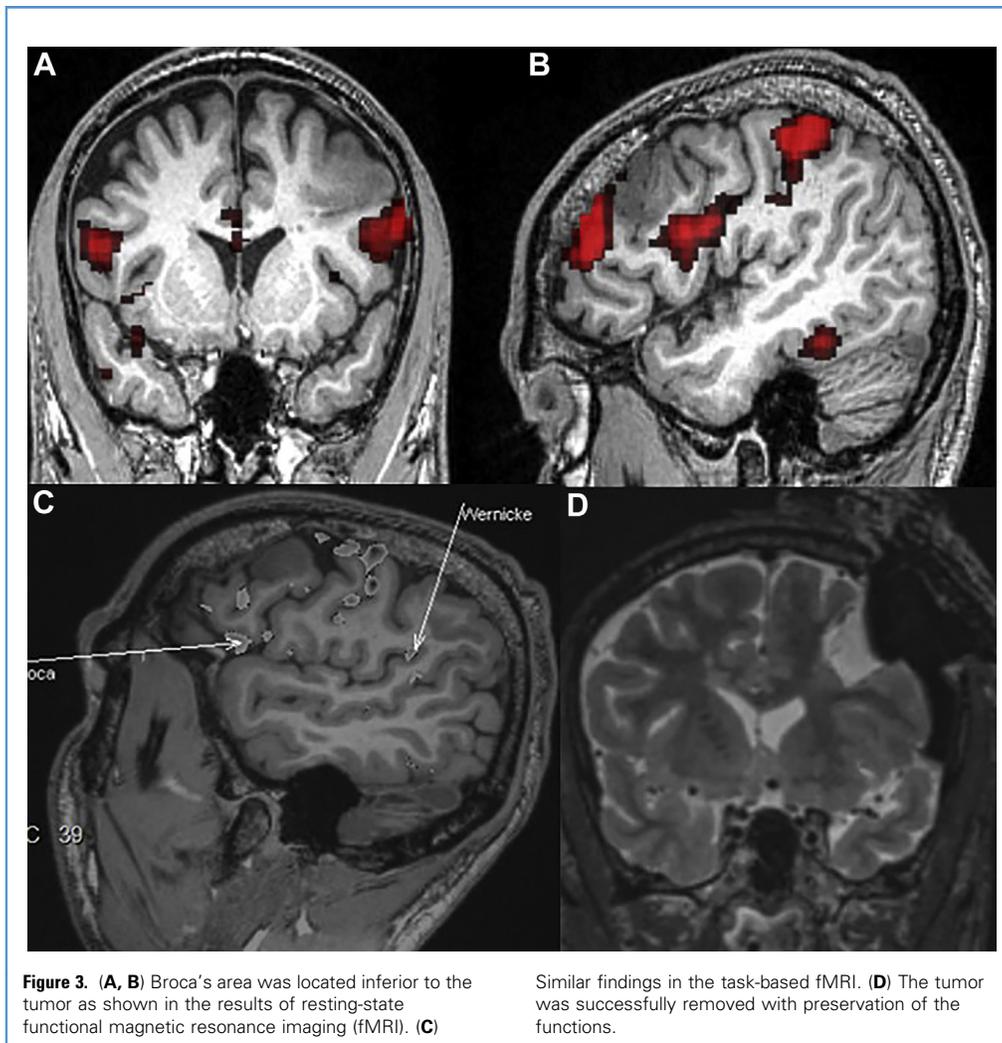
We recommended manual reorientation of the structural images in yaw, pitch, and roll directions. The origin was then set to the anterior commissure. The new orientation was applied to the structural and functional images. Manual reorientation decreases the time cost in the next preprocessing step and avoids being trapped into a local minimum. After reorientation, we used CheckReg (SPM) function to check matching of the functional and the structural image in the subject space.

We ran realignment of the functional images to correct the motion artifacts. Realignment results in changes in affine transformation matrix and reslices these images into new files containing interpolated bitmaps. Slice time correction, which depends on the MRI scanner, was performed. In this study, a Siemens scanner was used, which acquires the images in ascending even interleaved order. The structural images were normalized into the Montreal Neurological Institute (MNI) space, and were then segmented into gray matter, white matter, and

cerebrospinal fluid. The functional images were also normalized into the MNI space and coregistered to the structural images. The normalized functional images were smoothed to 6-mm Gaussian full width half maximum, which was twice a single dimension of the voxel size. A band-pass filter [0.008–0.09 Hz] and linear detrending were applied.

#### ROIs Identification

The CONN toolbox provides predefined 164 ROIs, which compose an atlas of cortical and subcortical areas from the FSL Harvard-Oxford atlas,<sup>18</sup> as well as cerebellar areas from the automated anatomical labeling atlas.<sup>19</sup> The atlas is normalized in MNI space and could be applied to the normalized images of the subject(s). Adequate coregistration between the atlas and each subject should be confirmed by either the use of CheckReg function of SPM, or the overlay function of MRIcron (Figure 1A–C). However, a subject-specific ROI can be manually



drawn using MRICron and then used in the analysis. **Figure 1D** shows an ROI drawn on the anatomical hand area of the left side. Furthermore, the subject-specific ROI can also be defined using a mask created from the task-based fMRI.

