Resting-state Spontaneous Fluctuations in Brain Activity:

A New Paradigm for Presurgical Planning Using fMRI[1]

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Rationale and Objectives. Task-evoked functional MRI (fMRI) has been used successfully in the study of brain function and clinically for presurgical localization of eloquent brain regions prior to the performance of brain surgery. This method requires patient cooperation and is not useful in young children or if the patient has cognitive dysfunction or physical impairment. An alternative method that can overcome some of these disadvantages measures the intrinsic function of the brain using resting-state fMRI. This method does not require any task performance and measures the spontaneous low-frequency (<0.1 Hz) fluctuations of the fMRI signal over time. Our objective in the present work is to provide preliminary information on the possible clinical utility of this technique for presurgical planning and on possible future applications.

Materials and Methods. Data from prior fMRI resting-state studies were reviewed for their potential use in preoperative mapping. Structural and resting-state fMRI data from normal subjects and patients with brain tumors were preprocessed and seed regions were placed in key regions of the brain; the related functional networks were identified using correlation analysis.

Results. Several key functional networks can be identified in patients with brain tumors from resting-state fMRI data.

Conclusion. Resting-state fMRI data can provide valuable presurgical information in many patients who cannot benefit from traditional task-based fMRI. Adoption of this method has the potential to improve individualized patient-centered care.

Key Words. Functional MRI; brain mapping; CNS tumors; neurosurgery; neuroradiology.

Blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI) measures neuronal activity using the ratio of oxyhemoglobin to deoxyhemoglobin as a contrast mechanism. In a typical application, the patient alternates between a passive resting state and performing a task, such as finger tapping, that activates a region of interest in the cerebral cortex. During these periods, the BOLD signal is measured in the magnetic resonance scanner, and the two images are subtracted from each other to reveal areas of the brain that were activated during the prescribed task (1–3) (Fig 1A). This technique has been an invaluable research tool in the laboratory and has helped increase our understanding of normal and abnormal brain function. Clinical applications of fMRI have focused on localizing areas of critical function for presurgical planning (4). The accurate localization of eloquent cortex (eg, somatomotor, language) in relation to a tumor mass can help optimize resection and minimize morbidity and mortality. Functional foci identified using fMRI have been shown to correlate well with foci identified using more invasive techniques, such as intraoperative electrophysiology (5) and Wada testing (6,7). Furthermore, the distance from an fMRI-identified functional region to the surgical margin has been shown to correlate with loss of function postoperatively

