Utility of resting fMRI and connectivity in patients with brain tumor

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Abstract

Background: Resting state (task independent) Functional Magnetic Resonance Imaging (fMRI) has opened a new avenue in cognitive studies and has found practical clinical applications. **Materials and Methods:** Resting fMRI analysis was performed in six patients with brain tumor in the motor cortex. For comparison, task-related mapping of the motor cortex was done. Connectivity analysis to study the connections and strength of the connections between the primary motor cortex, premotor cortex, and primary somatosensory cortex on the affected side was also performed and compared with the contralateral normal side and the controls. **Results:** Resting fMRI in patients with brain tumor in the motor cortex mapped the motor cortex in a task-free state and the results were comparable to the motor task paradigm. Decreased connectivity on the tumor-affected side was observed, as compared to the unaffected side. **Conclusion:** Resting fMRI and connectivity analysis are useful in the presurgical evaluation of patients with brain tumors and may help in uncooperative or pediatric patients. They can also prognosticate the postoperative outcome. This method also has significant applications due to the ease of image acquisition.

Key words: *Blood oxygenation level dependent, functional magnetic resonance imaging, resting state*

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Introduction

Brain tumors located near or invading the eloquent areas represent a challenge in neurosurgery, as the resection of lesions may induce a permanent neurological deficit. Precise localization may help in reducing postoperative neurological deficits. For achieving this, a detailed knowledge of the functional topography in and around the tumor is crucial.[1] Functional neuroimaging has been found to be useful in localizing certain functions in the brain. Functional magnetic resonance imaging (fMRI) is a noninvasive technique to assess the changes in the blood-oxygenation-level-dependent (BOLD) signal to map the neuronal activity of the brain. In the last two decades this technique has helped us understand the brain activity. Perhaps the area with greatest promise is preoperative functional brain mapping for guiding neuronavigation. This is used most often to identify the eloquent brain areas, so that these areas can be preserved during surgical resections. A distance of 2 cm from a fMRI-identified functional region to the surgical margin has been considered safe for resection and correlates well with the postoperative loss of function.[2,3] However, in approximately 75% of the patients referred for preoperative planning, the utility of fMRI for predicting the postoperative functional outcome was uncertain.[1,4] The use of fMRI for studying cognitive functions is not yet optimized.[5-7] A major limitation of fMRI is that the patient's ability to perform the given task is crucial, which is often impaired, rendering localization as well as comparison with the normal controls difficult or near impossible. This may related to the associated neurological deficits or pediatric age group.[1,8,9]

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Resting fMRI, in which BOLD fluctuations are used to identify functionally related regions, can overcome many of the limitations associated with task-dependent fMRI. Instead of examining changes in blood oxygenation associated with a task, one can simply examine the spontaneous modulations in the BOLD signal, while subjects are resting in the scanner. Activation of the brain in the resting state addresses not only noise or cognitive information, but also provides information of various eloquent brain networks and their connectivity, which may help to explain the clinical picture.[10,11] Studies looking for the utility of connectivity analysis and resting fMRI in epilepsy, found variable and decreased connectivity in multiple networks, including in the medial temporal lobe and within the default mode network (DMN). These findings indicate that a study of alterations in the brain resting state connectivity may be of clinical use.[12-14]

The aim of this study was to establish the utility of the resting state fMRI as a clinical tool for mapping eloquent motor cortex in patients with brain tumors. We hypothesized that the eloquent brain area can be mapped by resting state fMRI, and diminished functional connectivity in a distributed network of motor centers would correlate with motor weakness in subjects with brain masses. Furthermore, we hypothesized that motor network connections would be most vulnerable to subtle disruptions in functional connectivity in a tumor located at the motor cortex.

Materials and Methods

Study subjects: Six adult, right-handed patients (three in each sex; mean age of 25 ± 8 years) with brain tumors located near or extending to the motor cortex were included in the study. The patients were referred for fMRI, for presurgical planning. All the patients were cooperative and were able to perform the motor task based on the visual cues provided. The tumor location was left frontal in two patients, left frontotemporal in two patients, and right frontoparietal in two patients.

Control subjects: The control group included six age- and gender-matched healthy subjects. None of them had any history to suggest brain insult. All participants gave a written informed consent to participate in the study and the study was approved by the Institute Ethics Committee.

