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CLINICAL ARTICLE

A software tool for interactive exploration of intrinsic functional connectivity opens new perspectives for brain surgery

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Abstract
Background Functional connectivity analysis of resting-state functional magnetic resonance imaging data (fcrs-fMRI) has been shown to be a robust non-invasive method for localization of functional networks (without using specific tasks) and to be promising for presurgical planning. However, in order to transfer the approach to everyday clinical practice, fcrs-fMRI needs to be further validated and made easily accessible to neurosurgeons. This paper addresses the latter by presenting a software tool designed for neurosurgeons for analyzing and visualizing fcrs-fMRI data.

Methods A prototypical interactive visualization tool was developed to enable neurosurgeons to explore functional connectivity data and evaluate its usability. The implementation builds upon LIPSIA, an established software package for the assessment of functional neuroimaging data, and integrates the selection of a region-of-interest with the computation and visualization of functionally connected areas. The tool was used to explore data from a healthy participant and eight brain lesion patients. The usability of the software was evaluated with four neurosurgeons previously unacquainted with the methodology,

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who were asked to identify prominent, large-scale cortical networks.
Findings With this novel tool, previously published findings, such as tumor displacement of the sensorimotor cortex and other disturbances of functional networks, were reproduced. The neurosurgeons were able to consistently obtain results similar to the results of an expert, with the exception of the language network. Immediate feedback helped to pinpoint functional networks quickly and intuitively, with even inexperienced users requiring less than 3 min per network.
Conclusions Although fcrs-fMRI is a nascent method still undergoing evaluation with respect to established standards, the interactive software is nonetheless a promising tool for non-invasive exploration of individual functional connectivity networks in neurosurgical practice, both for well-known networks and for those less typically addressed.

Keywords Resting-state · fMRI · Visualization · Interactivity · Surgical planning

Introduction

The outcome of neurosurgical interventions benefits from knowledge about the location of specific functional areas in the brain. For example, pre-surgical identification of circumscribed functional regions in relation to a tumor can be a substantial advantage in surgical planning. The gold standard method for such functional localization, intraoperative electrical stimulation mapping, is invasive and limited to the localization of a few main cortical functional areas accessible during intracranial interventions. In contrast, a non-invasive imaging technique, "task-based" functional magnetic resonance imaging (fMRI), is capable of non-invasively showing the location of a diverse array of functional regions by using task paradigms to identify the implicated areas [38].

Although seemingly of great promise for clinical application, task-based fMRI has seen limited integration into the technical repertoire of neurosurgical planning because of several practical constraints: special experimental setup, relatively long measuring time, high demand on patients for cooperation, and the substantial training and expertise required for processing the data (for a detailed review of these limitations, see [6]). Furthermore, localization of each functional area using task-based fMRI requires a specialized task.

A novel technique in functional neuroimaging termed "resting-state fMRI," in contrast to traditional task-based fMRI, measures changes in the blood oxygen-level dependent (BOLD) signal without the patient being subjected to any task (i.e., spontaneous fluctuations). A formidable body of research in brain and neurological science over the past 15 years has demonstrated the feasibility of using spontaneous fluctuations in fMRI data to map functional systems. The methodology has recently been applied to presurgical planning; however, the current design of the software used for analysis is more suitable for brain researchers rather than being programmed specifically for daily neurosurgical practice.

The purpose of this article is to address this obstacle by introducing a novel interactive visualization tool designed for neurosurgical use in exploring resting-state fMRI data. Because of the relative novelty of the method for neurosurgery, we first review the resting-state methodology, especially as it is applied to neurosurgical patients. Following that, we describe the development of our prototypical software, our experience while applying the tool to explore eight brain lesion cases, as well as a first evaluation of its usability for neurosurgeons previously unacquainted with resting-state analysis.

Introduction to resting-state fMRI

Previous research points out that resting-state fMRI has several practical advantages over task-based fMRI in the clinical setting [8, 9, 24, 35, 39]. Firstly, no stimulation devices are required, and acquisition time can be as little as 5 min. Furthermore, no demands are made of the patient other than to lie motionless throughout the duration of the scan. The patients are usually instructed to rest with their eyes either opened or closed and to simply remain still and not think of anything in particular. The utility of the method does not depend on the precise condition; it has also been successfully used for sleeping [11, 12], sedated [14] and anesthetized [21] participants.

Various functional areas and networks throughout the entire brain can be mapped using a single resting-state fMRI scan. The basic underlying observation is that, even in a task-independent state, the fMRI activity of the brain reveals spontaneous fluctuations that are far from random. The correlation between spontaneous fluctuations across different regions reflects areas that are functionally relevant to each other and can be described as "functionally connected" [10]. The resulting methodology is termed "functional connectivity analysis of resting-state fMRI" (fcrs-fMRI). The classic method for the analysis of functional connectivity is based on taking the signal from a region-of-interest (ROI) and assessing its correlation with all other regions of the brain (termed: "seed-based" functional connectivity [1]). See Fig. 1A for a visual overview of the methodology.

Functional connectivity can be used to describe distributed networks that subserve cohesive functional roles. Such networks are not restricted to the cortex and have been applied to the brainstem [29], thalamus [40], striatum [7], and cerebellum [15, 23, 31]. Nevertheless, the most promising