#### First-Level Analysis

In ROI-ROI/seed-voxel analysis, the connectivity of the key ROIs of the brain to other ROIs (ROI-ROI analysis) and all brain voxels (ROI-voxel analysis) were tested. CONN display was checked to evaluate the spatial configuration of the connectivity of each ROI between subjects. We evaluated the commonly used ROIs in the literature,<sup>14-16</sup> which are presented in **Table 2**. The correlation coefficient of each ROI to other ROIs was calculated. We set the correlation threshold to  $R > 0.5$ . A list of ROIs was automatically exported in the results file created by the CONN toolbox. The resulting components could be overlaid over structural images using the overlay function of MRICron.

#### Second-Level Analysis

After first-level (single-subject) analysis, we performed a group ROI-voxel analysis to detect the average effect of the tumor on the

functional connectivity and RSNs across subjects (highest threshold  $P < 0.001$ , cluster threshold  $P \leq 0.05$ ). We used the same ROIs that we used in the single-subject analysis.

## RESULTS

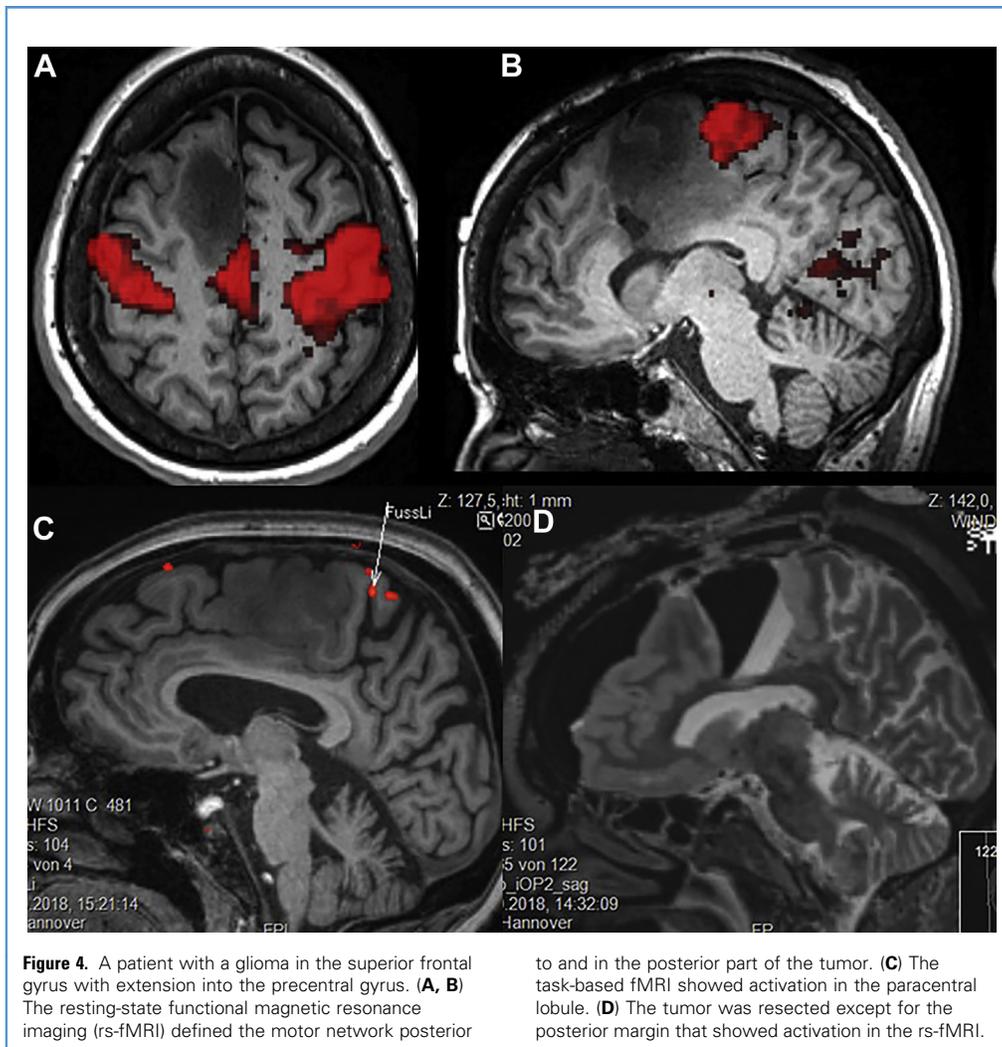
The acquisition time for the rs-fMRI was 5 minutes. There were no technical complications. The preprocessing, denoising, and analysis for a single patient required around 10 minutes. The time needed for each step is presented in **Table 3**.

#### First-Level Analysis

The low-level resting networks (motor, visual, language, sensory) could be identified in all patients. Some networks showed spatial alteration due to tumor mass effect, edema, or infiltration.