Paradigm for resting state: The fMRI was performed during eyes-closed, relaxed, and awake conditions. The subjects were instructed as follows: "Please close your eyes and be relaxed, don't think of any specific object or past situation and refrain from any cognitive, language or motor tasks as much as possible, please be awake". The patients and control subjects were instructed not to fall asleep and inform the examiner if they felt any irritation or developed a headache at the time of recording.

Paradigm for task: Depending on the tumor location, the motor task paradigm was decided, contralateral to the tumor location.

Functional magnetic resonance imaging data acquisition for resting state: Functional MR-images were acquired using a 3T scanner (Skyra, Siemens, Erlangen, Germany). The subject's head was positioned within a 32 channel radio-frequency coil, with foam padding, to provide comfort and to minimize head movements. The preliminary anatomic images included a sagittal localizer. Initially, T1-weighted, three-dimensional, high-resolution imaging was performed to facilitate localization of fMRI activation. All axial sections were oriented parallel to the anterior commissure–posterior commissure (ac–pc) line. After obtaining the anatomical MR images, echo-planar images (EPI) using BOLD contrast were obtained; 185 slices were obtained applying the following EPI parameters: Thirty-four slices, 6 mm slice thickness, without any inter-slice gap, FOV 192 × 192 mm, matrix 64 × 64, repetition time (TR) 3000 ms, echo time (TE) 35 ms, refocusing pulse 90°, matrix 256 × 256 × 114, and voxel size 1 × 1 × 1 mm.

Functional magnetic resonance imaging data acquisition for motor task: For motor task, echo-planar images (EPI) using BOLD contrast were obtained; 95 volumes were obtained applying the following EPI parameters: Thirty-four slices, 6 mm slice thickness, without any inter-slice gap, FOV 192 × 192 mm, matrix 64 × 64, repetition time 3000 ms, echo time 35 ms, refocusing pulse 90°, matrix 256 × 256 × 114, and voxel size 1 × 1 × 1 mm. The acquisitions were grouped in blocks of 10 dynamics each. The hand motor task was performed on the opposite side of tumor location, so as to map the activation in the region of interest.

Data analysis

The fMRI data was analyzed using the following steps, to obtain activation in the motor cortex of brain: (1) fMRI data analysis for resting state; (2) fMRI data analysis for motor task; (3) comparison and correlation of resting state and motor task data; and (4) connectivity analysis.

Functional magnetic resonance imaging analysis for resting state: *f*MRI analysis was carried out using different modules of the FSL-software package (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-processing procedure was performed: The first five functional image frames of each time series were discarded to allow for signal equilibration, giving a total of 180 frames used in the analysis. We conducted motion correction using MCFLIRT,[15] non-brain removal using BET,[16] spatial smoothing using the Gaussian kernel of FWHM 6 mm, and mean-based intensity normalization for all the volumes by the same factor. These temporal filtering parameters were selected based on prior work, demonstrating that spontaneous fluctuations, upon which functional connectivity analyzes were based, existed in the range of 0.01 – 0.1 Hz.[9,10] Following this, independent component analysis (ICA) was carried out using MELODIC.

Visual inspection of the different independent components for artifact identification*:* Since it is a resting BOLD fluctuation and not task-related activations, the artifacts represent a challenging confounding factor, which often account for a large part of data variance, which may lead to problematic data interpretation. An approach to deal with such confounds is to model them (i.e., motion-related noise) within the General Linear Model.[17] Independent components are selected visually, by searching for anatomically relevant areas that may potentially depict functionally relevant resting state networks. Components that are excluded from further analysis show clearly interpretable, distinct artifact patterns such as motion-related artifacts, due to high spatial and temporal frequency noise, or artifacts related to susceptibility artifacts by large vessels. We have referred to the study of Beckmann and Smith *et al*.[18-21] for identifying these 'non motion-related' noise sources. After identifying the artifact components, they are filtered out using the MELODIC tool 'reg_filt' (FMRIB's Software Library).

Evaluating the components for different brain networks: Different components of the resting brain were obtained and the sensorimotor component of the resting state was identified after automatic template matching, based on the study by Smith *et al*.[18,19,21] The relation of the motor-induced fMRI changes with respect to the tumor and its margins was noted in all patients individually. The resultant images were demonstrated in the patients' structural images (MPRAGE) using the SPM display module for comparison with the task fMRI result.

