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Clinical Resting-state fMRI in the Preoperative Setting:

Are We Ready for Prime Time?

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Abstract

The purpose of this manuscript is to provide an introduction to resting-state functional magnetic resonance imaging (RS-fMRI) and to review the current application of this new and powerful technique in the preoperative setting using our institute's extensive experience. RS-fMRI has provided important insights into brain physiology and is an increasingly important tool in the clinical setting. As opposed to task-based functional MRI wherein the subject performs a task while being scanned, RS-fMRI evaluates low-frequency fluctuations in the blood oxygen level dependent (BOLD) signal while the subject is at rest. Multiple resting state networks (RSNs) have been identified, including the somatosensory, language, and visual networks, which are of primary importance for presurgical planning. Over the past 4 years, we have performed over 300 RS-fMRI examinations in the clinical setting and these have been used to localize eloquent somatosensory and language cortices before brain tumor resection. RS-fMRI is particularly useful in this setting for patients who are unable to cooperate with the task-based paradigm, such as young children or those who are sedated, paretic, or aphasic. Although RS-fMRI is still investigational, our experience indicates that this method is ready for clinical application in the presurgical setting.

Keywords

brain tumor; fMRI; resting-state fMRI

GENERAL

Resting-state functional magnetic resonance imaging (RS-fMRI) has been instrumental in understanding brain function but is also becoming a valuable tool in the clinical setting. RS-fMRI allows for investigation of brain connectivity based on low-frequency fluctuations in the blood oxygen level dependent (BOLD) signal. In patients who are not performing a task, RS-fMRI reveals areas of the brain that have synchronous BOLD activity, called resting-

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state networks (RSNs). These networks include the somatosensory, language, and visual networks, which provide valuable information for the neurosurgeon in the preoperative setting. Other RSNs that are easily identified and are of research interest include the default mode, control, and attention networks. The importance of RSNs lies in the fact that their topography corresponds to well described neuroanatomical correlates to task-based fMRI elicited by a wide variety of sensory, motor, and cognitive paradigms.¹

Resting-state Functional MRI Background

RS-fMRI evaluates low-frequency fluctuations in BOLD signal (<0.1 Hz). Specific areas of the brain have synchronous low-frequency fluctuations when the brain is not performing any type of cognitive, motor, or language task. This was first noted in 1995 by Biswal et al.² In this study, functional MRI was performed while subjects performed a hand movement task, which activated the sensorimotor regions. RS-fMRI was subsequently executed while the subjects were at rest. During RS-fMRI, similar regions in the sensorimotor cortex were found to have a high degree of temporal and neuroanatomical correlation (Fig. 1).³

In addition to the sensorimotor network, other RSNs that involve eloquent cortex have been defined. These include the language network,⁴ the visual network,^{1,5-8} and the auditory network,¹ and these have been the primary focus in clinical applications of RS-fMRI (Fig. 1).

The study of RS-fMRI has also identified multiple networks that are of great interest from a research perspective. The default mode network is the collection of areas that shows increased activity while the brain is at rest and decreased activity while the subject is performing a task. This network was first identified using PET data by Raichle et al.^{9,10} The default mode network includes the posterior cingulate cortex, precuneus, and medial prefrontal cortex (Fig. 1). It has been hypothesized that there are 2 opposing systems in the brain, and the default mode network is the basis of the “intrinsic” or “task-negative” network.^{3,11-15} The alternate system is composed of those networks that include brain regions used when performing a task, such as somatosensory or attentional activities.