#### Case Example 1

A 25-year-old male patient presented with an attack of generalized convulsions. An MRI of the brain showed a lesion in the right frontal operculum posterior to the pars triangularis. The lesion did not show enhancement after contrast material



injection. A functional MRI was performed and showed activation of the face region posterior to the lesion. rs-fMRI and SCA were performed with an ROI on the precentral gyrus on the left side (the healthy sand showed the extension of the motor cortex posterior to the tumor (Figure 2A and B) corresponding to the of the task-based fMRI (Figure 2C). The patient was operated, and the tumor was resected with preservation of the eloquent cortex (Figure 2D). Postoperatively, the patient showed partial upper motor facial paresis on the left side, which recovered completely after 1 week.

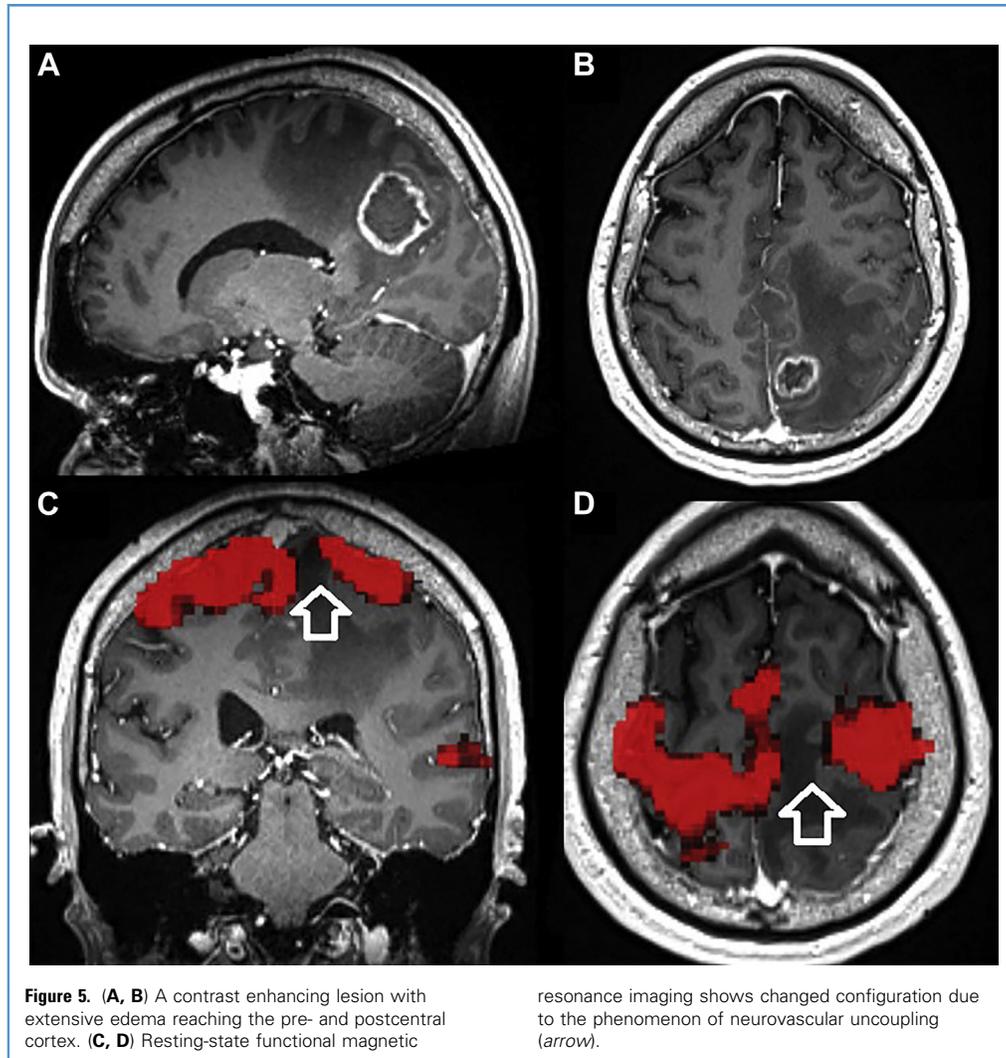
#### Case Example 2

A 33-year-old male patient presented with attacks of dizziness and headache. An MRI of the brain revealed a left frontal lesion without contrast enhancement. The resting-state fMRI showed Broca's area together with other language-associated areas (Figure 3A and B) using a seed on Wernicke's area. A preoperative fMRI was performed and showed Broca's area located inferior to the tumor corresponding to the finding of rs-fMRI (Figure 3C).

The patient was operated for tumor resection (Figure 3D) and showed no neurologic deficits after surgery.