Functional magnetic resonance imaging analysis for motor task: The motor task fMRI analysis was performed using statistical parametric mapping (SPM8; Welcome Department of Cognitive Neurology, London). The first five functional image frames of each time series were discarded to allow for signal equilibration, giving a total of 90 frames used in the analysis. After that the data were realigned for motion correction by registration to the mean image. The images were then normalized to the Montreal Neurological Institute (MNI) space. Finally images were smoothed with a Gaussian kernel of 6 mm. Statistical Parametric Mapping (SPM) combined the general linear model (GLM)[22] and Gaussian field theory, to draw statistical inferences from the BOLD response data regarding deviations from null hypotheses in the three-dimensional brain space. The realigned, normalized, and smoothed data were modeled using a boxcar function convolved with a canonical hemodynamic response function.[23,24] Reference functions were performed separately for the left hand motor task and right hand motor task. The relation of activity with respect to tumor margins were demonstrated in the patient structural images (MPRAGE) using the SPM display module for comparison with the resting fMRI result.

Functional connectivity maps: For this study, we focused on the nodes involved in motor task such as the primary motor, premotor, motor, and the sensory cortex, bilaterally. A region of interest (ROI)-based connectivity analysis was implemented with the primary motor cortex area as the seed point. Correlation values corresponding to the strength of the connections of the primary motor cortex with premotor and sensory cortex were noted, bilaterally. The CONN toolbox (http://www.alfnie.com/software/conn) performed seed-based analysis by computing the temporal correlation between the BOLD signals from a given voxel to all other voxels in the brain. The CONN software used graph theoretical network analysis and topology of the cerebral network for analysis. The white matter, cerebrospinal fluid (CSF), and physiological noise source reduction were taken as confounds.[16,25] The whole brain BOLD signal was excluded as a regressor, to eliminate erroneous anti-correlations,[25] as also ROI-based analysis, by grouping voxels into ROIs based upon the Brodmann areas. The left and right primary motor cortex (Brodmann area four (BA-4) was considered as the ROI and its connections with premotor (Brodman areas six (BA-6) and primary somatosensory cortex (Brodmann areas three (BA-3) was considered. Two millimeter radius spheres, centered on MNI coordinates, were used to identify the corresponding networks. Bi-variate correlations were calculated between each pair of ROIs, as reflections of connections. All Brodmann areas were imported as possible connections for our selected seed ROIs. The signal change (BOLD response) was averaged.[26] The time course of the signal intensity was filtered with a low pass filter and corrected for motion. Cross-correlation coefficients between all ROIs were calculated and finally Fisher z-transform was performed. Functional connectivity values with motor network (P < 0.05 uncorrected) for the two sides were analyzed.[27]

Results

Results of resting state functional magnetic resonance imaging: Primary motor cortex, premotor cortex, and sensory cortex were identified in the motor components of the resting state in the healthy controls after automatic template matching with the data and components, as described by Smith *et al*.[18,24] This component was used for comparison in the patient group resting state fMRI by using the same methodology. The relation of these motor cortices with respect to the tumor margin was noted in all patients individually. All the hemodynamic substrates of neuronal activity identified in the motor component of the resting state fMRI were well seen in all our cases individually, as shown in Figures 1a and b. An overlay with the structural image was performed to map the location of the motor cortex to the tumor margins. Also the motor substrates in the contra lateral unaffected side were noted, which served as the internal comparison.

Results of motor task functional magnetic resonance imaging: Clinically, the patients had mild weakness with motor power ranging from 4 to 5. However, all the patients could perform the motor task adequately. The primary motor cortex (BA6) was identified in close relation to the tumor margin and activations were located in all patients individually, as noted in Figures 1a and b. The statistics was set at $P < 0.05$, uncorrected.

Comparison of resting state functional magnetic resonance imaging with motor task functional magnetic resonance imaging: The motor network component was demonstrated bilaterally, with activation noted in close proximity to the tumor margin in the resting state fMRI. On comparison with the motor task fMRI, the areas activated were similar and are represented in Figures 1a and b. The advantage of resting fMRI was that contralateral unaffected hemisphere motor substrates were also visualized for internal comparison. The motor task paradigm was designed to map the unilateral activations of the motor cortex. Similarly, in healthy controls, the resting fMRI and motor task fMRI were analyzed. The mapping was similar in both the task-free (resting fMRI) [Figure 2 a] and the motor task states [Figure 2 b and c].