In addition to the somatosensory and default mode networks, other RSNs include the dorsal and ventral attention networks (Fig. 1).^{7,8,16,17} The dorsal attention network is involved in voluntary orienting and attention to the environment, and the ventral attention network is involved in detecting salient cues. The dorsal attention network includes the intraparietal sulcus and frontal eye field, and the ventral attention network includes the temporoparietal junction and ventral frontal cortex. Regions in these two networks are also activated in task-based paradigms. Additional attentional and control networks that have been identified include the frontoparietal control network¹⁸ and cinguloopercular network.^{7,19}

MATERIALS AND METHODS

Data Analysis: Preprocessing

Preprocessing of fMRI data varies across laboratories. The following describes the procedures used in our laboratory.²⁰ Briefly, these include compensation for slice-dependent time shifts, elimination of systematic odd-even slice intensity differences due to interleaved

acquisition, and rigid body correction for head movement within and across runs. The fMRI data are intensity scaled (1 multiplicative factor applied to all voxels of all frames within each run) to obtain a mode value of 1000. This scaling facilitates assessment of voxel-wise variance for purposes of quality assessment but does not affect computed correlations. Atlas transformation is achieved by composition of affine transforms connecting the fMRI volumes with the T1- and T2-weighted structural images. Head movement correction is included in a single resampling to generate a volumetric time-series in 3 mm³ atlas space.

Additional preprocessing in preparation for seed-based correlation mapping includes the following: (1) spatial smoothing (6 mm full-width half-maximum Gaussian blur in each direction), (2) voxelwise removal of linear trends over each run, (3) temporal low-pass filtering to retain frequencies <0.1 Hz, and (4) reduction of spurious variance by regression of nuisance waveforms derived from head motion correction and extraction of the time series from regions of noninterest in white matter and CSF. In our laboratory, this step includes regression of the global signal averaged over the whole brain.²¹ A consequence of global signal regression is that all subsequently computed correlations are effectively partial correlations of first-order controlling for widely shared variance. Global signal regression before correlation mapping is a highly effective means of reducing widely shared variance and thereby improving the spatial specificity of computed maps.²¹ However, it has been criticized on the grounds that it induces artifactual anti-correlations^{22,23} and thus remains controversial.

Data Analysis: RSN Identification

Several analysis methods have been used to identify the resting-state networks once the preprocessing steps are completed. The simplest of these, the seed-based method, is the one that was used by Biswal et al² to identify the sensorimotor network. This involves selecting regions of interest (that can be as small as a single voxel, but are usually larger), averaging the time course of the voxels within the region of interest, and correlating it with the time course of all other regions²⁴ to determine a connectivity matrix of the brain. Although this method is relatively simple to implement, the a priori selection of regions of interest introduces bias and may also be difficult in patients who have significant anatomical distortion.

Our preferred method for mapping the topography of known RSNs in patients for presurgical planning uses a multilayer perceptron (MLP).²⁵ Perceptrons are machine learning algorithms that can be trained to associate arbitrary input patterns with discrete output labels. Here, an MLP was trained to associate seed-based correlation maps with particular RSNs. Running the trained MLP on correlation maps corresponding to all voxels in the brain generates voxel-wise RSN membership estimates. Thus, RSN mapping using a trained MLP exemplifies supervised classification. An example of the RSN produced by the MLP algorithm in 3 subjects is presented in Fig. 2. Our implementation of MLP-based RSN mapping utilizes the same preprocessing steps described above in connection with seed-based correlation mapping.

Figure 3 demonstrates the degree to which the MLP captures individual variability, by showing that, in each subject, the location of the central sulcus in the cortical surface

segmented using FreeSurfer²⁶ is highly correlated with the location of the sensory-motor network (SMN) centroid calculated by the MLP. Detailed quantitative evaluation of the MLP performance is presented in reference.²⁵ MLP performance was also compared with alternative RSN estimation schemes such as dual regression and linear discriminant analysis and was found to provide improved area under the curve estimation, with better orthogonal estimates of RSN membership.

In summary, the MLP accurately generates RSN topography estimates in individuals consistent with previous studies, even in brain regions not represented in the training data. Our data suggest that the MLP method of analyzing RS-fMRI data can be used for generating individual RSN maps in brains distorted by the presence of tumor. These findings are important to future applications because they demonstrate that this approach can reliably and effectively map multiple RSNs across individual subjects.