Acad Radiol 2009; 16:578–583

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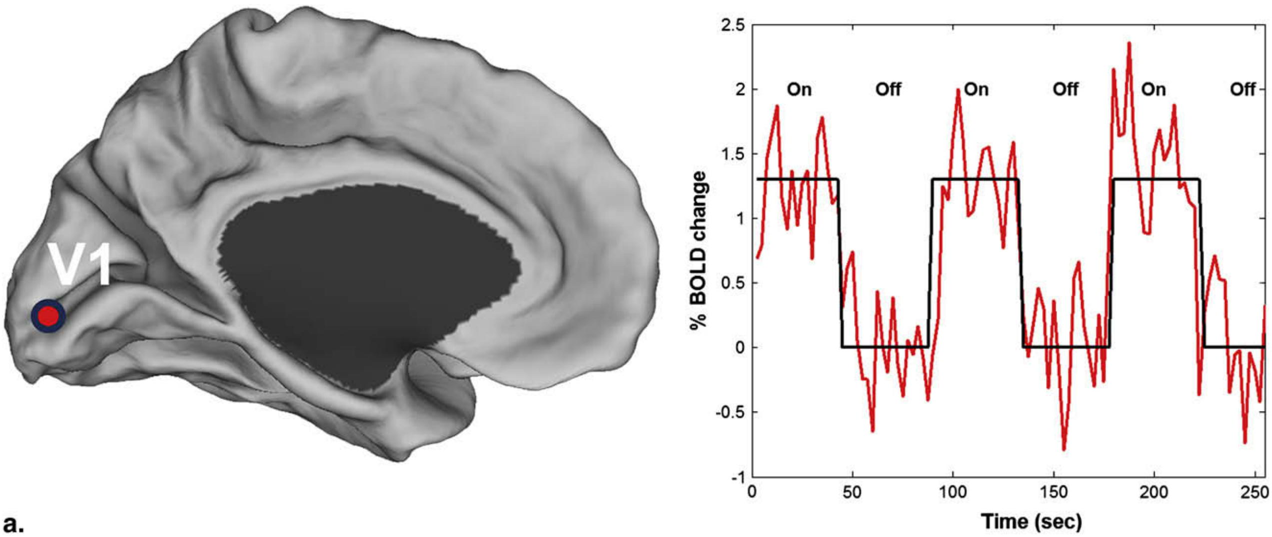
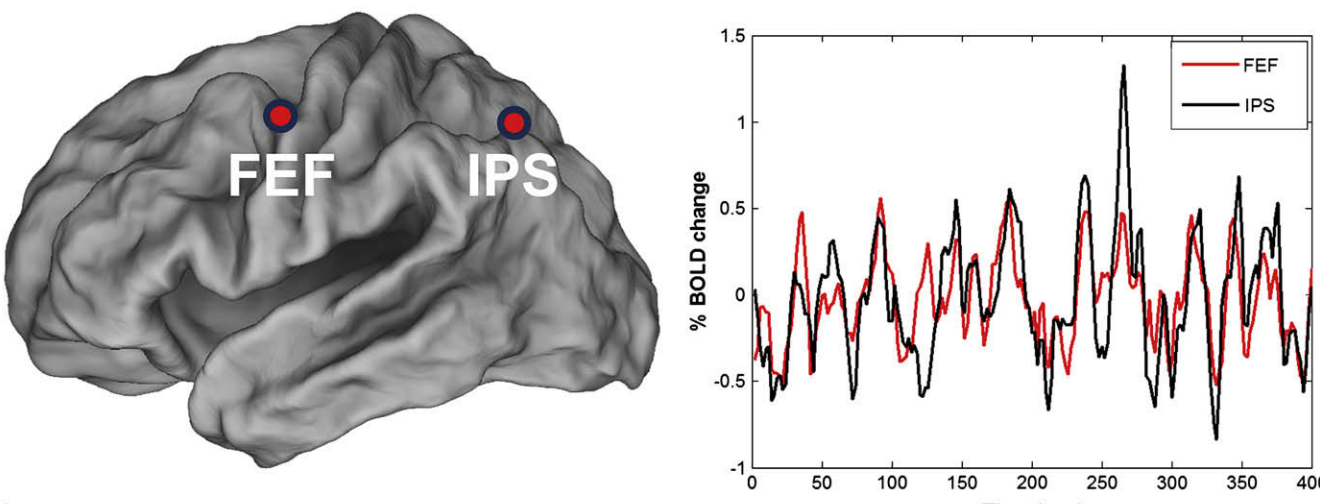
doi:10.1016/j.acra.2009.02.001



a.



b.

Figure 1. The blood oxygen level–dependent (BOLD) signal during task-based functional magnetic resonance imaging (fMRI) **(a)** and during intrinsic resting-state fMRI **(b)**. **(a)** The subject focused on a flickering checkerboard pattern that was periodically turned on and off. The measurement was made in the V1 region of the visual cortex *(red circle)*. Ongoing spontaneous fluctuations can be seen in this task paradigm. **(b)** Spontaneous fluctuations from two regions of the dorsal attention system. The regions are the intraparietal sulcus (IPS) and the frontal eye fields (FEF) *(red circles)*. The two time curves demonstrate a high degree of correlation (r = 0.60).

(8). Although there is much accumulated evidence for the benefit of fMRI use in presurgical planning, large-scale studies to demonstrate improved patient outcomes have not been performed.

Task-based fMRI has several disadvantages that limit its application. The results are dependent on how well the patient can perform the prescribed task. Patients with brain tumors may be impaired and unable to cooperate (9). The patient must be awake during the procedure, so sedation cannot be used. Finally, the task effects are small, which may require long acquisition times to improve the signal-to-noise ratio of the measurement. We propose the method of localization of functional regions with spontaneous BOLD fluctuations as being able to overcome some of these problems (10).

