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Original Article

Motor and language deficits correlate with resting state functional magnetic resonance imaging networks in patients with brain tumors

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ABSTRACT

Background and purpose. – Evidence of pre-operative resting state functional magnetic resonance (RS-fMRI) validation by correlating it with clinical pre-operative status in brain tumor patients is scarce. Our aim was to validate the functional relevance of RS-fMRI by investigating the association between RS-fMRI and pre-operative motor and language function performance in patients with brain tumor.
Materials and methods. – Sixty-nine patients with brain tumors were prospectively recruited. Patients with tumors near precentral gyrus (n = 49) underwent assessment for apparent (paresis) and subtle (finger tapping) deficits. Patients with left frontal tumors in the vicinity of the inferior frontal gyrus (n = 29) underwent assessment for gross (aphasia) and mild language (phonological verbal fluency) deficits. RS-fMRI results were extracted by spatial independent component analysis (ICA).
Results. – Motor group: paretic patients showed significantly (P = 0.01) decreased BOLD signal in ipsilesional precentral gyrus when compared to contralesional one. Significantly (P < 0.01) lower BOLD signal was also observed in ipsilesional precentral gyrus of paretics when compared with the non-paretics. In asymptomatic patients, a strong positive correlation (r = 0.68, P < 0.01) between ipsilesional motor cortex BOLD signal and contralesional finger tapping performance was observed. Language group: patients with aphasia showed significantly (P = 0.01) decreased RS-fMRI BOLD signal in left BA 44 when compared with non- aphasics. In asymptomatic patients, a strong positive correlation (r = 0.72, P < 0.01) between BA 44 BOLD signal and phonological fluency performance was observed.
Conclusions. – Our results showed that RS-fMRI BOLD signal of motor and language networks were significantly affected by the tumors implying the usefulness of the method for assessment of the underlying functions in brain tumors patients.

Introduction

Pre-operative localisation of eloquent cortex is essential to optimise neurosurgical tumor resection and minimise post-operative neurological deficits. In clinical setting, one of the most widely used pre-operative functional mapping techniques is the task-based functional magnetic resonance imaging (fMRI). However, task-based fMRI has several limitations which reduce its clinical effectiveness [1,2]. A recent advance that may address several of the limitations of task-based fMRI mapping is the use of spontaneous blood oxygen level dependent (BOLD) fluctuations in a resting subject to identify functionally related regions [3]. Task-free functional magnetic resonance has provided a tool for investigation of several functional regions with the two most famous types of methods to be independent component analysis (ICA) and the seed-based analysis [4]. Compared with existing task-based methods, resting state fMRI (RS-fMRI) can be performed on patients who may not be able to co-operate with task-based paradigms, such as patients with altered mental status, paresis or aphasia. Another advantage of RS-fMRI over task-based fMRI is the ability to identify many networks simultaneously, saving thus scanning time if information from multiple networks is required. Furthermore, task-based fMRI may be highly variable in the task design and administration that makes

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difficult to validate it across institutions, [5] whereas RS-fMRI is theoretically less limited by such issues.

Before the clinical utility of RS-fMRI in neurosurgical setting can be demonstrated, there is need to correlate the RS-fMRI activation on the corresponding anatomical substrates with underlying neurological functions in patients with brain tumors. However, evidence of correlations between pre-operative RS-fMRI networks and specific neurological pre-operative (dys) functions in brain tumors patients is scarce. Since, pre-operative functional imaging provide us with information on "how the brain works" before surgeon intervention we thought that, and according to future research directions of current literature, [6] correlation of pre-operative RS-fMRI networks with pre-operative functional status would add significantly in the validity of this technique. In this context, aim of the present study is to validate the functional relevance of RS-fMRI motor and language networks, extracted by ICA, by correlating them with underlying pre-operative neurological functions' status, depicted by clinical examination and neuropsychological testing, in brain tumor patients undergoing brain surgery.

Methods

Patients

During a 2-year period, 69 right-handed patients with intracranial masses (mean age = 50 y, SD = 15.5 y, range = 18–78 y, 37 female and 32 male patients), undergoing tumor excision, were prospectively recruited and examined with RS-fMRI. Exclusion criteria were:

- recurrent tumors;
- other neurological disorders;
- psychotropic medication.