Clinical Applications

Although task-based fMRI is more commonly used in presurgical planning, we believe that RS-fMRI can also be useful to identify eloquent cortex before surgery. RS-fMRI is particularly helpful in situations wherein the patient may not be able to cooperate with a task, such as young children, patients with altered mental status, or patients who are paralyzed or aphasic. Resting state can also be performed while the patient is sleeping or under light sedation. An additional advantage of RS-fMRI is that multiple networks can be identified from the same scan, whereas different scans must be performed for each network in the task-based paradigm. An additional logistical advantage of RS-fMRI is that it is very easy to acquire and can be done at night and over the weekend without extra equipment and personnel highly trained in delivering and monitoring task-based fMRI necessary to acquire task fMRI.

Localization of Eloquent Cortex in the Preoperative Setting

RS-fMRI is currently being extensively used in our institute and others to identify eloquent cortex in patients requiring surgery for brain tumor resection or for intractable epilepsy. Examples from the literature include the identification of the sensorimotor cortex in 4 preoperative patients using a seed-based approach.²⁴ Another study identified the sensorimotor cortex in patients with brain tumors using independent components analysis and found agreement between resting-state and task-based functional MRI.²⁷ Mitchell et al²⁸ identified RSNs in patients with brain tumors and epilepsy, and their results were concordant with that of intraoperative electrocortical stimulation mapping.

To date, our neuroradiology and neurosurgery departments have performed RS-fMRI and surgical resection on over 300 patients over the last 4 years. The next sections address the practical issues in implementing this technique in the clinical setting from our local experience, followed by a few illustrative case examples.

Implementation of Resting-state Functional MRI in the Clinical Setting: Neuroradiology Perspective

RS-fMRI is a standard component of our advanced imaging (AI) protocol for presurgical planning. Our standard data acquisition for this protocol include anatomical imaging, diffusion tensor imaging (DTI) for tractography, task fMRI with motor and language paradigms, and RS-fMRI. The DTI and RS-fMRI data are acquired while the neuroradiology fellow processes and reviews the task fMRI at a workstation located in the MRI control room, thus optimizing scanner time utilization. We provide the neurosurgeons flexibility in tailoring the presurgical planning AI protocol to their specific needs, including processing visual RSN with tractography of the corticospinal tracts, arcuate fasciculus, and optic radiations and adding perfusion-weighted imaging. Task fMRI may be excluded from the presurgical planning protocol for patients deemed unsuitable candidates for task fMRI, such as young children, patients requiring sedation for MRI, and patients with cognitive impairment or neurologic deficits that preclude them from cooperating with task fMRI instructions. Orders for the presurgical planning MRI are reviewed by an MR protocol coordinator and questions involving the order are resolved by a neuroradiologist in advance of the MRI appointment, ensuring that the appropriate data are acquired and reducing the need for repeat MRI appointments. All task fMRIs are performed on a single 3-Tesla MRI scanner (Skyra; Siemens Healthcare, Erlangen, Germany) equipped with a video task paradigm presentation system (Nordic Neuro Lab, Bergen, Norway) during normal weekday business hours by an experienced MRI technologist and neuroradiology fellow. Presurgical planning examinations that exclude the task fMRI component may be acquired on any of our 3-Tesla MRI scanners within the medical center and may be performed outside of normal business hours, as acquisition of RS-fMRI and DTI does not require specialized task presentation equipment, monitoring by a neuroradiology fellow, or technical expertise beyond that expected of our routine MRI technologists. This allows increased flexibility in scheduling patients for presurgical planning imaging before surgery. The billing codes for the presurgical planning MRI remain the same despite the addition of RS-fMRI, as these already include the acquisition of the BOLD data and the 3D processing.