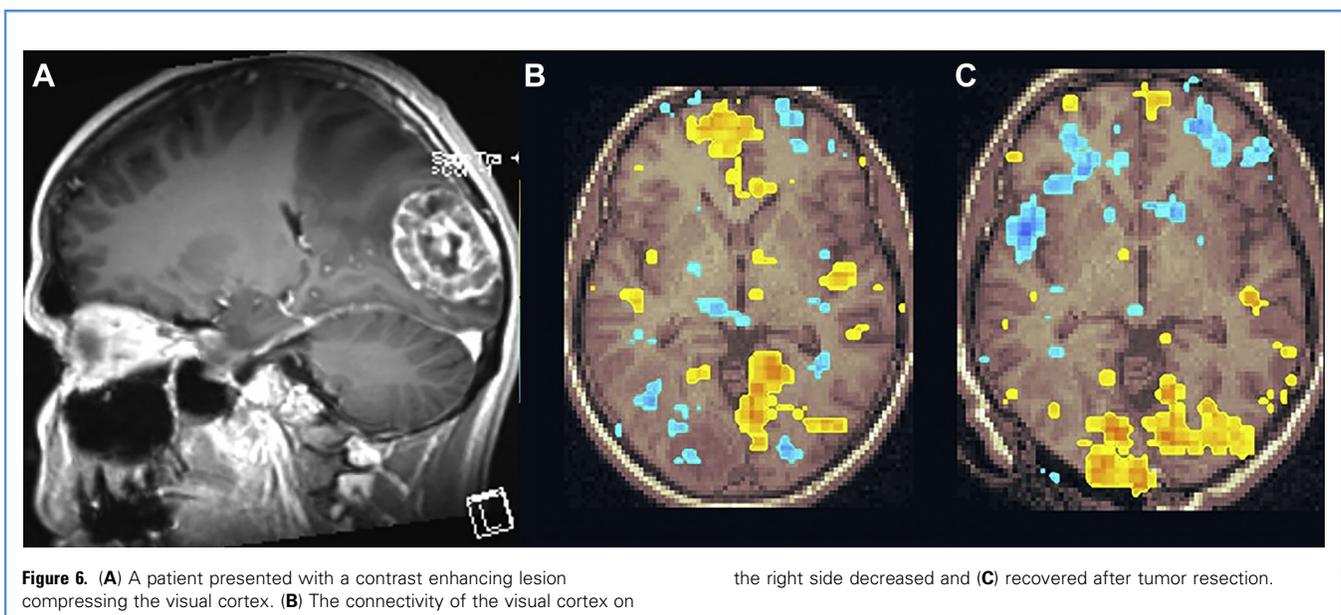
#### Case Example 3

A 50-year-old female patient suffered from an attack of convulsions 7 years ago. An MRI of the brain performed at that time showed a precentral dorsal glioma, which was managed by a wait and see for 6 years, and the tumor was stable. A recent MRI showed tumor progress and the patient presented herself in our hospital for tumor debulking. Before surgery, an fMRI was performed to delineate the motor functioning area in relation to the tumor. A resting state was also performed, and showed that the posterior tumor margin showed activation in both rs-fMRI (Figure 4A and B) and task-based fMRI (Figure 4C). The tumor was resected, but the posterior margin of the tumor, which showed positive fMRI activation, was left to avoid motor deficits after surgery (Figure 4D). The patient suffered from temporary weakness in the left lower limb after surgery, mainly in the foot



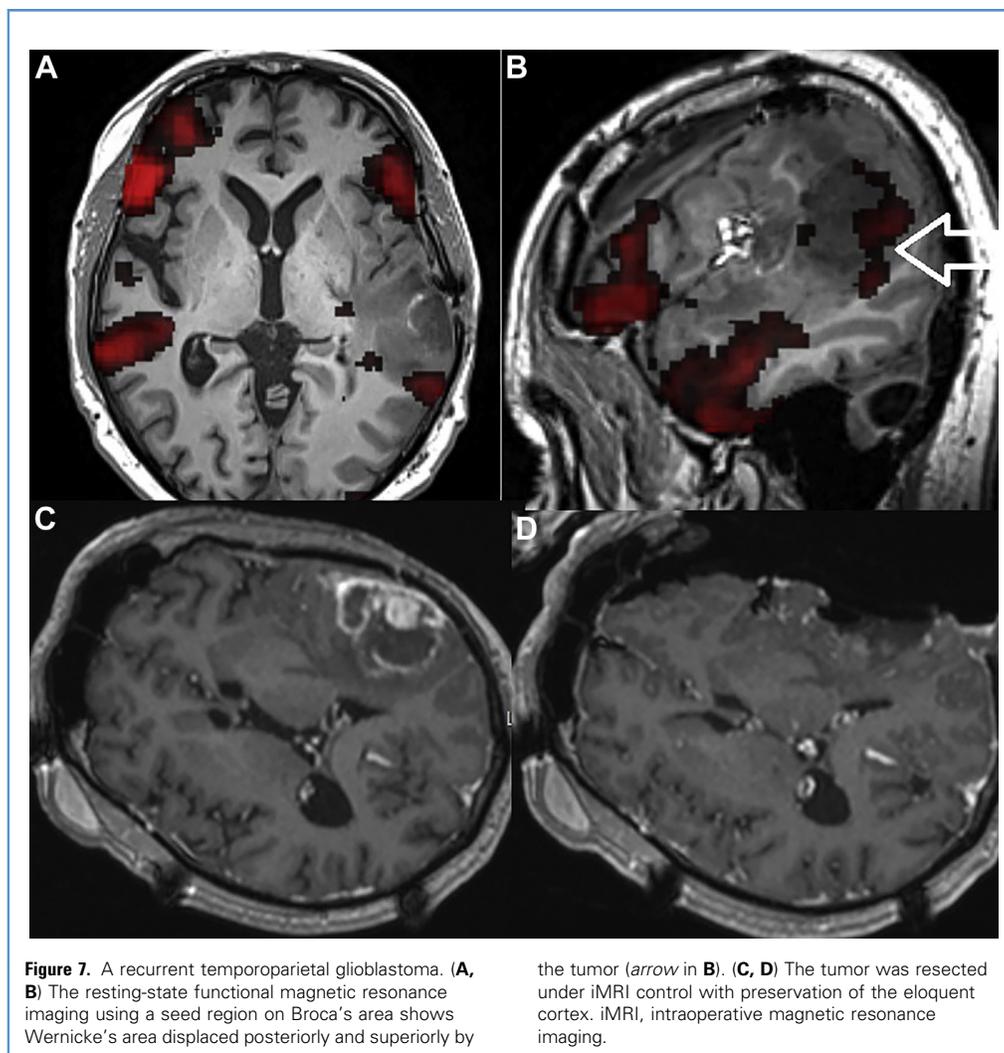
**Figure 5.** (A, B) A contrast enhancing lesion with extensive edema reaching the pre- and postcentral cortex. (C, D) Resting-state functional magnetic