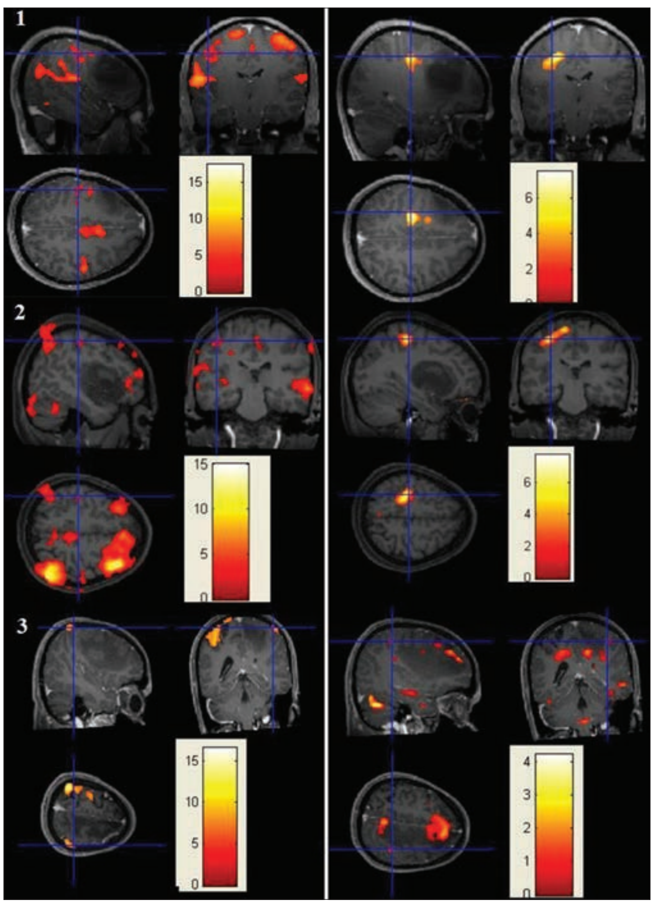

Figure 1a: Brain activation for Resting fMRI (left column) and task fMRI (right column) are demonstrated in patients 1, 2, and 3. The motor component of resting fMRI was obtained after ICA analysis. Task fMRI, as processed by using GLM analysis in SPM. The peak z scores are overlaid on the patients' T1 volume image. The cross-hairs are placed in the primary motor cortex (Brodman area 6) in all the patients for both resting fMRI and task fMRI

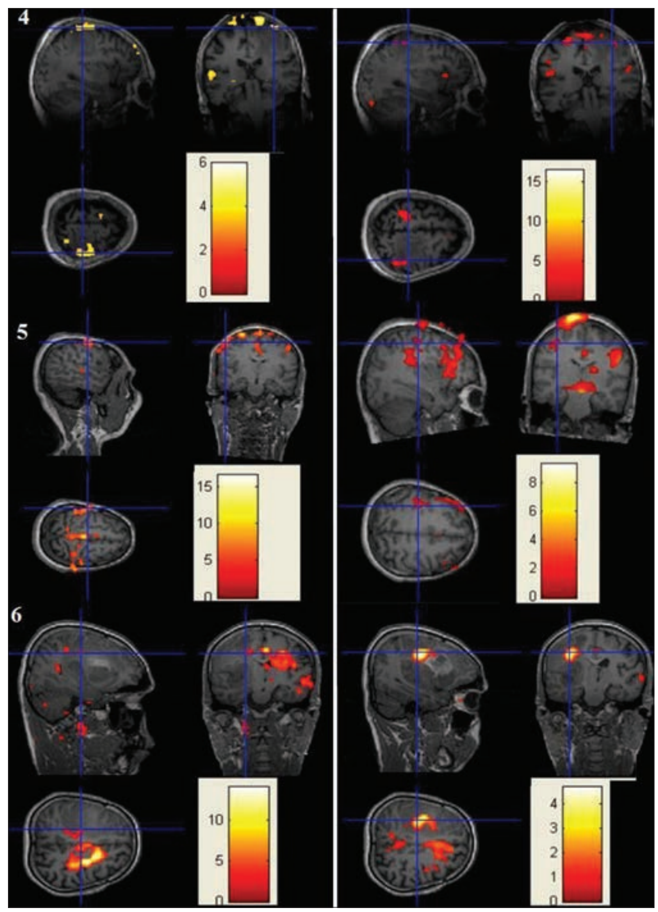

Figure 1b: Brain activation for Resting fMRI (left column) and task fMRI (right column) are demonstrated in patients 4, 5, and 6. Motor component of resting fMRI was obtained. Task fMRI was processed using GLM. The peak z scores are overlaid on the patients T1 volume image. The cross hairs are placed in the (primary motor cortex (Brodman area 6) in all the patients for both resting fMRI and task fMRI