SPONTANEOUS BOLD FLUCTUATION fMRI

Spontaneous BOLD fluctuations are fluctuations in neuronal activity that are correlated within distinct functional networks (10). This effect was first identified in a seminal paper by Biswal et al (11). For example, strong coherence is reproducibly present between the left and right somatomotor cortices (11–17), between language areas (12,18), and between numerous other functional regions

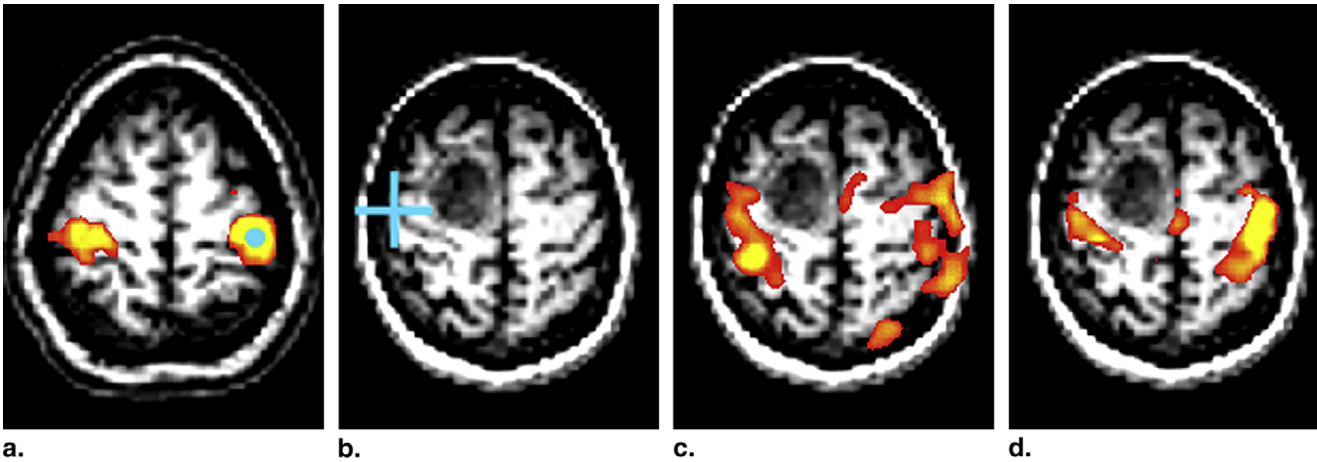


Figure 2. Resting-state correlation maps showing the distribution of the somatomotor network in a normal subject **(a)** after the selection of a seed region in the left somatomotor cortex *(blue circle)*. The correlation with the right somatomotor cortex is evident. **(b–d)** Images from a 58-year-old woman with a diagnosis of glioblastoma multiforme (GBM). Intraoperative cortical mapping **(b)** shows evoked hand responses with stimulation posterolateral to the tumor *(blue cross)*. Task-evoked activity with finger tapping in the tumor-affected motor cortex **(c)** shows a spatial distribution that approximates the resting-state map, although several other foci of activity are seen that encompass part of motor cortex as well as extending posteriorly to parts of the parietal cortex. Resting-state correlation map **(d)** after placement of a seed in the left somatomotor cortex (same coordinates as in **a**). The posteriorly displaced somatomotor cortex is seen, consistent with the cortical stimulation mapping and the task functional magnetic resonance imaging activity.

(Fig 1B), even in the absence of overt task performance. Using spontaneous activity, one can generate resting-state correlation maps that replicate the functional maps obtained from task activations.

The use of resting-state fMRI for the evaluation of spontaneous fluctuations in the BOLD signal has several benefits over traditional task-based fMRI. One important advantage of this method is that it can be performed even when the patient is unable to cooperate with the functional task. This will enable us to perform fMRI mapping on many populations previously excluded from traditional task-based techniques, such as young children, patients with cognitive impairments, and patients who are paralyzed, aphasic, or hard of hearing. Spontaneous fluctuations have been shown to persist under conditions of sleep (19,20) and different levels of anesthesia (21–23), so a second advantage of this technique is that is can be performed in agitated patients and in young children under sedation. A third advantage of this method is that one data acquisition can be used to study many different brain networks, thus possibly reducing the acquisition time when many systems are evaluated. This is in contrast to task activations, which require dedicated data acquisitions for each function one is attempting to localize. Preliminary data (24) indicate that this technique compares favorably to task-based fMRI, as illustrated in Figure 2.