resonance imaging shows changed configuration due to the phenomenon of neurovascular uncoupling (arrow).



**Figure 6.** (A) A patient presented with a contrast enhancing lesion compressing the visual cortex. (B) The connectivity of the visual cortex on

the right side decreased and (C) recovered after tumor resection.



dorsi and planter flexors. The weakness recovered completely after 3 weeks.

#### Case Example 4

A 70-year-old dentist suffered from progressive coordination and fine motor disorders in the left upper and lower limbs. MRI of the brain showed a contrast enhancing lesion in the dorsal parasagittal region, with extensive edema reaching the post- and precentral gyri on the right side (Figure 5A and B). A rs-fMRI was performed and showed changes in the configuration of the motor cortex on the right, with a decrease in the volume more in the edematous part of the precentral gyrus, demonstrating the phenomenon of neurovascular uncoupling (Figure 5C and D).

#### Case Example 5

A 56-year-old female patient presented with blurring of vision. Clinically, the patient suffered from incomplete homonymous hemianopsia to the left. The MRI showed a right occipital contrast enhancing lesion (Figure 6A). The preoperative and intraoperative preresection rs-fMRI showed decreased connectivity in the right

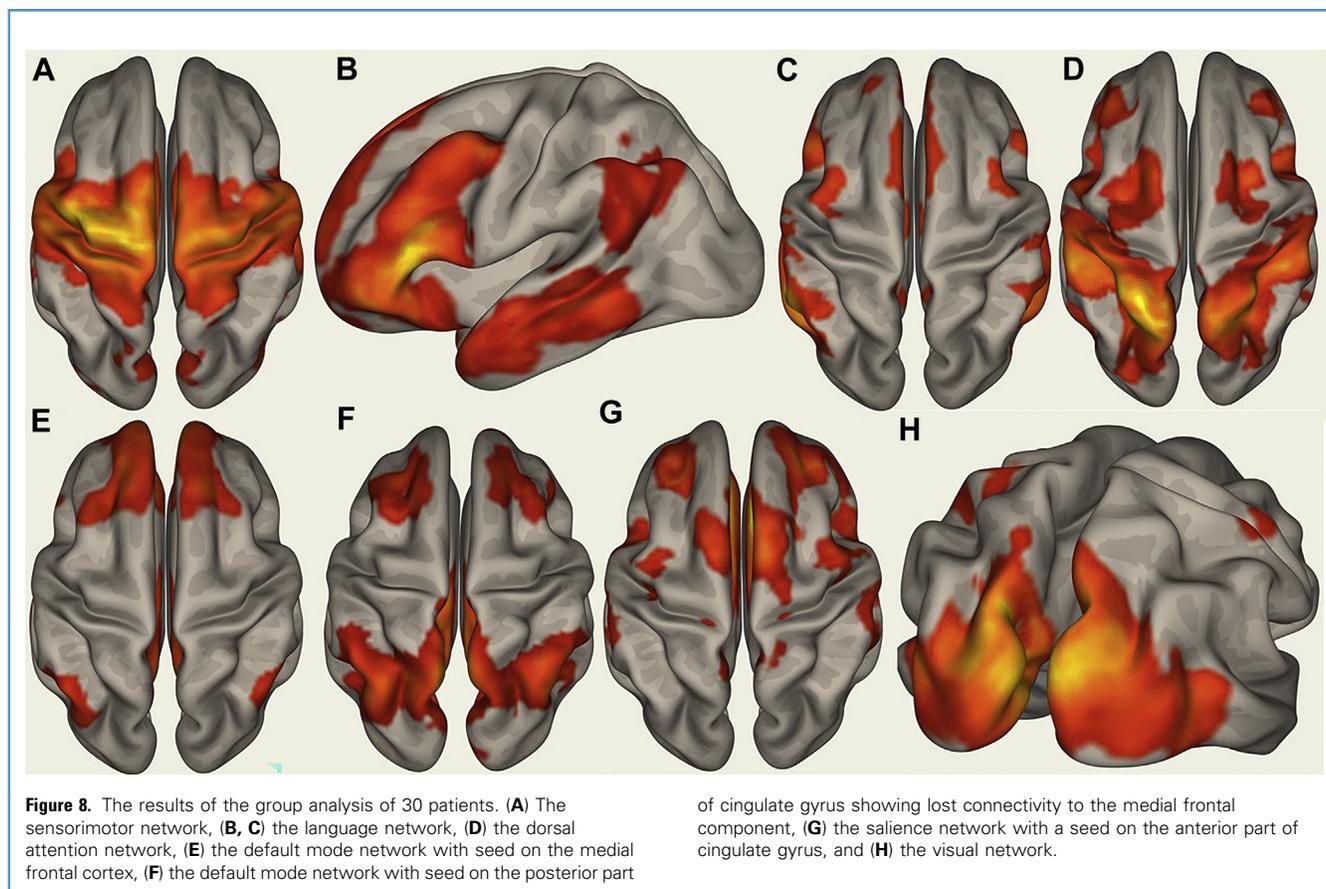
visual cortex (Figure 6B). The patient was operated for tumor resection, and the intraoperative postresection rs-fMRI showed recovering of the connectivity after tumor resection (Figure 6C). The homonymous hemianopsia recovered after surgery.