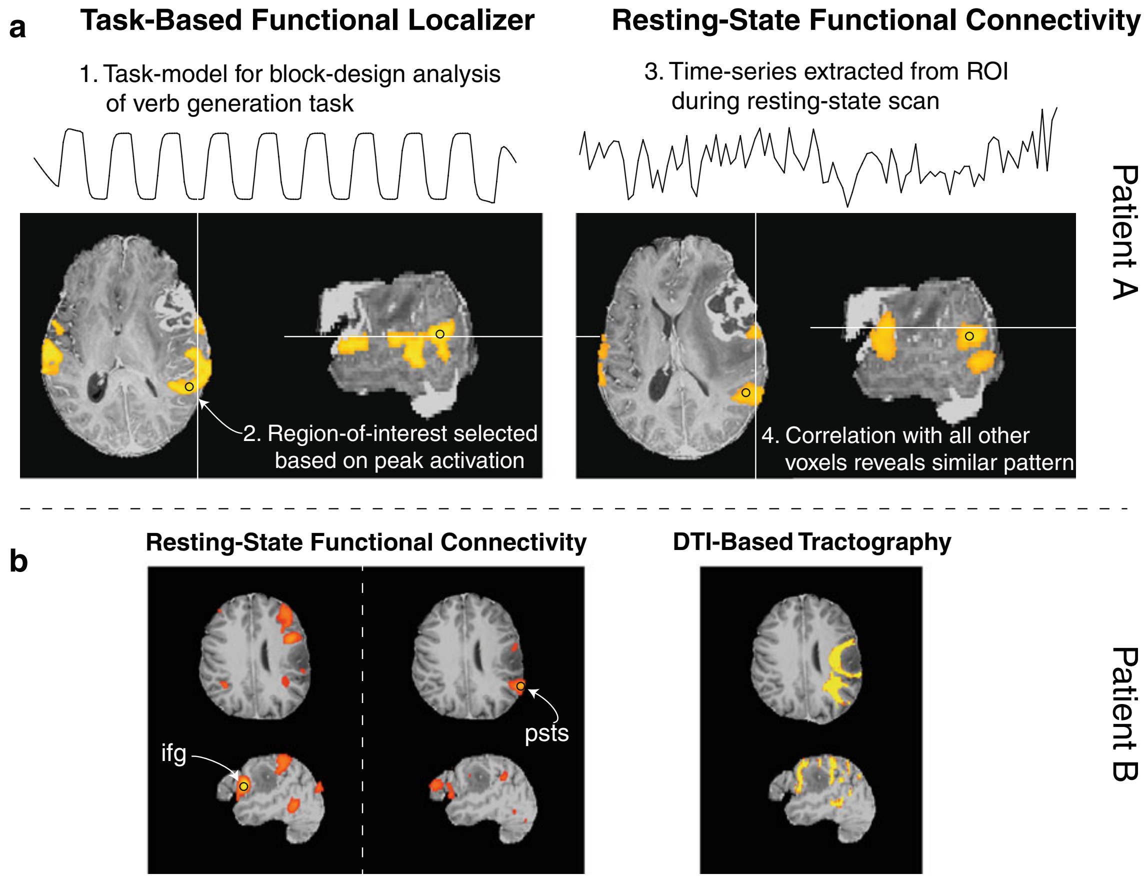

Fig. 1 (**A**) Significant functional activation during performance of a verb generation task (left). The peak region of the posterior superior temporal sulcus (psts) was taken as a region-of-interest and used for subsequent functional connectivity analysis (right). Note the spatial similarity of the two maps, particularly the shift of the inferior frontal gyrus (ifg) portion of the network anterior to the tumor. (**B**) Functional connectivity in another patient from regions-of-interest located in the ifg and psts (left). Diffusion tensor-based tractography from the same patient (right). More information can be found in Online Resource 1

area of clinical application so far is the individual mapping of prominent networks in the cortex, whose architecture is consistent in healthy populations [3–5, 18] and can vary significantly across various patient populations (for reviews, see [13, 22]). While the number of networks varies across studies, here we selected four stable and reproducible networks to explore (see Fig. 2):

- The *sensorimotor network* is located in the pre- and post-central cortex and supplementary motor area [18].
- The *language network* consists of functional connectivity between Broca's and Wernicke's areas [16, 26].
- The *dorsal-attention network* consists of the lateral frontal and parietal cortex [4, 5]. This network has been associated with top-down orienting and conscious direction of attention ("executive control") [34, 37].
- The *default-mode network* consists of the posterior cingulate cortex, medial prefrontal, and medial temporal cortex, and has been associated with self-related processing, mind-wandering, and autobiographical memory [2, 33].

Supporting evidence for the validity of using fcrs-fMRI to identify these networks stems from the comparison of functional connectivity with diffusion direction of white matter, as derived from tractography using diffusion tensor imaging (DTI) data. Van den Heuvel et al. [19] have been able to show that major fcrs-fMRI networks of the healthy brain are indeed interlinked by anatomically well-known DTI tractography. We have reproduced these findings for the language system of a tumor patient, as can be seen in Fig. 1B, and described more fully in the Supplementary Material (Online Resource 1).

Neurosurgical applications

While fcrs-fMRI has been widely used for the characterization of the healthy brain and neurological diseases, its application to neurosurgery is rather recent [9]. In a pioneering study, Shimony and colleagues [35] demonstrated the utility of resting-state fMRI for the resection of tumors close to functional centers. Their new paradigm for neurosurgical