According to tumor localization, patients were located into 2 groups (few patients whose lesions affected both motor and language areas, were located in both groups) resulting in 78 subjects analyzed: patients with tumors near motor cortex (motor group, $n = 49$, mean age ± SD 50.2 ± 16.7 y, male/female ratio 25/24) underwent motor clinical assessment and correlation with the motor network components from the RS-fMRI datasets; patients with tumors near left inferior frontal gyrus-IFG (language group, $n = 29$, mean age ± SD 45.8 ± 14.7 y, male/female ratio 12/17) underwent clinical assessment of language and language network RS-fMRI mapping. Paradigms of tumors' localization for motor and language groups can be seen in Figs. 1 and 2, respectively. Regarding lesion size, mean of tumor maximum diameter was 4.3 ± 1.4 cm (range = 1.5–7.4 cm). According to histopathology, 33 patients had glioblastomas, 16 meningiomas, 11 astrocytomas, 5 oligodedrogliomas, 2 hemangiomas, 1 ependymoma and 1 neurocytoma. The study was conducted according to the guidelines of the Declaration of Helsinki, and permission was given by the local Ethics Committee. Informed consent was obtained from all patients prior to commencing the study.

Clinical assessment

Gross motor function was assessed by clinical examination for unilateral paresis. Fine motor function was assessed by the finger tapping [7] according to which patients place their hand palm down, with their index finger resting on a lever attached to a counting device and they tap it as quickly as possible for ten seconds (5 trials).

Gross expressive language function was clinically assessed by the Boston Cookie theft picture description task [8]. Fine language function was assessed by the Controlled Oral Word Association Test (COWAT) [9] according to which subjects produce within one minute as many as possible words beginning with a certain letter – phonemic subtest (3 trials).

RS-fMRI acquisition

For RS-fMRI acquisition, patients were instructed to close their eyes and refrain from any structured thinking. Functional MRI time series were acquired on a 1.5T scanner (Siemens Symphony-Vision, Siemens Medical Solutions, Erlangen, Germany) operated with a standard transmit-receive quadrate head coil. To optimize the acquisition, regarding as such, the best image quality in the shortest possible time, we performed RS-fMRI in 34 age-matched healthy volunteers using different scanning parameters [repetition time (TR) 3000 ms or 2000 ms; echo time (TE) = 40 ms or 50 ms; 223, 250 or 300 dynamics with a gradient-echo (GRE) echo-planar imaging (EPI) sequence using axial slice orientation and covering the brain from vertex to the roof of 4th ventricle. We ended up with the following protocol: 223 multi-slice T2*-weighted images were acquired with a gradient-echo (GRE) echo-planar imaging (EPI) sequence using axial slice orientation and covering the brain from vertex to the roof of 4th ventricle (21 slices; voxel size $4 \times 4 \times 4$ mm^3; matrix size $64 \times 64 \times 64$; TR 2000 ms; TE 50 ms; flip angle (FA) 90°, field of view (FOV) 256×256 mm^2. The 3 initial volumes were discarded to avoid T1 saturation effects. For anatomical reference, a high-resolution isotropic (voxel size: $1.3 \times 1.3 \times 1.3$ mm^3) transverse T1-weighted sequence

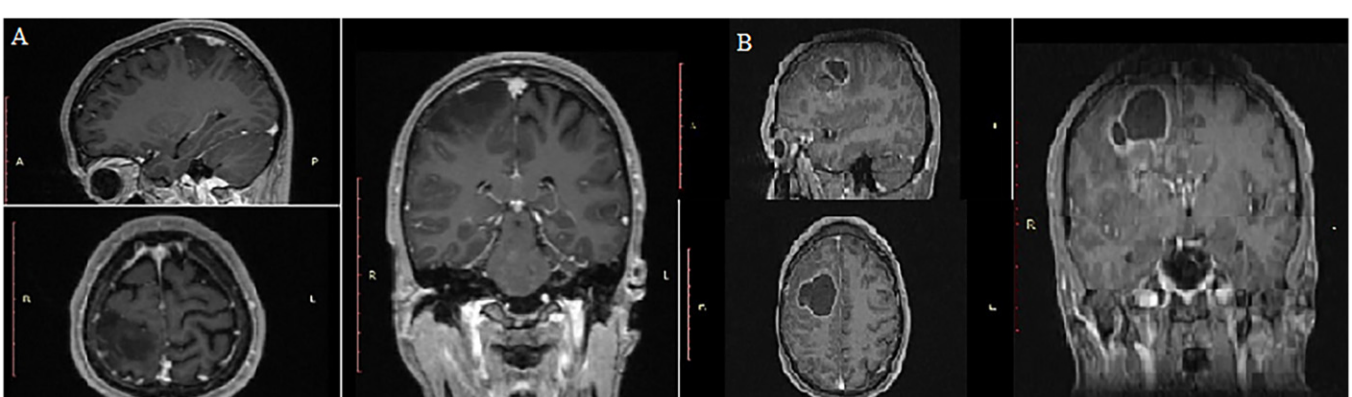

Fig. 1. Paradigms of tumors' locations for the motor group. Sagittal, axial and coronal view of (A) T1-weighted post-gadolinium MRI of a subject with a secondary Glioblastoma occupying left superior parietal lobule including postcentral gyrus-primary sensory cortex and (B) T1-weighted post-gadolinium MRI of a subject with glioblastoma de novo occupying right superior and middle frontal gyri.