#### Case Example 6

A 63-year-old male patient presented with a recurrent glioblastoma temporooccipital region. At the time of presentation, the patient was aphasic. The task-based fMRI was not possible, and we performed rs-fMRI that showed the location of Wernicke's area at the cortex posterior to the tumor and displaced superiorly and posteriorly (Figure 7A and B). The patient was operated for tumor resection. The eloquent cortex was preserved (Figure 7C and D). The patient recovered after surgery and the aphasia was markedly improved.

#### Second-Level Analysis

We performed ROI-voxel group analysis. Motor, sensory, visual, language networks showed a normal spatial configuration (Figure 8). However, the default mode network (DMN) showed a



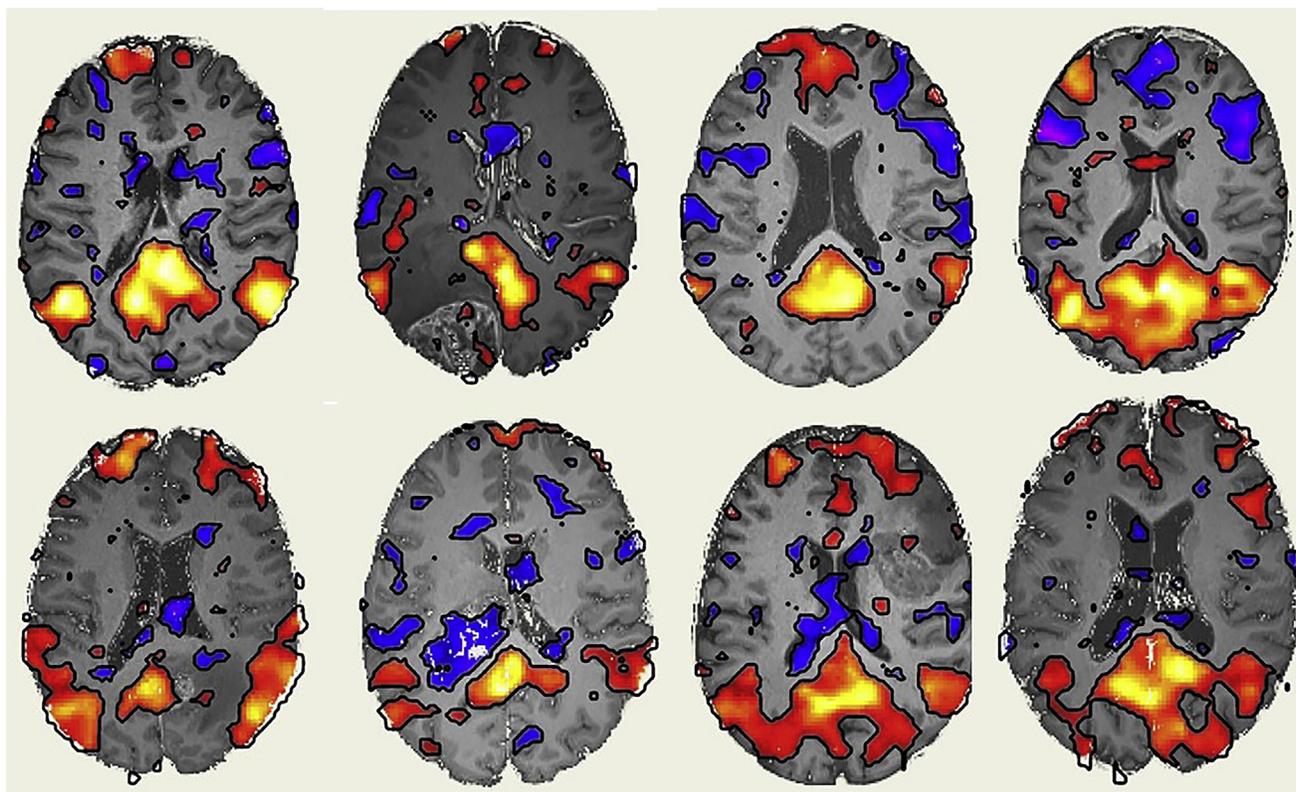
disconnection between the medial frontal components and the cingulate/parietal components (Figure 8). Similar disconnections were observed in dorsal attention and salience networks (Figure 9). A single-subject inspection of the default mode (Figure 9), salience (Figure 10), and dorsal attention networks showed wide variations in the spatial orientation between subjects. We could not correlate this variation to specific tumor location or grade or clinical status.