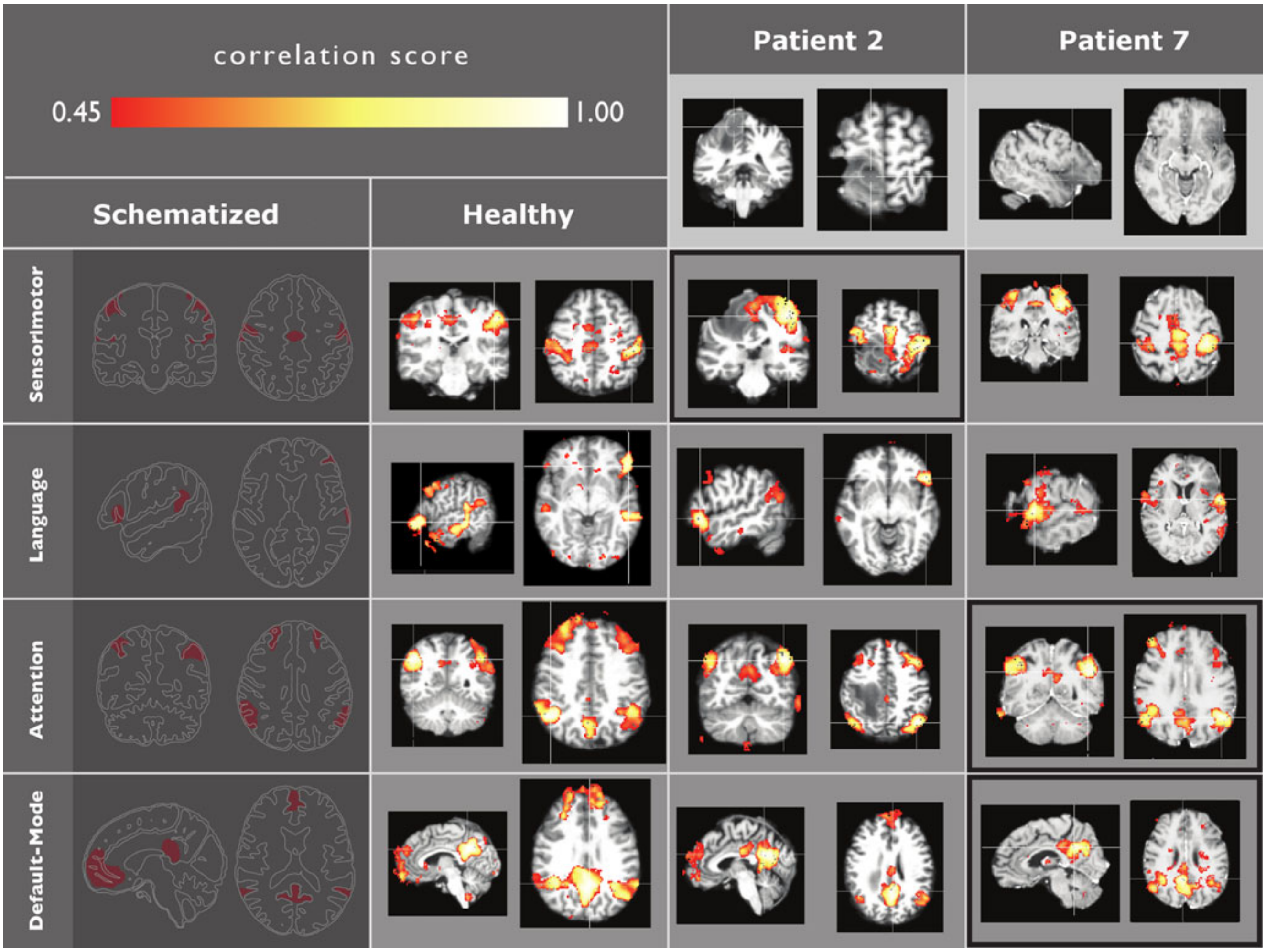

Fig. 2 Four schematized (left) intrinsic functional connectivity networks, and reference networks for our data with manually selected seed regions-of-interest in a healthy individual brain and two example pathological cases (right). Abnormal networks in the patients emphasized with black frame

application took advantage of the high degree of bilateral symmetry in the sensorimotor network [1, 19, 30, 36]. An ROI was chosen in the motor cortex of the healthy hemisphere using specific anatomical landmarks, and the BOLD signal from that region was extracted. Then, the contralateral precentral cortex, in which severe distortion prohibited localization of equivalent landmarks, was localized by looking for areas with highly similar fluctuations in signal. In the extended description of the same work, Zhang et al. demonstrated good overlap with task-based fMRI and the gold standard, intraoperative cortical stimulation [39].

Liu et al. [24] also indirectly localized cortical hand and tongue motor areas in a lesion patient using anatomical landmarks and functional connectivity, and compared these results with task-based fMRI measurements. Taking into account six typical cases, they report highly similar activations, sufficient selectivity to distinguish between hand and tongue centers, and robustness across different imaging resolutions. Their comparison in one case with direct cortical stimulation showed substantial consistency with fcrs-fMRI.

Summarizing, fcrs-fMRI seems to be able to localize even displaced eloquent cortex with resolution comparable to task-based fMRI, but with many practical advantages in the clinical setting. Despite these advantages, applying fcrs-fMRI in a clinical setting remains impractical without the ability to analyze the data quickly and efficiently. For example, as Shimony and colleagues explain [35], in one case the region of interest had to be "determined empirically by shifting […] until the normal spatial pattern of the sensorimotor network was seen," for a distance of approximately 2 cm. With the commonly available processing tools, this trial-and-error process is tedious and could benefit from the development of specialized interactive visualization tools designed with attention to clinical needs.

Thus, building upon the fMRI data analysis toolbox LIPSIA, we developed an interactive tool for rapid and convenient exploration of functional connectivity in the human brain [25]. The impact of the software is illustrated with neurosurgical case examples and an evaluation. The ultimate goal of the prototypical implementation is to make it easy for neurosurgeons to directly explore the functional connectivity of different ROIs selected in real-time and to localize functional networks for assistance in presurgical planning.

Methods and technical development

We report here on our development of a prototypical tool for fcrs-fMRI exploration. This is followed by its application to eight case examples with lesions close to functionally relevant cortical areas, reproducing alterations of main functional connectivity networks that are similar to previously reported findings (see above). Additionally, the usability of the tool was evaluated with four neurosurgeons without previous expertise in the methodology.

Software implementation

We implemented a prototypical interactive exploration tool building on LIPSIA, a freely available MRI data processing suite. LIPSIA already implements certain pre-computation steps as well as the masking-out of voxels outside the brain in order to optimize correlation computation. We chose to implement real-time interaction using a further restriction of correlation computation to only three currently visible slices present in the standard LIPSIA triplanar visualization. The combination of these approaches yields redraw rates of approximately 0.1 s during a shift of the seed ROI, which is sufficiently fast for fluent interaction.

AFNI recently introduced interactive functional connectivity visualization as part of its standard distribution. Using highly optimized computational methods, “InstaCorr” (afni.nimh.nih.gov/pub/dist/doc/misc/instacorr.pdf) achieves comparable speed of calculation while conducting correlation across the whole brain. While AFNI’s computational methods are more sophisticated than our current method, our tool is streamlined for the singular purpose of rapid exploration of functional connectivity with minimal prior knowledge.

Application of the software

Data acquisition and patient selection

Resting-state fMRI data were acquired from eight patients (age 31–69, 6 male, 2 female) with lesions localized close to components of the default-mode, attention, or sensorimotor networks. The lesions include metastases and gliomas located in the frontal or parietal lobes. In Table 1, clinical symptoms and signs as well as the histopathology and the age of the patients at the time when the rs-fMRI scan was performed are described. In addition, data from a healthy 35-year-old male were acquired for the evaluation. All protocols were approved by the Charité hospital ethics board and have, therefore, been performed in accordance with the ethical standards of the Declaration of Helsinki (1964). Informed consent was received from all participants prior to the scan.