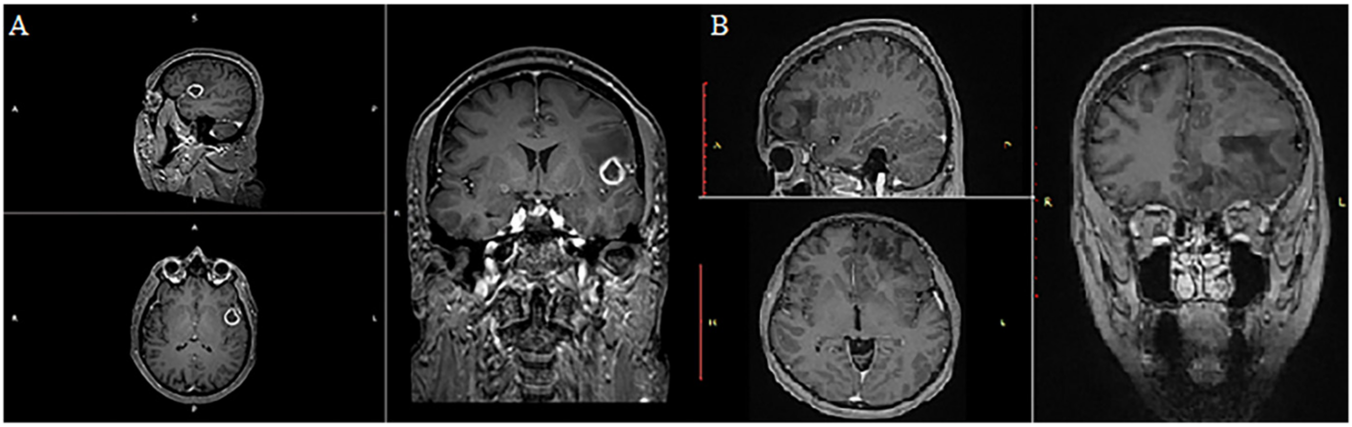

Fig. 2. Paradigms of tumors' locations for the language group. Sagittal, axial and coronal view of (A) T1-weighted post-gadolinium MRI of a subject with glioblastoma de novo occupying posterior third of the left inferior frontal sulcus; (B) T1-weighted post-gadolinium MRI of a subject with oligodendroglioma grade II occupying orbital gyrus, rectus gyrus, part of the inferior frontal gyrus (pars orbitalis, pars triangualaris) and part of the middle frontal gyrus in the left cerebral hemisphere.

was acquired for each subject [T1-weighted 3D magnetization-prepared rapid gradient-echo sequence (MPRAGE)].

RS-fMRI analysis

Pre-processing

RS-fMRI data analysis was conducted by using a software package (SPM8, Statistical Parametric Mapping, (http://www.fil.ion.ucl.ac.uk) running in Matlab (The MathWorks Inc., Natick, MA, USA). Original images were corrected by manual re-orientation due to shifting in yaw direction before entering the pre-processing stage. Pre-processing consisted of the following steps: realignment, co-registration of functional and anatomical images, segmentation, and normalization to the T1 standard template in Montreal Neurological Institute space. Finally, functional data were smoothed using a Gaussian kernel of 10 mm full width at half maximum (FWHM). For a detailed and comprehensive view of data pre-processing please see papers [10,11] published previously by co-authors of the present work.

Post-processing

Post-processing was conducted by spatial ICA using the GIFT software (http://icatb.sourceforge.net, version1.3b). Smoothed data were decomposed into 75 spatial correlated independent components (IC) in each subject [12]. For each of the 75 ICs characteristic time course and spatial maps were generated. The voxel information in the spatial maps was converted into *z*-Scores, describing the similarity of the time course within the voxel with the characteristic time course of each component. In order to determine ICs corresponding frontal-language and sensorimotor networks a spatial template matching technique provided by the GIFT toolbox was applied. According to this technique one or more components are identified by comparing the spatial maps with selected templates. Those components that showed a high spatial regression coefficient to the respective network templates, as in the publication by Allen et al. [12], were selected. Frequency distributions of these time courses were evaluated and the ratio between the accumulated frequency power components for low (0–0.1 Hz) and high (0.15–0.25 Hz) frequencies was calculated. Components with a ratio of lower than 1.8 were considered as noise components and excluded from the analysis. From the remaining components, the ones that showed a spatial correlation to the sensorimotor IC No. 7 and to the frontal IC No. 20 networks [12] were selected. The voxel with the highest *t*-value was then determined and *z*-Scores were used to depict intensity of the signal. Main anatomic localizations of the ICA peak BOLD signal are [12]: the left or right precentral gyrus (including the hand area) for IC7 and the left (dominant) or right IFG for IC20 (BA44, 45). For a detailed and comprehensive view of ICA post-processing please see papers [10,11] published previously by co-authors of the present work. Before we proceed to the main analysis, we conducted an inter-rater reproducibility study for a subgroup.