In addition to the somatomotor and language networks previously discussed, additional networks that have been characterized using resting-state correlations from other seed regions include the visual system (12,16), auditory (12), episodic memory (25,26), default mode (27–30), and dorsal and ventral attention (30,31). Additionally, abnormalities of these networks could potentially be defined. Most relevant from a surgical standpoint are aberrant connections created by epilepsy (32). Networks associated with a seizure focus may aid in guiding surgical resection and improving seizure-free outcomes. When further automated, this method could potentially provide a comprehensive set of customized network localizations for each patient, thus substantially increasing the information available to neurosurgeons and potentially improving patient-centered care.

For the subject presented in Figure 2, seed-based correlation maps were generated by extracting the BOLD fMRI time course from a spherical seed region of interest (radius, 6 mm) and computing Pearson's correlation coefficient between this reference time course and the time course of every voxel in the brain. Resting-state maps in patients with tumors were obtained by placing seeds in morphologically normal cortical tissue when possible. For example, when evaluating the somatomotor system, the seed was placed in the hand motor area on the tumor-unaffected hemisphere on the basis of known coordinates established by prior fMRI activation studies or on an anatomic basis as determined by structural magnetic resonance imaging. In one of four patients with tumors, the coordinate of the seed in right sensorimotor cortex was determined empirically by shifting placement of the seed from the standardized coordinate until the normal spatial pattern of the sensorimotor network was seen.

In a separate study (24) focusing on the somatomotor system, we reported on our initial experience with this technique. The method compared well with intraoperative cortical stimulation mapping in a small number of subjects. Additionally, resting-state fMRI gave consistent results within individuals scanned multiple times. In comparison to task-based fMRI, resting-state analysis was more specific to the somatomotor cortex and showed less variability. These results are preliminary, based on a small number of patients, and focused on only the somatomotor system. Future studies are required to confirm these findings in larger cohorts and in other functional networks.

Resting-state fMRI demonstrated great promise in this initial study. However, several technical challenges need to be addressed in the postprocessing phase of analysis. We rely on atlas coordinates for the placement of our seed regions. Several networks, such as the language system, are known to be more variable across subjects compared to the somatomotor system (33). In addition, there are distortions in the brain configurations of patients with tumors that make the realignment task more difficult and hard to automate. We have partially solved these problems by masking out the tumor during this phase of the processing, but this was done by hand in the present study, and automated algorithms for this masking are needed. We are testing other methods to improve the realignment, such as nonlinear registration. Even with perfect alignment, a tumor may destroy functional tissue and lead to functional reorganization that makes seed-based characterization of resting-state networks difficult. This is less of a problem in bilateral networks, such as the somatomotor system, for which we can use the healthy undistorted side for localization, but it remains a challenge in unilateral systems, such as the language and dorsal attention system. Independent component analysis, which does not require the placement of a priori seed regions, stands out as a possible solution to this problem (21,24,34,35).

Other challenges relate to the routine use of this method in the operating room. Of central concern will be the speed and efficiency of implementation. Whether it be in the extraoperative or in the intraoperative setting (ie, intraoperative magnetic resonance imaging), this method of signal acquisition and analysis will need to occur in a time frame that makes its use feasible. Currently, the time of acquisition is reasonable, but analysis for the creation of functional images requires a dedicated researcher to perform the requisite processing to create useful image sets. This could not be practically done on a large scale. Further work will require a more automated version of analyses and image creation. This would allow for utilization to occur on a broader clinical scale (nontertiary medical centers) or in real time as neurosurgeons begin to incorporate intraoperative magnetic resonance imaging more frequently in their surgical management.