All participants were instructed to “think of nothing in particular” and remain still with their eyes open. Subjects were scanned at different hospitals equipped with two different MR scanner systems, and the following parameters were established to optimize measurements on each system, respectively. On a GE 3-T scanner equipped with an eight-channel head coil, fMRI was acquired using a standard echo-planar imaging sequence (repetition time=2,500 ms, echo time=30, flip angle=83º, voxel dimensions=1.71873×1.71873×4 mm). High-resolution “anatomical” images were obtained using a T1-weighted pulse sequence (MPRAGE, TR=7,224 s; TE=3.1 ms; TI=900 ms; flip angle=8; 154 slices, FOV=240 mm). On a Siemens 3-T Tim Trio scanner equipped with a 12-channel head coil, fMRI was acquired using a standard echo-planar imaging sequence (repetition time=2,300 ms, echo time=30, flip angle=90º, voxel dimensions=3×3×4 mm). Anatomical scans were obtained using a T1-weighted pulse sequence (MPRAGE, TR=1,900/2,300 ms; TE=2.52/2.98 ms; TI=900 ms; flip angle=9; 192/176 slices, FOV=256 mm).

Data preprocessing

The data were preprocessed using a combination of Freesurfer (http://surfer.nmr.mgh.harvard.edu/), AFNI (http://afni.nimh.nih.gov/), and FSL (http://www.fmrib.ox.ac.uk/fsl/)—all freely available standard data analysis packages. Preprocessing for the functional data, which has been described previously [7, 27], included: slice-timing correction for interleaved slice acquisition and motion correction in six degrees-of-freedom (AFNI). The six motion components and a “global” signal (extracted from the average signal over the entire brain) were used as covariates in a general linear model. The residual data were then bandpass-filtered between 0.02–0.08 Hz and spatially smoothed using a 6-mm full-width half-maximum Gaussian kernel (AFNI).

The anatomical volume was skull stripped using the standard Freesurfer processing path. A single functional volume was then registered to the skull-stripped anatomical volume using FSL’s linear registration tool, and the resulting transformation matrix was applied to the entire functional data set. Both data sets were co-registered to Montreal Neurological Institute (MNI152) space.

The preprocessing takes advantage of the availability of technically matured software tools and usually requires no manual intervention.

Table 1 Eight focal lesion cases with clinical patient information and observations of abnormal fcrs-fMRI networks (see Fig. 4)

Patient no.	Age	Sex	Signs and symptoms	MRI findings/diagnosis	fcrs-fMRI network observations
1	66	F	Personality changes with reduced impulsion, disorientation	Right frontal lesion (38 × 30 × 39 mm)/ astrocytoma IV°	Sensorimotor: functional connectivity correlation borders the edema around the lesion Attention: strongly diminished correlation on the frontal component on the lesion side Default-mode: correlation appears with a laterally shifted and diminished frontal component next to the lesion
2	50	M	Simple partial motor seizures in the left leg	Right central lesion (17 × 20 × 27 mm)/ metastasis of a malignant melanoma	Sensorimotor: displaced and weakened functional connectivity correlation of the motor region anterior to the lesion
3	52	M	Focally induced generalized tonic-clonic seizures, no persisting sensorimotor deficits	Left pre-central lesion (32 24 22 mm)/menin gioma WHO grade I	Sensorimotor: displaced and weakened functional connectivity correlation of the motor component on the lesion side
4	47	M	Tonic-clonic seizures, right-sided lower extremity plegia and upper extremity paresis	Left central, paramedian lesion (32 × 25 × 35 mm)/astrocytoma WHO IV°	Sensorimotor: substantially diminished functional connectivity signal in the left paramedian motor cortex
5	69	M	Hypesthesia mainly of the right, upper extremity, with impaired coordination and fine motor skills	Left post-central subcortical lesion (27 × 27 × 20 mm)/ astrocytoma WHO IV°	Sensorimotor: substantially diminished functional connectivity of the motor network on the lesion side, especially in the hand region Default-mode: lateral component of the default-mode network displaced
6	31	M	Right-sided hemiplegia	Left central lesion (23 × 28 × 28 mm)/ resulting from bridging vein thrombosis	Sensorimotor: absence of functional connectivity correlation of the sensorimotor system of the right arm and hand
7	49	M	Secondary generalized tonic clonic seizures	Lesion in the left frontal operculum (no clear contour)/astrocytoma WHO III°	Attention: reduced degree of functional connectivity correlation of the frontal component ipsilateral to the lesion Default-mode: disconnection between frontal and posterior components
8	42	F	Auto-motor and grand mal epileptic seizures with bilateral tonic-clonic seizures and affective disorders (frontal brain syndrome), slight mental retardation (caused by perinatal asphyxia), intermittent tremor of the right hand	Bilateral frontobasal lesion (70 × 60 × 50 mm)/atypical menigioma WHO II°	Default-mode: frontal component almost not visible

Interactive exploration

Our tool was then used by an experienced fcrs-fMRI researcher to interactively explore the preprocessed data. In the process, previously described observations, as well as other observations described below, were reproduced. Towards this aim, the four functional systems depicted in Fig. 2 were explored: sensorimotor, language, dorsal-attention, and default-mode networks. The quick redraw rates yielded a fluent interaction, which let the user conveniently maximize correlation patterns. See Fig. 3 for the example of the motor network and also Online Resource 2 for a video of the interactive exploration of the networks described below.

To detect the **sensorimotor network**, the mouse cursor was placed on the lateral motor cortex, anterior to the

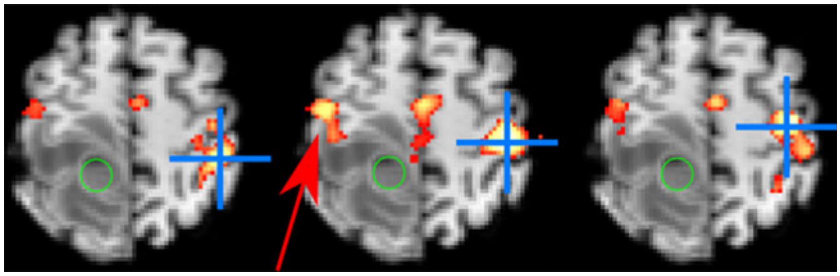

Fig. 3 Interactive movement of the region-of-interest (marked with blue coordinate cross) makes it possible to quickly maximize the functional connectivity patterns, such as in this case example for the bilateral motor network: Dragging the ROI in the anterior-posterior axis on the healthy side contralateral from the tumor (marked green) results in an optimal delineation of the component ipsilateral from the tumor (middle, marked with arrow)

central sulcus, and the ROI shifted until a symmetrical network appeared across the pre- and post-central gyri, as well as supplementary motor area. For the **language network**, the mouse cursor was placed in the left inferior frontal gyrus, adjacent to the precentral sulcus, which corresponds to Broca's area (anterior operculum). By shifting the location slightly, it was possible to detect functional connectivity in the sagittal plane to the posterior portion of the superior temporal gyrus (Wernicke's area) and adjacent to the inferior parietal cortex. For the **dorsal-attention network**, the cursor was placed in the superior frontal gyrus and shifted until functional connectivity in the axial slice was visible bilaterally in both frontal regions and the intraparietal sulcus. The **default-mode network** was identified with the cursor placed in the posterior cingulate. Functional connectivity from this region was visible in the medial prefrontal cortex along the sagittal plane, as well as in the bilateral inferior parietal cortex along the coronal plane. During the exploration, it was possible to manually adjust a threshold for the visualization of correlation using a slider.