## DISCUSSION

In this study, we present a pipeline for the analysis of rs-fMRI in patients with brain tumors based on evaluation of 30 patients with brain tumors. We used seed-based functional connectivity analysis. The technique was robust and was able to provide useful information about different networks of the brain, which could be used for preoperative brain mapping. We reported not only the low-level networks (visual, language, and motor networks) but also the in-literature-commonly-investigated high-level networks (dorsal attention, default mode, and salience networks). Furthermore, we were able to use the technique in patients with neurologic deficits, who could not perform the tasks required for task-based fMRI, and also with uncooperative patients, or patients

under anesthesia. Alterations of specific networks were also analyzed at the level of the single subject and in group analysis.

In the neurosurgical practice, Quigley et al<sup>20</sup> reported the presence of the functional connectivity in patients with focal brain lesions. After that, Shimony et al<sup>21</sup> reported that several key functional networks could be identified in patients with brain tumors using rs-fMRI. Zhang et al<sup>6</sup> reported that the sensorimotor cortex could be reliably detected using rs-fMRI and its localization showed good correspondence with cortical stimulation mapping. The language-associated cortex can also be identified using rs-fMRI in patients with brain tumors.<sup>7</sup> Functional connectivity has also been investigated as a prognostic tool in patients with intra-axial lesions close to eloquent cortices.<sup>8</sup> The significance of the rs-fMRI was further elaborated in additional studies that described the functional connectivity in patients with brain tumors.<sup>9-11</sup> Hart et al<sup>14</sup> reported about using rs-fMRI to define different RSNs in 5 patients with brain tumors. Roland et al<sup>22</sup> reported about using rs-fMRI for presurgical planning in the pediatric age group. In this study, we present our experience with rs-fMRI as a tool for presurgical planning and exploration of neural functions in patients with brain tumors. It is capable of defining the spatial orientation of the motor cortex in relation to the tumor (case examples 1 and 3), demarcation of the language cortex (case examples 2 and 6), identification of the eloquent



**Figure 9.** Examples from 8 patients showing the different patterns of spatial organization of the default mode network with decreased

connectivity between the posterior part of the cingulate gyrus (seed) and the medial frontal lobe/the parietal lobe components.

cortex in patients with neurologic deficits, when the task-based fMRI was not feasible (case example 6), and brain mapping and prediction of functional recovery, even in patients under anesthesia (case example 5).

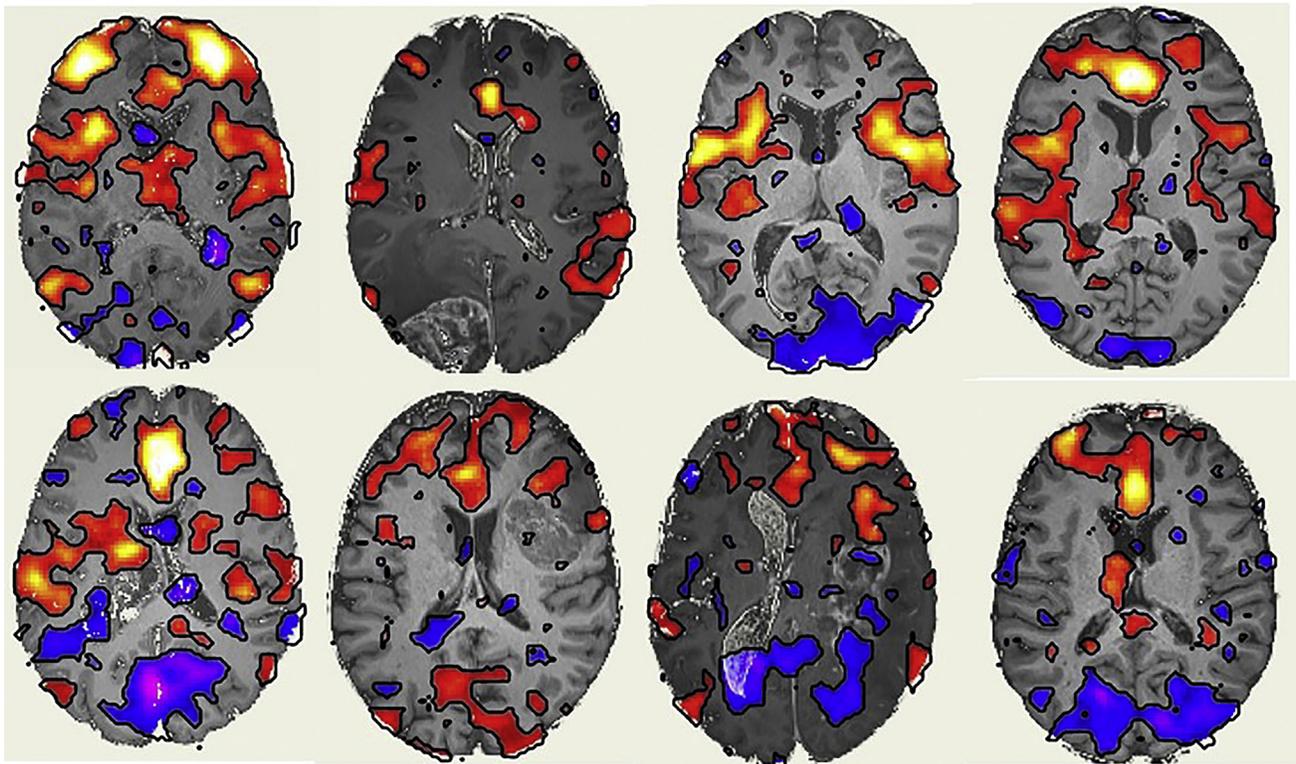
Brain tumors can affect functional connectivity. Esposito et al<sup>23</sup> reported about reduced DMN connectivity in patients with gliomas in comparison with control. There was also an altered connectivity of the DMN detected by pseudo-resting-state fMRI.<sup>24</sup> The long-distance functional connectivity was decreased, and the network topology also showed changes in patients with supratentorial gliomas.<sup>25</sup> Our group analysis showed a decrease in the connectivity of the posterior cingulate gyrus and the parietal components of the DMN with the medial frontal components. A similar decrease in the connectivity of the components of the dorsal attention network and the salience networks has been observed. A wide variation in the spatial characteristics of each network has been observed between subjects, even subjects with similar tumor locations. This could be explained by the decrease in long-range connectivity, as previously reported by Park et al.<sup>25</sup> However, these changes in the connectivity could be associated with subtle changes in the high cortical functions. Further studies are required to clarify this association, and also the impact on surgical planning and outcome. Furthermore, neuropsychometric analysis should be introduced to evaluate the clinical impact of the changes in the high-level networks. An