ASSESSING A NEW fMRI PARADIGM

When performing a technology assessment (36,37) of presurgical planning with spontaneous BOLD fluctuations, it is clear that it meets the criteria for technical performance, and preliminary data (24) indicate that it will at a minimum equal the diagnostic performance of current task-based fMRI methods. Only a small number of reports have addressed the issue of diagnostic and therapeutic impact of presurgical planning with fMRI. In one report (8), presurgical functional information from fMRI is mentioned in approximately 75% of patients' neurosurgery notes. It is not clear if fMRI provides a benefit beyond that obtainable from anatomy or intraoperative functional localization, and there is no evidence that its use results in better patient outcomes (survival or morbidity) or in an impact on patient health.

To date, functional imaging has played a valuable but largely ancillary role in the localization of eloquent cortex for neurosurgical procedures. It has been additive to the current gold-standard techniques, such as cortical stimulation and somatosensory evoked potentials. From a neurosurgical perspective, identification of zones essential for the implementation of a critical cognitive function, such as speech and motor movements, are what are sought with current electrophysiologic methods. A surgeon wishes to fundamentally know ''if this region is resected, can the patient still perform the given task?'' Task-based functional imaging to date has largely identified cortical regions that are associated with given cognitive functions. Thus, activated sites may not only be those essential to the commission of the task but also those that are secondarily associated with its performance (eg, attention, memory). These additional areas are essentially ''localization noise'' for finding cortex that is critical to preserve. Although it gives the surgeon improved awareness of where the critical zones are located, it does not provide more precise information on where the essential sites are. Beyond the current lack of precision, current imaging requires patient participation, which further limits the number of patients who can benefit from these modalities because of a number of different clinical factors ranging from age to functional impairment. These same factors also adversely restrict a surgeon's ability to perform classic neurophysiologic methods in the operating room. It is in this context of imaging imprecision and participation limitations that we have sought magnetic resonance imaging methods that can enhance essential site localization and expand to populations not currently amenable to standard techniques.

Potential future developments of this technique could provide valuable benefits but will require additional investigation and software development. In some complicated functional networks, such as the language network, intraoperative cortical stimulation is confined to the gyri. Resting-state correlation mapping offers information throughout the gray matter and may provide information on previously inaccessible areas, such as the intrasulcal language areas. Frameless stereotactic navigation is widely used by neurosurgeons to define brain anatomy in real time. An integration of this technique with our fMRI paradigm could allow surgeons to navigate the anatomy simultaneously with several functional networks of their choosing. This would provide significant flexibility in intraoperative decision making. Combined anatomic and functional information could also be obtained from intraoperative magnetic resonance imaging, providing a comprehensive picture of the shifts that occur in the brain during tumor resection surgery. Substantial progress will be needed in both computing hardware and software to realize this in real time for intraoperative evaluation. Finally, resting-state fMRI could also be used to monitor postoperative patient progress, such as evaluating the reconstitution or lack thereof of functional networks that were disrupted during surgery (38).

CONCLUSIONS

In this report, we present a new paradigm for the use of resting-state fMRI data in presurgical planning. This technique analyzes spontaneous fluctuations in the BOLD signal across the brain and is substantially different from routine task-based fMRI. BOLD fluctuations are correlated within neuroanatomically and functionally related areas of the brain and can help identify the location of critical functional networks, such as the somatomotor and language systems. This information can help guide the surgical approach. This method has substantial advantages over the traditional task-based techniques but also provides substantial challenges in postprocessing methods. One major advantage of the resting-state method is that it does not require cooperation from patients and can be conducted during sleep or under sedation, thus expanding the ability to obtain fMRI data in patients of all ages and all medical conditions. A second important advantage is that one data acquisition of clinically acceptable duration provides information on numerous different functional networks, thus saving time and increasing signal-to-noise ratio. Remaining postprocessing challenges include automating the atlas registration and localization of functionally reorganized systems. Ultimately, the utility of preoperative functional mapping to neurosurgical planning will need to be evaluated in terms of benefit for postoperative functional outcomes and survival.

ACKNOWLEDGMENT

The contents of this work are solely the responsibility of the authors and do not necessarily represent the official view of the National Center for Research Resources or the National Institutes of Health. We wish to thank Dr Raichle and Dr Snyder for their helpful comments and editing.

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