Results of connectivity analysis: Functional connectivity analysis was performed to investigate the neuronal mechanism underlying the motor task dysfunction by motor task fMRI. The primary motor cortex (BA6) was considered as a region of interest and its relation with the ipsilateral and contralateral normal premotor and sensory cortex was analyzed. We included four patients with a tumor located in the left motor cortex for connectivity analysis. The ROI was selected using the predefined MNI coordinates in the left and right primary motor cortex (BA-4). The connectivity values with premotor (BA-6) and primary somatosensory cortex (BA-3) were analyzed [Figures 3 and 4]. In total we had two ROIs and four connectivity networks for analysis in each patient.

On connectivity analysis, the Fisher Z correlation coefficient values were obtained between the primary motor cortex and the premotor cortex, and also between primary motor cortex and the somatosensory cortex. In healthy subjects, the correlation values were 1.2 and 1.4 on the left side, 1.1 and 1.3 on the right side respectively [Figure 5a]. The correlation values in the patient group were 0.8 and 0.9 on left side, (on the affected side of tumor) and 1.2 and 1.3 on right side (unaffected side) [Figure 5b]. These reduced values on the affected side may represent hypo-connectivity, that is, reduced inter-regional functional integration[27] of the affected motor cortex in relation to the premotor and primary somatosensory cortices.

Discussion

Functional MRI is an established noninvasive tool in mapping human brain cortices. Motor task fMRI has been validated as a presurgical tool to map the motor cortex in patients with brain tumor.[5] However, the limitations of fMRI are that it cannot be used if the patient is unable to perform a task, due to disability or lack of cooperation. This technique is limited in evaluating pediatric and geriatric subjects, as also anesthetized patients. Moreover, this technique has not been found useful in predicting the postoperative functional outcome in patients.[3,6,7,17]

Resting state fMRI examines the spontaneous modulations in the BOLD signal when the subjects are in a resting condition in the scanner. There is noise mixed with the signal. Beneath the noise is an elegantly structured, mysterious, but reliable, neuronal phenomenon of unclear etiology and limitless functional relevance. This technique has been extensively used and has found clinical utility in different pathologies, such as, attention-deficit hyperactivity disorders, Alzheimer's, head injury, schizophrenia, and so on.[5,10,11,26,28]

We used resting state fMRI as a tool to map the motor cortex in patients with tumors located adjacent to the motor cortex. The motor components of healthy controls were also analyzed using the same technique (MELODIC). The motor cortex was well-demonstrated in both patient and healthy control groups and was comparable. In all the six patients, we were able to demonstrate the motor cortex using resting fMRI. For better co-localization of the activations to the tumor margins we used the SPM display module, to overlay the structural images. The activations noted around the tumor margins were visually very similar to task fMRI [Figures 1 and 2]. The resting fMRI reflected the entire motor sensory network, and hence, the contralateral motor cortex was also noted. We analyzed the motor task fMRI data using SPM, as the same data was later used for connectivity analysis. The strength of this kind of resting fMRI analysis lay in the ease of obtaining the image even in an uncooperative patient. Demonstration of the bilateral motor cortices simultaneously, which could be used for internal comparison in the same subject, was an added benefit in this technique.

Functional connectivity refers to the correlations between the oscillatory brain activities in different