Statistical analysis

Data were analysed using statistical software package (IBM SPSS statistics 21 for Windows, SPSS Inc.) and satisfied the normality assumptions, according to Shapiro–Wilk test. For motor data, Pearson's correlations between maximum *z*-Scores of motor IC7 network and scores on finger tapping task were performed in patients with non-zero finger tapping score; in patients with paresis (zero finger tapping score), two-sample independent *t*-test was conducted between ipsilesional and contralesional IC7 *z*-Scores. Independent *t*-test was also conducted between paretic's and non-paretic's ipsilesional IC7 *z*-Scores. Regarding language data, Pearson's correlations between *z*-Scores of language IC20 network and scores on phonemic verbal fluency test were performed in patients with no aphasia. Two-sample independent *t*-test was conducted between ipsilesional IC20 network *z*-scores of patients with aphasia and patients with no aphasia. Cut-off *P*-value was set at < 0.05. Finally, Cohen's Kappa statistics were used to explore inter-rater reliability for *z*-values of RS-fMRI networks.

Results

Clinical data

Motor

In the motor group, 8 patients presented contralateral paresis and 41 patients were non-paretic. Ipsilesional finger tapping performance ($m = 46.3 \pm 11.2$) of non-paretic patients was significantly higher ($P < 0.01$) when compared to contralesional one ($m = 38.0 \pm 14.7$).

Language

In the language group 7 patients presented expressive aphasia with the remaining 22 patients showing no paraphasia. The mean score of phonemic verbal fluency *z*- in non-aphasic patients was -0.42 ± 1.3.

RS-fMRI data

To exclude any demographic confounding factors on the RS-fMRI activity, we examined the effect of gender and age on RS-fMRI

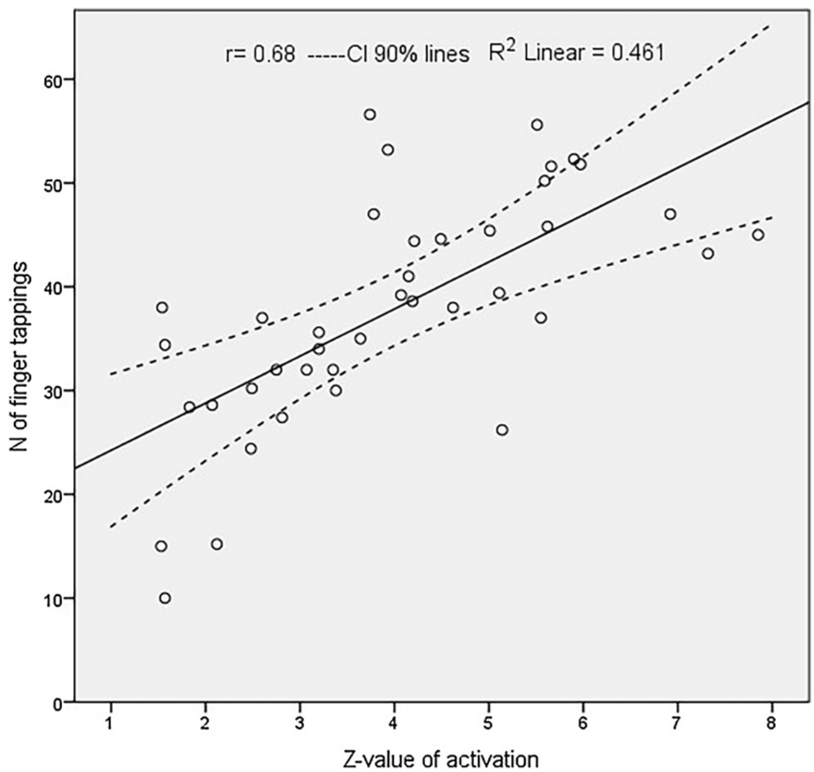

Fig. 3. Ipsilesional precentral gyrus' activation as a function of contralesional finger tapping performance in patients with lesions near motor cortex.

networks. Gender did not affect z-value networks' BOLD signal. There was not statistical significance ($P = 0.31$) in *z*-value BOLD signal between males (4.0 ± 1.6) and females (3.5 ± 2.1) for IC7 motor network neither between males (4.0 ± 1.4) and females (4.9 ± 1.9) for IC20 language network ($P = .19$). Age did not either affect *z*-value BOLD signal of networks; we did not observe any correlation neither for IC7 motor network ($r = -0.17$, $P = 0.23$) nor for IC20 language network ($r = -0.257$, $P = 0.17$).