Usability evaluation

Two representative cases (patient 2 and 7, see below) were then picked for an evaluation of the usability of our tool. Four neurosurgeons without previous knowledge of the functional connectivity literature were recruited to interactively explore the data. For familiarization, the schematic diagrams and anatomical localization of the four standard networks in Fig. 2 were presented, and the basic method was explained. The group of neurosurgeons was then asked to localize the networks in the one healthy and two representative pathological brain data sets. During this exploration, we recorded the seed ROIs they picked for optimal delineation of the networks for the different cases (for later visual comparison of the resulting correlation maps), the time for the respective searches, and any unprompted special observations made.

Results

Interactive exploration of the clinical cases

An experienced fcrs-fMRI researcher used the procedure described above to explore the four different networks in the eight patients with focal brain lesions. In Table 1, the specific networks that were shifted, or otherwise disturbed, are described.

Six cases of disturbance within the motor network were found (see Fig. 4), ranging from displacement of the functional region by the lesion in patients 1–3 (see Table 1) to the substantial absence of bilaterality in the network in patients 4–6 (see Table 1). These findings are consistent with those in the previous literature [24, 35, 39].

Furthermore, six examples of lesion effects on the default-mode network in patients 1, 5, 7, and 8 (see Table 1, and also Fig. 4) and attention network in patients 1 and 7 (see Table 1, and also Fig. 4) were observed. In patient 1, the frontal component of the default-mode network appeared displaced and weakened. In patient 5, the tumor-side lateral component of the default-mode network appeared dorsally displaced. In patients 7 and 8, components of the default-mode network, and in patients 1 and 7, components of the attention network appeared substantially weakened. For the figures, a threshold was manually chosen in order to match the spatial extent of networks traditionally observed.

Additionally, interactive exploration of tumors and their surroundings reproduced another previously described observation [8]: that functional connectivity can differentiate edema from surrounding healthy grey matter (for an example, see Online Resource 3).

Usability evaluation

Two representative cases were picked for the evaluation: patient 2 because the case presented a clear displacement of the functional motor cortex, which is valuable information

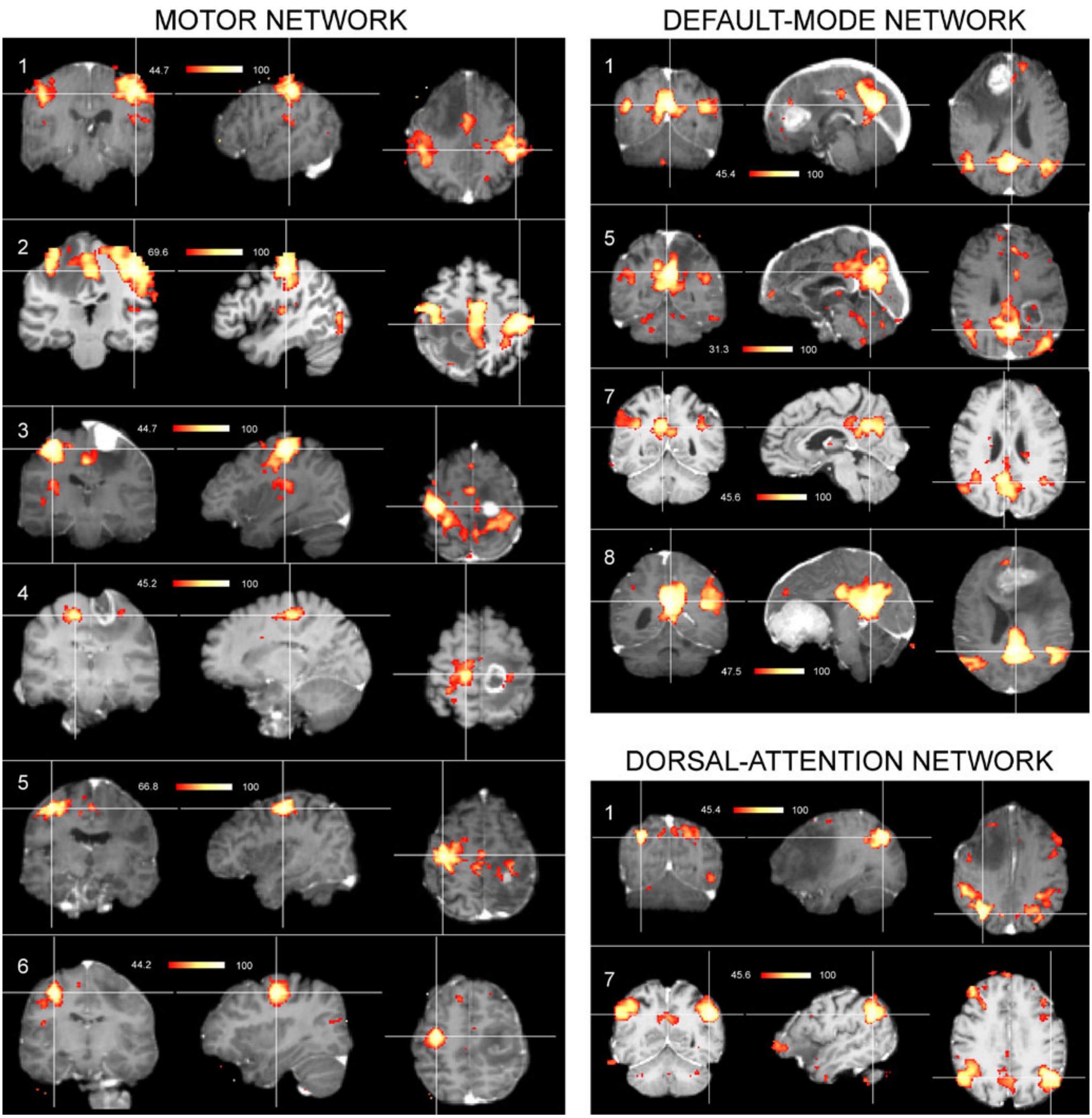

Fig. 4 Clinical cases with network changes. Motor network: patients 1-6 are ordered from weakest (top) to strongest (bottom) disturbance. Default network: patient 1 displays a distorted frontal component, patient 5 shows a displaced lateral lesion-side component, patient 7 lacks the frontal component, and patient 8 has a weak frontal component. Attention network: patient 1 shows a weakened frontal lesion-side component, and the tumor below the location of the missing frontal component in patient 7 appears to disturb the network