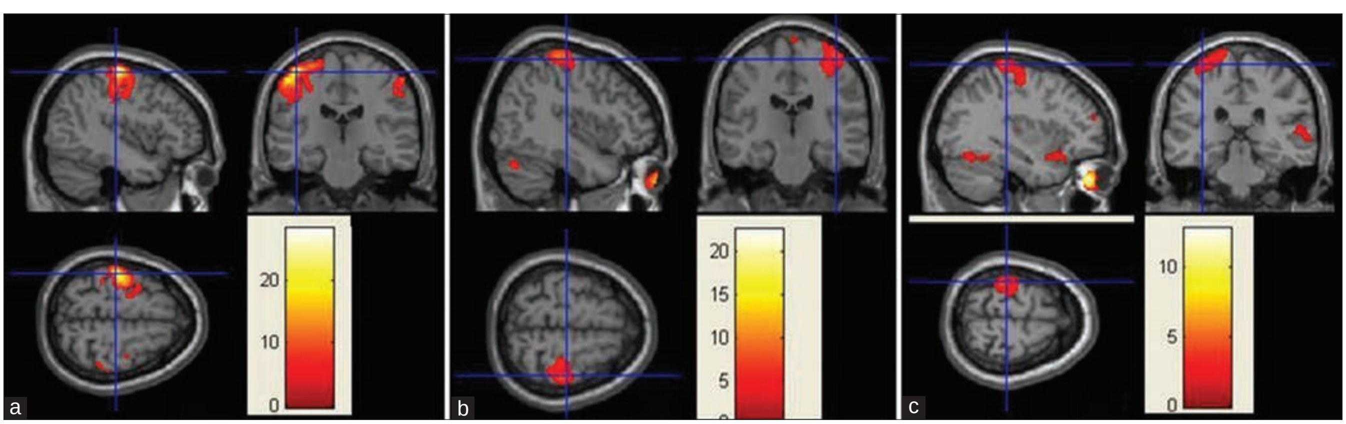

Figure 2: Brain activation for (a) Resting fMRI, (b) left hand task fMRI, (c) right hand task fMRI are demonstrated in healthy controls. The motor component of resting fMRI was obtained after ICA analysis. Task fMRI was processed using GLM analysis in SPM. The peak z scores are overlaid on the patients' T1 volume image. The cross-hairs are placed in the primary motor cortex (Brodman area 6) for both resting fMRI and task fMRI

brain regions. It is a marker of functional interaction between different substrates in a given neural network. In a study, they have evaluated the presurgical motor task fMRI in patients with glioma and compared it with the postoperative outcomes. They have noted that in 75% of the cases, the postoperative functional outcome is unpredictable.[1] Thus, it is not yet clear whether mere localization of the eloquent area using fMRI can predict the postoperative functional outcome. The relation between structural and functional connections needs to be studied to predict this. Depending on the type of brain tumor it can either cause infiltration or compression and can result in varying cortical deafferentation in these functional connections.[29-31] A study has reported that when a tumor infiltrates and damages the brain areas, the functional connectivity between these areas and the rest of the brain decreases and the measurement of functional connectivity reflects the information about the functionality of these networks.[1] Also functional connectivity does not depend on the subject's ability to perform a task correctly, in order to identify functional regions that are involved in that task, and hence, can be used in patients with moderate-to-severe deficits.

We studied connectivity in four patients with a left-sided tumor during a right hand motor task. The tumor, however, had mass effect on the adjacent structures, including the primary motor cortex. It was identified to be displaced laterally in both motor task fMRI and on resting fMRI. The opposite unaffected primary motor cortex was also identified for internal comparison. The patients with brain tumor demonstrated, on connectivity analysis with ROI at the displaced primary motor cortex, that there was interhemispheric recruitment from the opposite cerebral cortex as compared to the normal side, which could explain the neuroplasticity of these networks [Figure 3]. We could demonstrate by using connectivity coefficient values that a hypoconnectivity existed in the functionally connected motor network on the affected side, as compared to the normal side. Studies on healthy controls noted that the connections were the same irrespective of right or left hand motor tasks and the coefficient values were lateralizing to the left dominant hemisphere.[32] In our study both patients were right handed and on connectivity analysis of the cases with a left-sided tumor, the connectivity coefficients were higher on the right (1.2) in comparison with the healthy control data (1.1) [Figure 4]. This could explain the increased efficiency of the contralateral motor component.