Additionally, we examined any effects of the tumor histology on RS-fMRI networks. According to our results, there was not statistically significant difference in *z*-value BOLD signal when intra-axial versus extra-axial tumors were compared in both motor ($P > 0.05$) and language ($P > 0.05$) groups.

Regarding the inter-rater reliability analysis, depiction of *z*-scores for 10 random patients (5 sensorimotor/5 language network) was conducted by two blinded raters, providing a very high (0.98) inter-rater reliability.

RS-fMRI correlation with clinical examination results

Motor

Ipsilateral IC7 *z*-Scores showed a strong positive correlation ($r = 0.68$, $P < 0.01$) with the mean of contralateral finger tapping in non-paretic patients (Fig. 3). In addition, ipsilateral IC7 *z*-Score mean [4.1 ± 1.8 (95% CI = 3.5–4.7)] in the non-paretic group was significantly lower ($P < 0.01$) than the contralateral IC7 value [7.6 ± 2.7 (95% CI = 6.7–8.5)]. The mean of the ipsilesional IC7 *z*-Scores [4.1 ± 1.8 (95% CI = 3.5–4.7)] was significantly higher ($P < 0.01$) for the non-paretic group compared with the mean of ipsilesional IC7 *z*-Scores in the paretic group [2.0 ± 0.4 (95% CI = 1.6–2.3)]. Paradigms of motor networks can be seen in Fig. 4.

Language

A strong positive correlation ($r = 0.72$, $P < 0.01$) was observed between the IC20 *z*-Scores of the left IFG (BA44) BOLD signal intensity and the average scores of phonemic verbal fluency in the non-aphasic group (Fig. 5). Furthermore, RS-fMRI analysis showed that IC20 *z*-Scores of the left IFG (2.3 ± 1.2) were significantly lower ($P = 0.01$) in the aphasic group than the respective scores (4.5 ± 1.6) of the non-aphasic group. Left lateralization of IC20 template's peak BOLD signal [12], did not allow us to explore inter- hemispheric differences on IFG BOLD signal. Paradigms of language networks can be seen in Fig. 6.

Discussion

RS-fMRI has been studied in the context of pre-surgical mapping in brain tumors patients mainly by comparing its spatial anatomical extent with task-based fMRI [13–20]. However, resting-state networks' validation by means of correlation with the pre-operative underlying function in brain tumor patients is currently lacking. In the absence of a non-invasive pre-surgical golden standard method that fMRI can compared to, neuropsychological evaluation can provide valuable information on the functionality of a brain area. Therefore, in our study, we investigated the validity of the presumed functions depicted by RS-fMRI by correlating motor and language networks' BOLD signal with pre-operative performance of brain tumor patients in the respective neuro psycho-logical functions.

Resting-state motor networks and functions

Our study shows that motor network ipsilesional BOLD signals are strongly correlated with contralesional motor deficits. This underpins the applicability of RS-fMRI as diagnostic tool for even when those deficits are subtle to detect with gross neurological testing. Particularly, paretic patients showed reduced BOLD signal of ipsilesional precentral gyrus as compared to their contralesional one. Reduced ipsilesional BOLD signal in the precentral gyrus was also observed in these patients compared to ones with