in the planning of a resection, and patient 7, since the case contains a visible change in two other large-scale networks that are often not well known to neurosurgeons. The exploration of these two cases by an experienced user resulted in our 12 reference networks, shown in Fig. 2, used for the evaluation.

The evaluation sessions with the neurosurgical users typically lasted 20 min. After familiarization with the software and the introduction of the schematic figures, seed ROIs for the four described networks were selected in all three data sets. The neurosurgeons were able to quickly and consistently reproduce most of the reference networks with a high degree of similarity (see Fig. 5). The longest exploration time was needed to identify the language network, which does not stand out as clearly as the others. The solutions for this network were also not as similar to one another as for the other networks. Some neurosurgical users were able to pinpoint attention and default-mode networks in the pathological cases in less than 30 s and the sensorimotor cortex in less than 20 s.

All neurosurgical users consistently reported displacement of the motor cortex in patient 2. In patient 7, after observing the "normal" pattern of the attention network, a missing frontal component ipsilateral to the tumor was reported by all participants without prompting, while a disturbance of the default-mode network was seen by three of four neurosurgical users.

Discussion

In this paper, a novel interactive software tool is presented. The tool enables the analysis and visualization of functional connectivity using "resting-state fMRI" data at a speed that allows for real-time exploration. As an improvement over the classical iterative analysis of fcrs-fMRI data, it could be demonstrated that this tool enables experienced researchers to reproduce previously described effects like displacement or weakening of functional networks in less than 30 s in eight case examples of lesioned brains. Furthermore, after a short introduction, neurosurgeons without previous experience in the methodology were also able to rapidly explore functional connectivity data, requiring less than 2 min on average to localize functional networks.

Other studies have utilized fcrs-fMRI for the localization of functional areas: Liu et al. [24] in a study with six, and Zhang et al. [39] with four patients. These studies report high overlap with task-based fMRI and good consistency with direct cortical stimulation, making it a promising functional localization method.

Utility of interactive software

Previous studies predominantly used anatomical landmarks as a guide for functional connectivity. However, spatial disagreement of anatomical landmarks versus functional networks argues for the individual assessment of functional brain organization rather than relying on "average" landmarks [32]. For example, in the study by Shimony et al. [35] it was necessary to shift the ROI on the healthy side, which was initially placed in the hand knob, in order to discern the sensorimotor network. The data processing necessary for such an analysis required a technical expert. Our tool can facilitate intuitive and simple access of

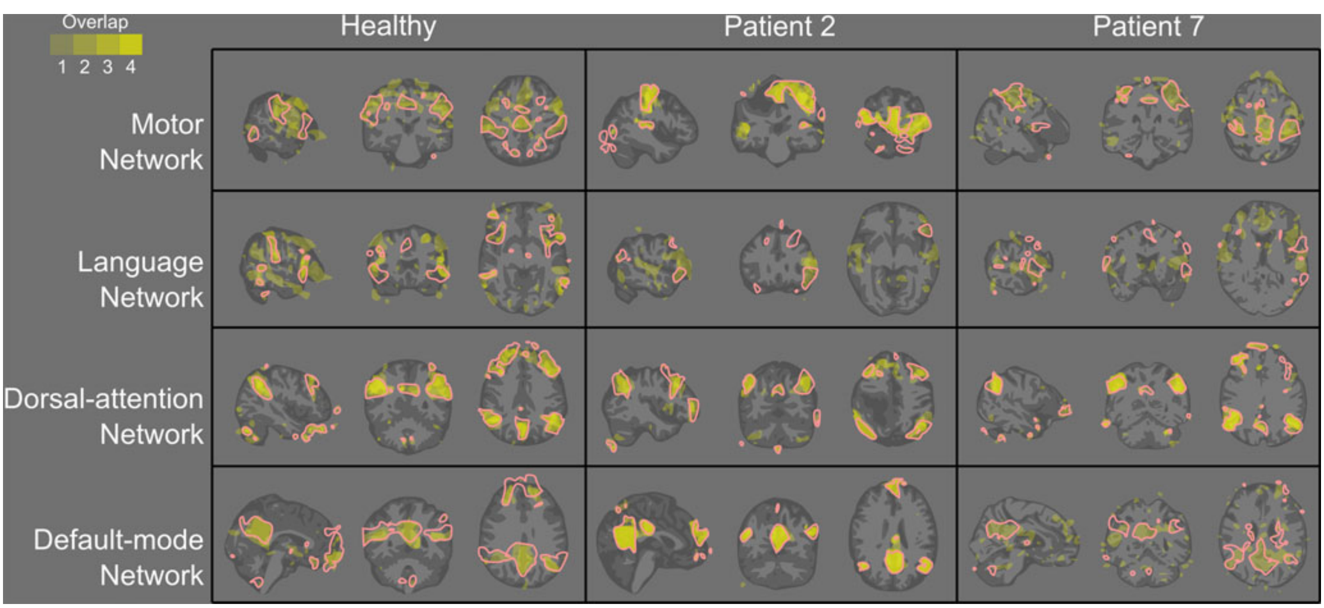

Fig. 5 The reference networks (in red, solid line) have been consistently reproduced for sensorimotor, attention and default-mode networks by a group of four neurosurgeons without previous knowledge of the relevant literature (marked in a gradient, representing the overlap of the four neurosurgeons' solutions) and allowed for identification of the abnormal networks. The language network seems to be harder to identify, as witnessed by large differences in solutions exhibited in the second row. The abnormal structure of the default-mode network in patient 7 also showed more variability in the selected networks; nevertheless, all but one neurosurgeon detected the abnormality in its structure

clinicians to resting-state fMRI data and differs from other analysis software in that it was designed specifically for use in neurosurgical practice.