The RS-fMRI is performed as two 6-minute runs at the same resolution and TR (2.2 s) as that used for the task fMRI for a total of 326 BOLD frames. The processing of the RS-fMRI data is performed using a locally developed set of algorithms previously described. This processing, with its respective quality control (QC) measures, is implemented within the translational imaging platform (TIP), a custom XNAT-based informatics system.²⁹ The TIP includes an interface to query for and retrieve patient studies from the clinical Picture Archiving and Communication System (PACS) and pipelines to fully automate the RS-fMRI processing. The pipelines generate DICOM-formatted images of the resting-state networks and a web-based QC report. Trained technicians manage the overall workflow, and for studies that pass QC review, the generated DICOM images are pushed back to the PACS for use by clinicians. Studies that fail QC are reprocessed with adjusted parameters. In rare cases, the study is unable to be processed, typically due to severe subject motion, image artifacts, or poor spatial alignment with anatomic scans. Once the generated images are available on the clinical PACS, a neuroradiology fellow integrates them with the task fMRI, tractography, and anatomic images on a surgical planning station (StealthViz; Medtronic,

Minneapolis, MN). The entire examination is reviewed by a neuroradiology attending, a report is dictated, and the intraoperative navigation-compatible fused imaging is transmitted to the operating room (OR). If the quality of the RS-fMRI data is determined to be suboptimal (either by the automatic QC measures or during the review by the neuroradiology fellow and attending), this will be included in the written report and the neurosurgery service will be notified.

The presurgical planning MRI generates a large amount of data that requires processing on multiple different systems. With a grant from the hospital's foundation, a dedicated advanced neuroimaging assistant was hired to coordinate data transfer, monitor RS-fMRI processing, and assist the neuroradiology fellow in processing the task fMRI and DTI data into the format required by the intraoperative navigation system. This set of procedures was refined over time in response to feedback from the personnel that implement the process and from the neurosurgeons that are the end users of this information. The service is frequently used by the neurosurgeons that perform tumor surgery at our institution.

Implementation of Resting-state Functional MRI in the Clinical Setting: Neurosurgery Perspective

From the neurosurgical point of view, the use of RS-fMRI has been implemented to complement and enhance the currently established methods of task fMRI and DTI tractography. As illustrated in some of the cases described below, the RS-fMRI information is especially valuable if the task fMRI is of poor quality or is nonexistent, such as can occur when patients are not able to cooperate with the task fMRI requirements. The RS-fMRI data arrive in a format that is similar to that used for the task fMRI, that is, instead of a graphical overlay of an activated region mapped on the brain, the RS-fMRI data are provided as a graphical overlay of the location of the motor or language networks mapped on the brain. This is typically provided in several versions that are distinguished from each other by different threshold values that adjust the relative sensitivity and specificity of the maps. As part of the presurgical planning phase, the neurosurgeon will review the RS-fMRI maps in addition to the more traditional task fMRI and DTI tractography data. During this phase, the neurosurgeon will use these data (and their assessment of its quality) to help inform various decisions in regard to the surgery itself. These decisions may include some or all of the following items: (1) the location and size of the craniotomy; (2) the direction and path of approach to the tumor; (3) the need for a ventriculostomy catheter and where to place it; (4) the need for electrocortical stimulation equipment to confirm the MRI findings; (5) the need for an intraoperative MRI scan; and (6) the need to vary the type of anesthesia depending on the type of anticipated stimulation mapping. Every case is different, and the MRI information can provide valuable help in decreasing morbidity and optimizing the tumor resection.

RESULTS

Case Example 1

A 57-year-old man with a history of rectal adenocarcinoma presented with persistent headache and blurred vision. Brain MRI examination demonstrated an enhancing left

frontoparietal mass, initially favored to represent metastasis. Preoperative RS-fMRI showed Broca area located anterior to the peri-tumor edema, while Wernicke area abutted the inferior portion of left frontoparietal junction mass (Fig. 4B).³⁰ Left motor activation center was located superior to the tumor, abutting the peri-tumor edema with minimal displacement (Fig. 4A). Given the close proximity of the mass with respect to the motor and language centers, it was decided that an awake-craniotomy would be performed with electrocortical stimulation.