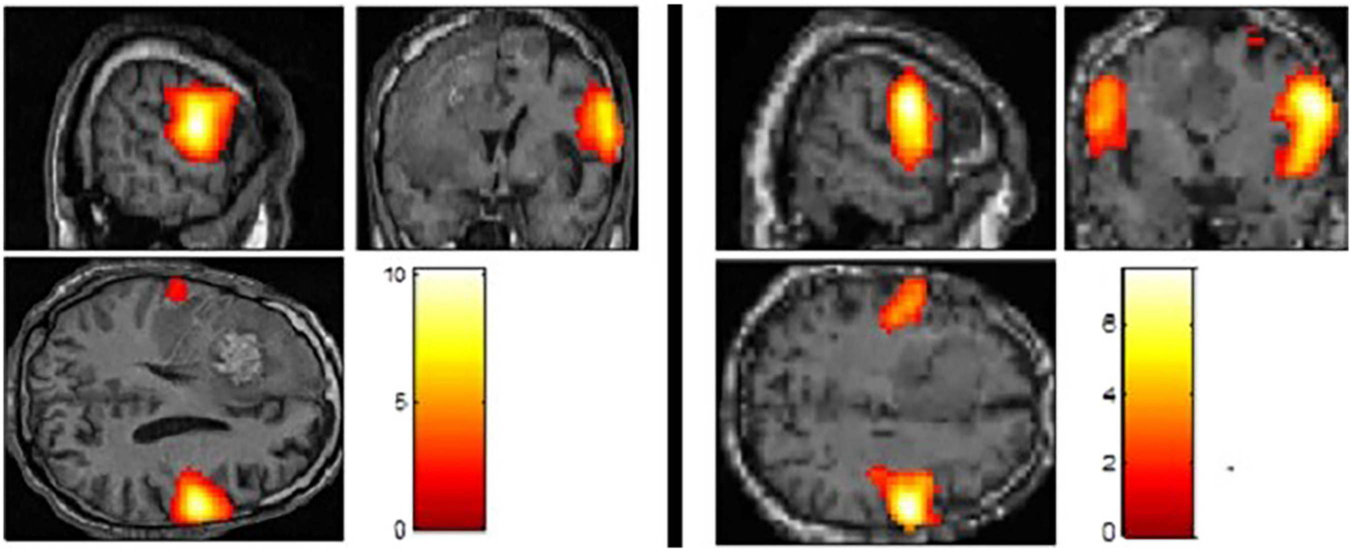

Fig. 4. RS-fMRI motor networks. Left part: sagittal, coronal and axial views of motor network in a patient with a left frontal high-grade glioma presented with right paresis. The ipsilesional network activation is significantly lower (z-value = 1.66) than the contralesional one (z-value = 10.2). Right part: sagittal, coronal and axial views of motor network in a patient with a left frontal meningioma presented with no paresis but low performance on finger tapping task. The ipsilesional network activation is lower (z-value = 2.6) than the contralesional one (z-value = 4.4). Functional images are superimposed onto anatomical images for both patients. Images are not radiological (left side is left hemisphere/right side is right hemisphere).

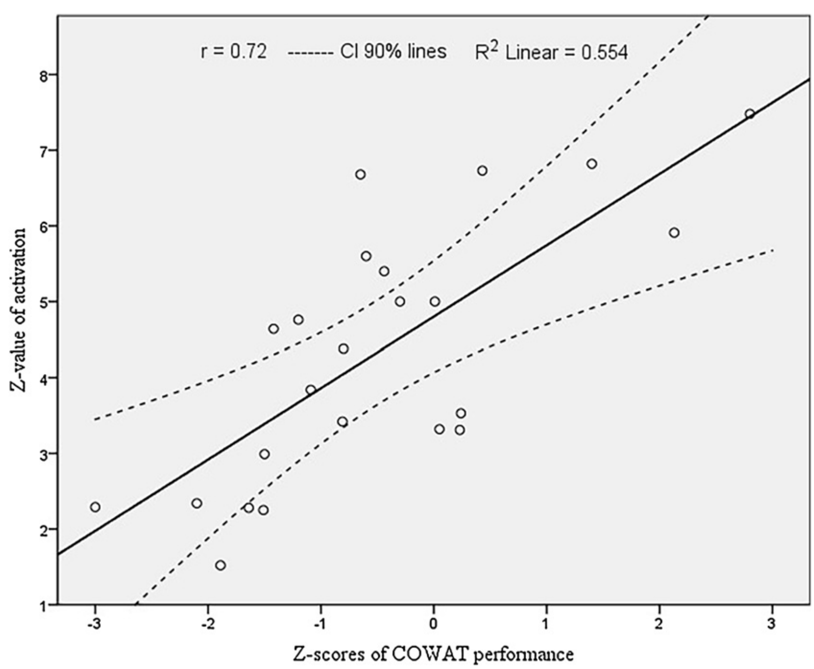

Fig. 5. Left inferior gyrus' activation (BA 44) as a function of verbal phonemic fluency in patients with lesions near Broca's area without aphasia. z-Scores of COWAT test are standardized data. Minus values represent standard deviations below the average normal performance (0-value); positive values represent standard deviations above average normal performance. BA: Brodmann area; COWAT: controlled oral word Association Test.

no motor weakness. Regarding the non-paretic patients, their precentral gyrus' BOLD signals were correlated well with patients' performance on fine motor behavior as assessed by finger tapping task. This finding gives further support on previous literature evidencing that brain functionality is affected by intra-axial [21] and extra-axial [22] lesions even when there is no overt deficit by gross neurological examination; it also provides further support for recent research suggesting that altered functional connectivity between motor cortical and subcortical areas is related with deficits in self-initiated finger tapping and bradykinesia in Parkinson's disease [23].

