Resting-State Functional Magnetic Resonance Imaging: Review of Neurosurgical Applications

Stefan Lang, MD*

Niall Duncan, PhD‡§

Georg Northoff, MD, PhD‡

*Department of Neurosurgery, University of Calgary, Calgary, Alberta, Canada; ‡Mind, Brain Imaging, and Neuroethics Unit, Institute of Mental Health Research, University of Ottawa, Ottawa, Ontario, Canada; §Center for Cognition and Brain Disorders, Hangzhou Normal University, Hangzhou, China

Correspondence:
Stefan Lang, MD,
1200 6th St SW, Unit 2309,
Calgary, AB, T2R 1H3, Canada.
E-mail: stefan.t.lang@gmail.com

Received, September 4, 2013.
Accepted, January 20, 2014.
Published Online, January 31, 2014.

Copyright © 2014 by the
Congress of Neurological Surgeons.

Recent research in brain imaging has highlighted the role of different neural networks in the resting state (ie, no task) in which the brain displays spontaneous low-frequency neuronal oscillations. These can be indirectly measured with resting-state functional magnetic resonance imaging, and functional connectivity can be inferred as the spatiotemporal correlations of this signal. This technique has proliferated in recent years and has allowed the noninvasive investigation of large-scale, distributed functional networks. In this review, we give a brief overview of resting-state networks and examine the use of resting-state functional magnetic resonance imaging in neurosurgical contexts, specifically with respect to neurooncology, epilepsy surgery, and deep brain stimulation. We discuss the advantages and disadvantages compared with task-based functional magnetic resonance imaging, the limitations of resting-state functional magnetic resonance imaging, and the emerging directions of this relatively new technology.

KEY WORDS: fMRI, Neurosurgery

Neurosurgery 74:453–465, 2014 DOI: 10.1227/NEU.0000000000000307 www.neurosurgery-online.com

In the resting state (ie, no task), the brain displays spontaneous, low-frequency neuronal oscillations with spatiotemporal correlations that define large-scale, functionally connected networks. These resting-state networks (RSNs) can be measured indirectly with resting-state or task-free functional magnetic resonance imaging (fMRI). This technology allows noninvasive identification of the functional connectivity of tissue before surgery and therefore has the potential to be used for preoperative planning in neurosurgical patients. The current gold standard for mapping functional cortex is intraoperative direct electric stimulation. Although accurate, this technique has the obvious limitation of being invasive, and it does not give preoperative information for prognostic and surgical planning. To overcome these shortcomings, task-based fMRI has been used, but its use is limited to patients with the ability to participate in the experimental paradigm. Resting-state fMRI (rs-fMRI) has several advantages over task-based fMRI, the foremost amongst these being the lack of any patient participation and the simple standardization of the experimental protocol. This allows the technology to be used in patients with neurological deficits that preclude their participation in task-based paradigms. The objectives of this article are to review the concept of RSNs and to summarize recent experimental use of rs-fMRI in the areas of neurooncology, epilepsy surgery, and deep brain stimulation (DBS). Limitations and future directions of rs-fMRI in neurosurgery are also discussed.

ABBREVIATIONS: BOLD, blood oxygen level-dependent; **DBS,** deep brain stimulation; **ICA,** independent component analysis; **MTLE,** medial temporal lobe epilepsy; **ROI,** region of interest; **rs-fMRI,** resting-state functional magnetic resonance imaging; **RSN,** resting-state network

RESTING-STATE NETWORKS

Since the discovery of functional networks characterized by cross-correlation of spontaneous, low-frequency (<0.1 Hz) blood oxygen level-dependent (BOLD) fluctuations in the resting brain,[1] studies of these so-called RSNs have become widespread in the neuroimaging literature.[2-5] Resting-state studies are defined as those that involve some measure of brain function such as intraregional neuronal changes or interregional synchrony in conditions that do not include any explicit external stimulation.[6] A range of modalities can be used to study the

CME

SANS LifeLong Learning and NEUROSURGERY offer CME for subscribers that complete questions about featured articles. Questions are located on the SANS website (http://sans.cns.org/). Please read the featured article and then log into SANS for this educational offering.

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

intrinsic activity of the brain, including fMRI, positron emission tomography, electroencephalography, and magnetoencephalography. These studies have demonstrated reliable, large-scale, coherent networks that may improve our understanding of the brain in health and in disease.[7,8] RSNs reflect the functional connectivity between the different regions as distinguished from mere anatomo-structural connectivity.[9-13] The number and specific spatial pattern of distinct RSNs vary in the literature, but, importantly for neurosurgery, a sensorimotor network and various language networks have been consistently replicated (Figure). Deco et al[16] have suggested a broad theoretical framework whereby RSNs generate a constant state of exploration in which the brain generates predictions about the likely network configuration that would be optimal for a given impending input. This review focuses on rs-fMRI because it has been the most common modality for resting-state studies in the context of neurosurgical applications. Other modalities are mentioned when relevant. A more general review of rs-fMRI is provided elsewhere.[17-19]