In the OR, the patient was noted to have significant aspiration with the gastric contents appearing at the patient's nose and mouth. Awake-craniotomy and brain mapping were of high risk. After consulting the patient's family, it was decided to proceed with surgical resection on the basis of the preoperative RS-fMRI that could offer therapeutic benefit albeit with an increased risk of developing permanent speech or motor deficits. The RS-fMRI helped define the spatial relationship between the motor and language centers and the mass, supporting a path through the parietal lobe for tumor resection. A standard craniotomy was then performed and continued stereotactic navigation was used to visualize the optimal gyrus for surgical approach. This surgical path was posterior and oblique relative to where the tumor was located and a nonintuitive cortical entry from anatomy landmarks alone. Along this deeper track, the tumor was subsequently resected. Adequate resection of the tumor was confirmed with intraoperative MRI.

The patient's postoperative course was unremarkable with no new speech or motor deficits. Following the tumor resection, the patient experienced complete resolution of headache and blurred vision. Surgical pathology results were consistent with grade 4 Glioblastoma.

Case Example 2

A 47-year-old man with left frontal lobe anaplastic oligodendroglioma undergoing chemotherapy treatment, status postpartial surgical resection, and postfractionated radiation treatment, was found to have new mass-like nodular areas of enhancement at the tumor resection site on the 1-year follow-up brain MRI examination. These imaging findings were concerning for tumor recurrence. The patient had profound expressive aphasia at the time of presentation. RS-fMRI demonstrated Broca area less than 1 cm from the edge of the previous resection cavity and abutting the edematous parenchyma surrounding the new foci of enhancement (Fig. 5B). Regions related to motor and Wernicke area were not in close proximity to the recurrent tumor and were therefore of less concern from a neurosurgical standpoint (Fig. 5A).

Consensus decision on the basis of the clinical picture and the imaging findings was to perform a repeat awake-craniotomy and resect the recurrent tumor. This was discussed with the patient. During standard awake craniotomy procedure, once the brain was exposed and the patient was roused, he was extremely combative and could not adequately follow the commands despite repeated attempts of mild sedation using narcotics to reduce his pain and discomfort. Given the patient's condition, intraoperative cortical mapping to identify Broca area could not be accomplished. A 2 × 2 cm block of tissue corresponding to the enhancing mass noted on the prior MRI examination was resected, furthest away from the speech and motor areas identified on preoperative RS-fMRI. Postoperatively, there was no worsening of

patient's speech or motor functions. Biopsy results for the resected tissue were consistent with radiation necrosis with no evidence of tumor recurrence.

Case Example 3

A 29-year-old man, diagnosed with grade 4 Glioblastoma status post chemoradiation treatment, had a new focus of enhancement in the white matter of the left frontal lobe identified on 1-year follow-up MR examination. The preoperative RS-fMRI (not shown) showed close proximity between the suspected tumor recurrence and the language network, with the tumor located deep to the activation corresponding to Broca area. The new focus of enhancement was located several centimeters anterior to the motor strip but in close proximity of less than a centimeter from the supplementary motor area. Considering these findings, awake-craniotomy and resection of tumor was planned.

During the awake-craniotomy, once the brain was exposed, stereotactic navigation was used to localize the site of the recurrent tumor. Electro-cortical stimulation mapping was performed at the tumor site and adjacent regions with multiple iterations using various speech paradigms, with no speech arrest. Of note, these negative sites included regions identified with task and RS-fMRI as belonging to the language network. Subsequently, sub-pial dissection and resection of the inferior frontal gyrus affected by the tumor was performed, while the patient was maintained in conversation without any difficulty.

During the postoperative hospital stay and at the time of discharge, the patient's sensory and motor components of speech did not demonstrate any worsening. Contrary to the previous cases, this example helps to illustrate that RS-fMRI, though useful for operative planning, can give false-positive or negative results, and should be used in conjunction with electrocortical stimulation when possible, which remains the gold standard technique for functional mapping of the brain during neurosurgery.

DISCUSSION

RS-fMRI is becoming a valuable tool not only in exploring brain physiology but also in the clinical setting wherein preoperative localization of eloquent cortex is needed. A distinct advantage of RS-fMRI is that it does not require patient cooperation, and thus can be used in young children and in patients who are aphasic, paretic, or sedated. Multiple networks can be identified with 1 scan, saving scanning time in patients who may not be fully cooperative. An additional advantage of RS-fMRI is the simplicity of the data acquisition, which can be done during evening and weekend hours without additional personnel that are commonly used for task-based fMRI. Currently, the main hurdle for the implementation of a RS-fMRI program is a lack of availability of the software tools that are needed for the data processing. This problem will be solved in the future as these software packages become available from the major manufacturers. It should be noted that the fMRI sequence used is FDA approved, but the processing method is investigational.