To our knowledge, this is the first study that validates ICA-generated pre-operative RS-fMRI cortical motor network by correlating it with gross and fine pre-operative motor deficits in a large sample of patients with brain tumors. Previous literature has focused on RS-fMRI validation as a pre-surgical mapping tool by comparing it with traditional task-based fMRI showing promising results [13–16]. Recent research [17] demonstrated good spatial correspondence between the two fMRI techniques for distinct primary motor areas (hand, foot and face representations). In the first four of them [13–16], motor dysfunction was also compared to RS-fMRI BOLD signal intensity demonstrating good agreement in a

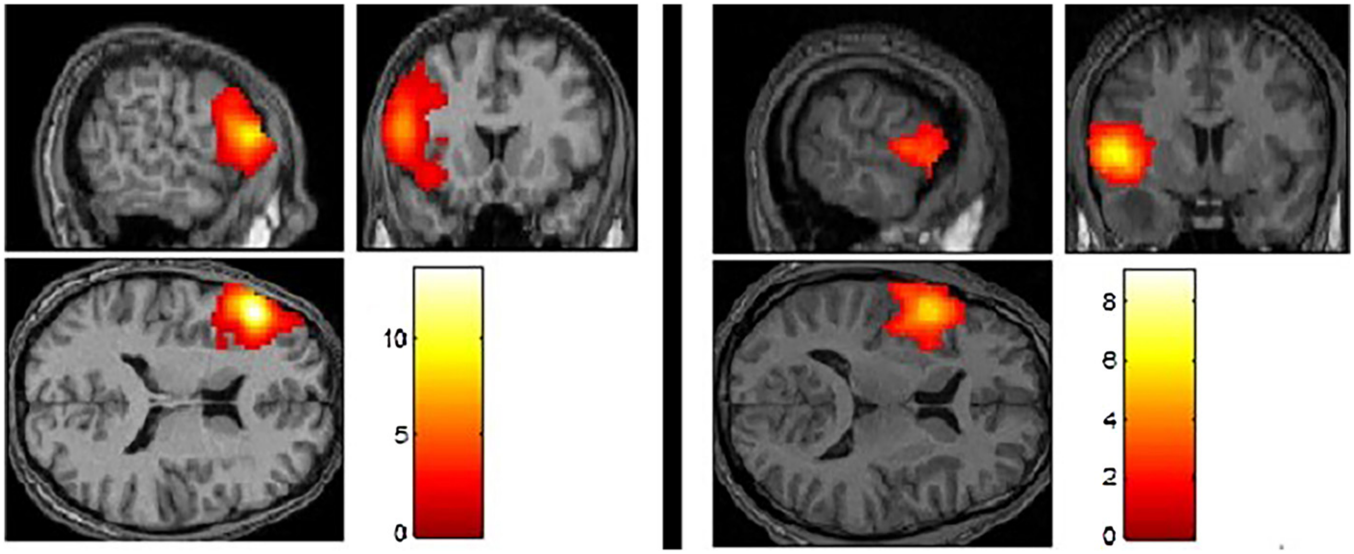

Fig. 6. RS-fMRI language networks. Left part: sagittal, coronal and axial views of frontal-language network in a patient with a left frontal low-grade glioma presented with a good performance on the verbal fluency test. Ipsilesional network *z*-value activation on BA 44 is 6.82. Right part: sagittal, coronal and axial views of frontal-language network in a patient with a left temporal low-grade glioma presented with low performance on verbal fluency test. Ipsilesional network *z*-value activation on BA 44 is 3.84. Functional images are superimposed into anatomical images for both patients. Images are not radiological (left side is left hemisphere/right side is right hemisphere). BA: Brodmann area.

small however number of patients. In these cases, motor dysfunction was elicited by intraoperative ECS by placing electrode grids over the sensorimotor cortex. Nonetheless, we need to consider that ECS in asleep patients can only produce the so-called positive symptoms (e.g. twitching) and not the negative ones (e.g. apraxia, paresis) that can observed during a clinical neurological and neuropsychological examination pre-operatively or intra-operatively when performing awake craniotomy [24]. So far, functional validation of motor cortical RS-fMRI networks by means of correlation with pre-surgical motor neurological and neuropsychological measures was lacking. Otten et al. [25] reported a strong correlation of motor deficits with motor resting-state networks connectivity between primary motor cortices and supplementary motor cortex. Although very interesting, their results do not provide information about the correlation between the cortical eloquent area eliciting the activation and neurological function. In contrast, our findings on positive correlations between cortical areas' BOLD signal intensity and pre-surgical functional status, suggest that RS-fMRI may help neurosurgeons to pre-operatively make a decision through which transcortical corridor the operation should be performed. Overall, our results suggest that motor RS-fMRI may be used in pre-surgical setting as a complementary tool, at least when task-based fMRI is difficult to be performed, in perioperative setting for comparing pre- and postsurgical connectivity alterations [26] or even in anesthetized patients with intraoperative MRI [10,11].