In our study we considered six tumor cases and analyzed them individually. This is hence a proof of concept that other than being just a research tool, it can be used in everyday patient care. This is a preliminary study

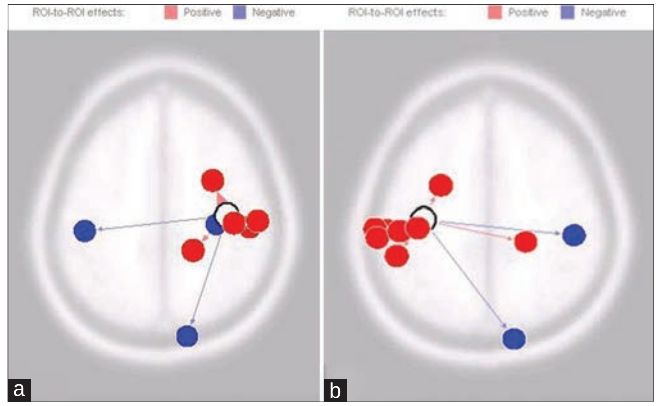

Figure 3: Functional connectivity values of the motor network (*P* < 0.05 with uncorrected). Bilateral primary motor cortices were defined as ROI (a) on the right side (b) on the left side in healthy subjects

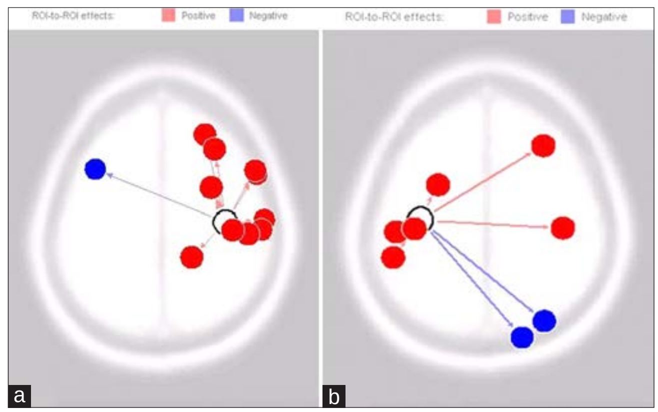

Figure 4: Functional connectivity values of the motor network (*P* < 0.05 with uncorrected). Bilateral primary motor cortices were defined as ROI (a) on the right side (b) on the left side in patients with left-sided tumor, and its connections with the rest of brain are demonstrated. Patients had lower connectivity values in the premotor and primary somatosensory cortices on the affected side (left primary motor cortex) as compared to opposite right primary motor cortex

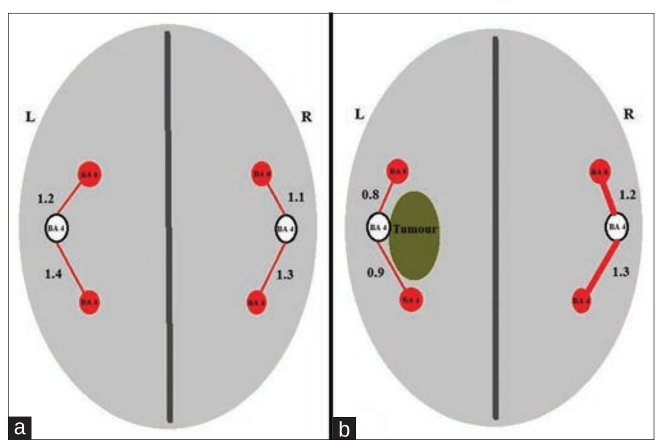

Figure 5: A representative image of the Fisher Z correlation coefficients obtained in the primary motor cortex (a) on healthy subjects (b) on patients: A representative image of the Fisher Z correlation coefficients obtained in the primary motor cortex located on the affected side by tumor with the premotor cortex and somatosensory cortex. Correlation values on the opposite normal side are also shown. The thick line represents the normal connection and the thin line represents hypo connectivity along with the correlation coefficients obtained after connectivity analysis

highlighting the role of resting fMRI and connectivity analysis in patients with brain tumor. Future studies for assessing the relation between the grade of tumor and how it affects the functional networks are required. Also the relationship between the degrees of hypoconnectivity on the affected side with the clinical disability must be further evaluated with presurgical and postsurgical evaluation, as also the extent of surgical resection, so that these values can be used for prognostication of the postoperative functional outcome.

Our observations demonstrate that by using the resting state network analysis we are able to demonstrate the motor cortex as efficiently as the task-based fMRI. We have also reported the use of the connectivity analysis to demonstrate disrupted functional connectivity in the side of the tumor. Our study is a proof of concept that resting fMRI and connectivity analysis can be used on individual patients. Also these automated methods have inherent statistical methods inbuilt in them for ease of use, and as we are demonstrating motor substrates bilaterally, they serve as an internal comparison, without the need to compare the activations with healthy controls. Further work will be required to use these analysis methods to predict surgical risk and potential functional outcome after surgery, to plan further interventions.

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