Fine movements (of the seed ROI) inside networks enable users to maximize correlation patterns and thereby pinpoint the maxima of a functional connectivity network. This mode of interaction is shown in Fig. 3 and in the video (Online Resource 2). Searching for a functional area in the vicinity of, for example, a tumor is thus rendered intuitive. The mouse pointer is used like a searchlight that is moved around within an ROI until typical connection patterns appear.

More advanced users tend to localize functional networks in less time than novices. Although there is a learning curve involved in developing an intuitive understanding and expertise for such a new modality, this is no different than for other explorative visualization diagnostics such as ultrasonography.

During the evaluation of the tool with a neurosurgical user group, it seemed that the symmetrical appearance of most networks, such as in the case of the motor network, makes it particularly easy to identify them and to observe disturbances of the underlying functional connectivity. Even for the "default-mode network" and the "attention network" (both of which might not be well known in a neurosurgical context) a short introduction was sufficient for most of the neurosurgical users to find the networks quickly and observe changes in their appearance. This concept may explain the "relative" difficulty in detecting the lateralized language network. Additionally, the language network has been shown [20] to present more complexly in fcrs-fMRI data than in the classical Broca/Wernicke model of two distinct centers prevalent in neurosurgery. Therefore, it is not surprising that exploring this network in our data proved difficult.

While our prototype was sufficient to test the applicability of interactive visualization for neurosurgery, it certainly has its limitations. The restriction to perpendicular planes in a triplanar view does not allow for an optimal overview. A logical next step therefore will be the development of our tool into a three-dimensional surgery planning system. We also plan to incorporate more advanced analytic methodologies. Statistical comparisons between individual pathological cases and a normative sample may also prove to be a valuable means of assessing localized damage of clinical relevance.

Clinical findings of the motor network

One further concern is the validity of fcrs-fMRI localization for the case of lesions, which destroy functional connectivity patterns instead of displacing components of functional networks. Liu et al. [24] reported as a preliminary finding one case of a diminished right motor cortex component, accompanied with clinical symptoms of the left hand. While not the focus of this paper, eight lesion cases were explored in order to support that fcrs-fMRI is effective in facilitating the presurgical localization of functional networks.

In seven of the eight described patients (that is, with the exception of patient 6), the sensorimotor cortex was bilaterally identifiable with fcrs-fMRI. The changes observed in the central region range from strong spatial displacement (patients 1–3) to substantially weakened correlation (patients 4 and 5) to complete interhemispheric asymmetry (patient 6).

While patients 1–3 showed no sensorimotor deficits, patients 4–6 suffered from different degrees of pareses. The most severe clinical symptom was observed in the case of absent bilateral functional connectivity in patient 6, who indeed had a total plegia of the right upper limb. The weakened functional connectivity in this case prohibited localization of the motor cortex ipsilateral to the lesion.

Although still only descriptive at this point, we can confirm Liu et al.'s observation of a connection between weakening of the connectivity and the severity of clinical symptoms. While this means that fcrs-fMRI seems to be most applicable in cases of non-infiltrated, lesion-displaced motor areas, further quantitative studies are required to assess the implications of weakened or missing functional connectivity.

Other fcrs-fMRI networks

In most of the described cases, the more complex networks, which are largely not taken into account in neurosurgery today (attention and default-mode), present with normal appearance. However, there are four cases where they seem to get displaced or their connections seem weakened by lesions (patients 1, 5, 7, and 8). Patient 1 presented clinically with changes in personality, reduced drive and disorientation, and diminished components in both the attention and the default-mode network.

Although at this point the clinical relevance of these specific networks is still not clear, research supports that brain functions rely on distributed networks rather than single areas, emphasizing the need for an assessment of such networks [28]. The clinical relevance of large-scale networks in brains with localized lesions has, for example, already been demonstrated in stroke patients [17], but must be further established for neurosurgical patients through future studies. We believe that interactive visualization might then become a viable option for easy network localization by neurosurgeons.

Similar to the clinical relevance of the attention and default-mode networks, the fcrs-fMRI methodology clearly has to be further evaluated with respect to accuracy and reliability with surgical patients and to be extensively compared with standard methods like direct cortical stimulation. By correlating clinical findings with observed changes in functional networks, we hope that neurosurgery will be able not only to establish fcrs-fMRI in clinical everyday practice, but also to contribute to basic neuroscience.

Conclusion

In this paper, we presented a novel tool for the interactive exploration of functional connectivity using resting-state fMRI data. As others have pointed out [9, 24, 35, 39], fcrs-fMRI has significant practical advantages in a clinical setting over activation-based, preoperative fMRI (e.g., less scanning time necessary, no task or need for a cooperative patient, and several networks can be assessed simultaneously). Given the limitations imposed on data collection in the clinical setting, the efficiency of this approach makes it a prime candidate for functional localization of distributed large-scale networks throughout the brain. In this way, this method can help to understand disturbances of functional areas surrounding a pathological structure and to contribute another tool to pre-surgical planning. Nonetheless, while the use of such networks may no doubt be of service to neurosurgical planning, rigorous future research is still necessary to assess how these functional connectivity-determined areas spatially relate to eloquent cortex, as defined by gold standard intraoperative cortical stimulation.

The interactive tool presented here is capable of quickly and easily reproducing previously reported findings such as the delineation of edema [8], the shift of cortical areas by tumors [24, 35, 39], and the impairment of large-scale networks [39] by clinical neurosurgeons without previous expertise in fcrs-fMRI. The tool is intended to be a step out of the ivory tower of basic neuroscience into the clinical realm of practicing neurosurgeons.

Conflicts of interest None.