analytic approach also should be applied to include a control group of healthy volunteer for better quantification of these changes in both neuropsychometric scores and resting networks.

Despite the great potential of rs-fMRI, the application of the technique is limited due to the complexity of the analysis, and the long duration of preprocessing and interpretation. In previous studies conducted on neurosurgical patients, 2 main methods for data analysis have been used: ICA<sup>9,26,27</sup> and SCA.<sup>6,14</sup> In this study, we present a reproducible pipeline to evaluate the rs-fMRI data for preoperative neurosurgical planning, taking into consideration the clinical questions and the time cost. The analysis of a single patient and presentation of the RSN on a personal Microsoft Windows-based computer required about 10 minutes. Acquisition of the rs-fMRI sequences required approximately 5 minutes.

#### Other Aspects of Brain Mapping

Task-based fMRI and rs-fMRI can provide useful information regarding the functional organization of the human cortex, and can be used for presurgical planning. Other methods of cortical mapping are the preoperative electromagnetic stimulation<sup>28</sup> and the intraoperative electrical cortical stimulation.<sup>29</sup> Fiber tracking plays an important role in the analysis of structural connectivity.<sup>30</sup> Incorporation of this information in an extended preoperative and intraoperative brain mapping can help to improve the understanding of individual 3-dimensional



**Figure 10.** Examples from 8 patients showing the different patterns of spatial configuration of the salience network and connectivity between the

anterior part of the cingulate gyrus (seed) and the insular cortex.

functional anatomy. This could potentially help to preserve neural function and improve outcome.

#### Precautions and Limitations of the Technique

Although the presented technique is robust, the match between the ROI mask, whether atlas-based or as subject-specific ROI, and the functional and structural images using CcheckReg (SPM) function is mandatory. The mismatch between the images due to failed registration can lead to false results.

We highly recommend placing the ROI on the healthy hemisphere when defining bilaterally presented networks, such as motor, sensory, visual, salience networks. This is due to the possible mass effect of the tumor, which can cause a structural shift and mismatch between the atlas and the local cortical topography. Furthermore, the tumor has a metabolic effect that can affect the BOLD signals if the ROI is placed on the tumor side.

Generally, fMRI and subsequently rs-fMRI suffer from potential limitations due to the phenomenon of neurovascular uncoupling. If a brain region is infiltrated by the tumor or is affected by edema but still functioning, the time course of its BOLD signals will change. This could lead to losing the expected correlation to the

other regions of the brain, which constitute a network with the affected region. The neurovascular uncoupling will thus result in false-negative results, where the functional region of the brain will be demonstrated as nonfunctional (case example 4). The observer should be aware of this phenomenon.

This study was planned to assess the feasibility of preoperative planning a part of multimodal extended brain mapping accompanied with task-based fMRI, fiber tracking, and cortical and subcortical stimulation. Further studies are needed to validate the technique and its clinical relevance.

#### CONCLUSIONS

rs-fMRI is a feasible method for identification of different RSNs in patients with brain tumors. The results of rs-fMRI analysis in this patient group can provide valuable information for extended brain mapping. SCA may provide specific clinically relevant information in a fast and reliable way to enhance neurosurgical brain mapping. However, further studies are still required to validate the technique.

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