Resting-state language networks and functions

Previous research on RS-fMRI language networks has focused on the temporal reproducibility and lateralisation of networks (including classic areas such as Broca's and Wernicke's) [27–29], the connectivity of different language networks, and the spatial reproducibility of them [30] in healthy volunteers. In clinical context, few studies have investigated RS-fMRI language networks by correlating their functional connectivity with verbal IQ performance in epilepsy [31] and verbal fluency in stroke recovery [32]. Concerning brain tumors, studies have focused on RS-fMRI comparison to traditional language task-based fMRI suggesting that RS-fMRI protocols maybe suitable to map language networks [18–20]. However, those studies do not give us insight on the functional relevance of RS-fMRI and their relationship with language function status as depicted by clinical-behavioral testing. So far, there is only one study addressing the aforementioned issue by providing behavioral data from intraoperative language cortical mapping in tumor patients and comparing them with pre-operative RS-fMRI networks [33]. Cochereau et al. support that, although there is heterogeneous inter-individual accuracy of RS-fMRI in language function, there is a significant overlap of language areas depicted by RS-fMRI and positive stimulation sites in glioma patients.

Aiming to validate RS-fMRI language network as a tool in pre-operative functional mapping, we were interested in specific areas' resting-state BOLD signal and their correlation with pre-operative performance on language clinical assessment, rather than in functional connectivity between language areas as described in most of the previous studies. According to our results, resting-state BOLD signal of left IFG was dramatically decreased in patients with aphasia compared to retained BOLD signal in non-aphasic patients. Regarding the latter, their left IFG resting-state BOLD signal was strongly correlated with their performance on verbal phonological fluency test. Verbal phonological fluency is a sensitive marker to frontal damage function and strongly supported by BA 44 [34,35]. Our findings give further support to Cochereau et al.'s study [33], indicating that the role of areas belonging to those networks identified at rest, are of linguistic function indeed and that those networks are not merely correlated anatomically with traditional brain areas of language.

Methodological considerations

Different methods have been recruited for analyzing RS-fMRI data. Seed-based analysis and ICA are the most popular ones. Compared to ICA, seed-based analysis requires a priori selection of regions of interest; this comes with a methodological "caveat" because, due to plasticity-induced reorganization of functions that may happen in benign and low-grade malignancy tumors, [36] it is uncertain whether anatomical seeds represent underlying functions. Identification of language areas can be even more challenging with seed-based analysis, due to the variability of language areas [37]. Therefore, using ICA rather than seed-based analysis, one would assume that the derived resting-state networks would depict underlying functions more reliably in the vicinity of lesions presenting with significant mass effect. On the other hand, ICA-acquired resting-state networks are components spatially matched to templates and in case of a component distortion, a specific network my appear in a different brain region than that of the template, making thus ICA potentially vulnerable in identifying specific functional components; however, in the present study we did not encountered distortions of motor and language components, strengthening thus the reliability of our method in identifying the functional networks of interest.

Another methodological issue is that of tumor-related neurovascular uncoupling which can lead to compromised signal detectability. False negative BOLD signal changes can be sometimes seen in RS-fMRI of gliomas – and especially glioblastomas – patients. However, the rate of RS-fMRI neurovascular uncoupling is comparable to that of task-based fMRI [38] and, additionally, we showed no significant difference between extra-axial and intra-axial tumors' BOLD signal suggesting that signal of our analyses was not affected by such a factor.

Conclusion

We addressed the functional relevance and the validity of ICA derived pre-operative RS-fMRI motor and language networks as a pre-surgical mapping tool, by prospectively correlating them with pre-operative neurological and neuropsychological testing in patients with a wide range of brain tumor entities. We showed that BOLD signal intensity of motor and language networks was significantly correlated with the underlying pre-operative clinical motor and language performance. This supports the validity of RS-fMRI ICA method in patients with brain tumors and indicates that RS-fMRI may be a useful complementary tool for pre-surgical brain mapping, given the limitations of task-based fMRI. Future studies are warranted to validate the functional relevance of this technique by comparing RS-fMRI networks' BOLD signal with post-operative functional outcomes.

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Disclosure of interest

The authors declare that they have no competing interest.

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