References

1. Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34:537–541
2. Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann NY Acad Sci 1124:1–38
3. Chen S, Ross TJ, Zhan W, Myers CS, Chuang K, Heishman SJ, Stein EA, Yang Y (2008) Group independent component analysis reveals consistent resting-state networks across multiple sessions. Brain Res 1239:141–151
4. Damoiseaux JS, Rombouts SARB, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci 103:13848–13853
5. De Luca M, Beckmann C, De Stefano N, Matthews P, Smith S (2006) fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage 29:1359–1367
6. Desmond JE, Annabel Chen SH (2002) Ethical issues in the clinical application of fMRI: factors affecting the validity and interpretation of activations. Brain Cogn 50:482–497
7. Di Martino A, Scheres A, Margulies D, Kelly A, Uddin L, Shehzad Z, Biswal B, Walters J, Castellanos F, Milham M (2008) Functional connectivity of human striatum: a resting state fMRI study. Cereb Cortex 18:2735–2747
8. Feldman S, Chu D, Schulder M, Barry M, Cho E, Liu W (2009) The blood oxygen level-dependent functional MR imaging signal can be used to identify brain tumors and distinguish them from normal tissue. AJNR Am J Neuroradiol 30:389–395
9. Fox MD, Greicius M (2010) Clinical applications of resting state functional connectivity. Front Syst Neurosci 4:19
10. Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8:700–711
11. Fukunaga M, Horovitz SG, van Gelderen P, de Zwart JA, Jansma JM, Ikonomidou VN, Chu R, Deckers RHR, Leopold DA, Duyn JH (2006) Large-amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages. Magn Reson Imaging 24:979–992
12. Fukunaga M, Horovitz SG, de Zwart JA, van Gelderen P, Balkin TJ, Braun AR, Duyn JH (2008) Metabolic origin of BOLD signal fluctuations in the absence of stimuli. J Cereb Blood Flow Metab 28:1377–1387
13. Greicius M (2008) Resting-state functional connectivity in neuropsychiatric disorders. Curr Opin Neurol 24:424–430
14. Greicius MD, Kiviniemi V, Tervonen O, Vainionpää V, Alahuhta S, Reiss AL, Menon V (2008) Persistent default-mode network connectivity during light sedation. Hum Brain Mapp 29:839–847
15. Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, Greicius MD (2009) Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci 29:8586–8594
16. Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC (2002) Detection of functional connectivity using temporal correlations in MR images. Hum Brain Mapp 15:247–262
17. He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M (2007) Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53:905–918
18. van den Heuvel M, Mandl R, Hulshoff Pol H (2008) Normalized cut group clustering of resting-state FMRI data. PLoS ONE 3:e2001
19. Heuvel MPVD, Mandl RC, Kahn RS, Pol HEH (2009) Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Hum Brain Mapp 30:3127–3141
20. Kelly C, Uddin LQ, Shehzad Z, Margulies DS, Castellanos FX, Milham MP, Petrides M (2010) Broca's region: linking human brain functional connectivity data and non-human primate tracing anatomy studies. Eur J Neurosci 32:383–398
21. Kiviniemi V, Kantola J, Jauhiainen J, Hyvärinen A, Tervonen O (2003) Independent component analysis of nondeterministic fMRI signal sources. Neuroimage 19:253–260
22. Kiviniemi V, Starck T, Remes J, Long X, Nikkinen J, Haapea M, Veijola J, Moilanen I, Isohanni M, Zang Y, Tervonen O (2009) Functional segmentation of the brain cortex using high model order group PICA. Hum Brain Mapp 30:3865–3886
23. Krienen FM, Buckner RL (2009) Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex 19:2485–2497
24. Liu H, Buckner RL, Talukdar T, Tanaka N, Madsen JR, Stufflebeam SM (2009) Task-free presurgical mapping using

functional magnetic resonance imaging intrinsic activity. J Neurosurg 111:746–754
25. Lohmann G, Muller K, Bosch V, Mentzel H, Hessler S, Chen L, Zysset S, von Cramon DY (2001) Lipsia-a new software system for the evaluation of functional magnetic resonance images of the human brain. Comput Med Imaging Graph 25:449–457
26. Lohmann G, Hoehl S, Brauer J, Danielmeier C, Bornkessel-Schlesewsky I, Bahlmann J, Turner R, Friederici A (2010) Setting the frame: the human brain activates a basic low-frequency network for language processing. Cereb Cortex 20:1286–1292
27. Margulies DS, Kelly AC, Uddin LQ, Biswal BB, Castellanos FX, Milham MP (2007) Mapping the functional connectivity of anterior cingulate cortex. Neuroimage 37:579–588
28. Mesulam M (2009) Defining neurocognitive networks in the BOLD new world of computed connectivity. Neuron 62:1–3
29. Nioche C, Cabanis E, Habas C (2009) Functional connectivity of the human red nucleus in the brain resting state at 3T. AJNR Am J Neuroradiol 30:396–403
30. Nir Y, Mukamel R, Dinstein I, Privman E, Harel M, Fisch L, Gelbard-Sagiv H, Kipervasser S, Andelman F, Neufeld MY, Kramer U, Arieli A, Fried I, Malach R (2008) Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. Nat Neurosci 11:1100–1108
31. O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H (2010) Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. Cereb Cortex 20:953–965
32. Pouratian N, Bookheimer SY (2010) The reliability of neuroanatomy as a predictor of eloquence: a review. Neurosurg Focus 28:E3
33. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci USA 98:676–682
34. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356
35. Shimony JS, Zhang D, Johnston JM, Fox MD, Roy A, Leuthardt EC (2009) Resting-state spontaneous fluctuations in brain activity: a new paradigm for presurgical planning using fMRI. Acad Radiol 16:578–583
36. Stark DE, Margulies DS, Shehzad ZE, Reiss P, Kelly AMC, Uddin LQ, Gee DG, Roy AK, Banich MT, Castellanos FX, Milham MP (2008) Regional variation in interhemispheric coordination of intrinsic hemodynamic fluctuations. J Neurosci 28:13754–13764
37. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL (2008) Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol 100:3328–3342
38. Vlieger E, Majoie CB, Leenstra S, den Heeten GJ (2004) Functional magnetic resonance imaging for neurosurgical planning in neurooncology. Eur Radiol 14:1143–1153
39. Zhang D, Johnston JM, Fox MD, Leuthardt EC, Grubb RL, Chicoine MR, Smyth MD, Snyder AZ, Raichle ME, Shimony JS (2009) Preoperative sensorimotor mapping in brain tumor patients using spontaneous fluctuations in neuronal activity imaged with functional magnetic resonance imaging. Neurosurgery 65:ons226–ons236
40. Zhang D, Snyder AZ, Fox MD, Sansbury MW, Shimony JS, Raichle ME (2008) Intrinsic functional relations between human cerebral cortex and thalamus. J Neurophysiol 100:1740–1748