Although our focus has been on applications in brain tumor resection, RS-fMRI may also be used in presurgical planning for patients with medically intractable epilepsy. RSNs have been successfully identified in epileptic patients with distorted anatomy.²⁸ Early

investigation in this area has been done by Stufflebeam et al.³¹ and by Weaver et al.³² Another study also reported increased connectivity in epileptogenic foci in patients with mesial temporal epilepsy.³³

In addition to localization of eloquent cortex, areas of future clinical applications may include the evaluation of patients with various neurological and psychiatric disorders. Patients with Alzheimer disease may also have RS-fMRI signatures, such as differences in connectivity in the hippocampus³⁴ and the default mode network.³⁵ Future applications of RS-fMRI may also include differentiating types of dementia,³⁶ identifying patients with traumatic brain injury,³⁷ stroke,³⁸ major depressive disorder,³⁹ and schizophrenia.⁴⁰

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FIGURE 1. Surface plots of RSNs derived using a clustering algorithm. A, Default mode network. B, Somatomotor network. C, Visual network. D, Language network. E, Dorsal attention network. F, ventral attention network. G, Frontoparietal control network. Reprinted with permission from Joshua S. Shimony.

FIGURE 2.

Single subject, voxel estimation of RSNs using the trained MLP in 3 subjects. The results are from the best, median, and worst performers as determined by RMS error. MLP output was converted to a percentile scale and sampled onto each subject's cortical surface.

Adapted from *NeuroImage* 2013; 82:616–633.

FIGURE 3.

MLP SMN validation results. Figures are of 5 individuals selected to represent the correspondence between SMN variability and anatomical variability in the central sulcus. The plot shows the correlation between the Talairach Y-coordinate of the centroid of the MLP SMN and the Y-coordinate centroid of the central sulcus traced over the anatomy (as determined by the Freesurfer program) in a large validation dataset. Adapted from *NeuroImage* 2013; 82:616–633.

FIGURE 4.

An example of the resting-state network (RSN) (in red) superposed on T1-weighted images in a 57-year-old man with a history of rectal adenocarcinoma who presented with persistent headache and blurred vision. The somatomotor (A) and language (B) RSNs are shown. Preoperative RS-fMR imaging showed that the left motor activation center was located superior to the tumor, abutting the peritumoral edema with minimal displacement (A). Broca area located anterior to the peritumoral edema, while Wernicke area abutted the inferior portion of left frontoparietal junction mass (B). During the operation, the patient was not able to comply with awake cortical mapping and the operation proceeded on the basis of the RS-fMRI data. The RS-fMRI data adjusted the surgical approach and the tumor was resected without any new neurological deficits. Pathology revealed a GBM. Adapted from *Neuroimag Clin N Am* 2014; 24:655–669 (see text for details).

FIGURE 5.

The resting-state network (RSN) (in red) superposed on T1-weighted images in a 47-year-old man with left frontal lobe anaplastic oligodendroglioma. The patient had profound expressive aphasia. RS-fMRI demonstrated Broca area less than 1 cm from the edge of the previous resection cavity and abutting the edematous parenchyma surrounding the new foci of enhancement (B). Regions related to motor and Wernicke area were not in close proximity to the recurrent tumor and were therefore of less concern from a neurosurgical standpoint (A and B). As in Figure 4, the patient was not able to comply with awake, intraoperative cortical mapping and resection of the lesion proceeded on the basis of the RS-fMRI data. Postoperatively, there was no worsening of patient's speech or worsening of patient's speech or motor functions. Pathology was consistent with radiation necrosis with no evidence of tumor. Adapted from *Neuroimag Clin N Am* 2014; 24:655–669 (see text for detail).