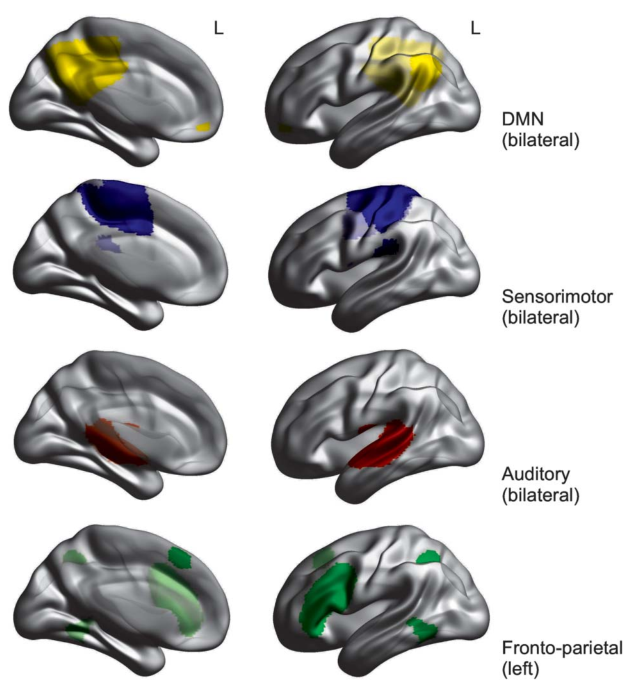

FIGURE. *Example resting-state networks with a high relevance for surgical planning. From top to bottom, these are the default mode network (DMN), the sensorimotor network, the auditory network, and the left frontoparietal network. The last 2 networks are of high relevance to language function. Networks were produced with MELODIC group independent component analysis[14] using temporally concatenated resting-state data from a group of 18 healthy participants (reported by Duncan et al[15]). Networks were thresholded at z = 4 and displayed on a Montreal Neurological Institute standard space brain template.*

rs-fMRI VS TASK-BASED fMRI

Classically, the application of fMRI in neurosurgery has depended on the subject's ability to perform a specific task. This so-called task-based fMRI has been used preoperatively to locate regions of eloquent cortex such as primary motor cortex,[20,21] supplementary motor cortex,[22] and language regions.[23-25] There are several obstacles to the widespread implementation of task-based fMRI in presurgical planning. Subjects must be able to perform the task appropriately, which can be difficult in patients with neurological deficits. In addition, many trials of the task may be necessary to achieve the desired activation maps, and this can result in long scanning times. Another limitation with task-based fMRI is that different tasks need to be used to assess for different functions (ie, motor and language). rs-fMRI can overcome these limitations by having no requirements for the subject during scanning. Subjects are often instructed to lie quietly in the scanner with their eyes closed, and the scanning period can be as short as 5 minutes. Importantly, different functional networks can be assessed in the same data set by the use of different analytical techniques. Resting-state neuroimaging thus offers several advantages to classic task-based approaches when considering its application to neurosurgical contexts (Table 1).

PROCESSING OF rs-fMRI DATA

Functional MRI uses changes in the BOLD signal to construct a 4-dimensional time series of the brain that reflects changing neuronal activity. Initially, the raw data are subjected to a series of preprocessing steps that typically include slice-time correction, regression of head motion, spatial smoothing, and band-pass filtering. Regression of the signal time course for regions of interest (ROIs) located in the white matter and ventricles is done because

TABLE 1. Advantages and Disadvantages of Resting-State vs Task-Based Functional Magnetic Resonance Imaging in Neurosurgery[a]

Advantages of r-fMRI	Can be used in patients with neurological deficits that preclude participation in task-based fMRI
	Multiple functional networks can be derived from the same data set
	Easy experimental design with minimal demands on clinician and patient
	Less time required for scanning
Disadvantages of rs-fMRI	Test-retest reliability may be lower in the identification of RSNs
	Functional significance of resting-state measures is unclear
	ROI analysis may be confounded by pathology

[a]fMRI, functional magnetic resonance imaging; ROI, region of interest; rs-fMRI, resting-state functional magnetic resonance imaging; RSN, resting state networks.

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

these areas are thought to contain noise pertaining to respiratory and cardiac fluctuations.[26,27] When comparing across subjects, normalization to a standard brain space is performed. Some of these steps, particularly head motion correction and global signal regression, are controversial.[28-30] There are many ways of statistically analyzing the data, and a full discussion is beyond the scope of this review.[31,32] The main approaches can be categorized into those that target connections between regions and those that target connections within a region. Two popular methods of targeting connections between regions include hypothesis-driven seed-based analysis and data-driven independent component analysis (ICA). The seed-based approach uses an extracted BOLD time course from an ROI (defined a priori) and determines the temporal correlation between this signal and the time course from all other brain voxels.[1,33,34] In this way, a whole-brain voxel-wise functional connectivity map of covariance with the seed region is created. When it is not feasible to define a region to correlate a priori, data-driven methods can be used. The most widely used is ICA, which is a mathematical technique that decomposes the fMRI data set into independent components, each of which represents a distinct spatial map that is associated with the time course of the source signal.[35] ICA also can separate noise into distinct components, which obviates the need for regressing out these signals during preprocessing. Other methods for determining or analyzing RSNs include graph theory,[5,36] multivariate pattern analysis,[37] and clustering analysis.[38] As mentioned, some analytic techniques are measures of local connectivity. These include the amplitude of low-frequency fluctuations, defined as the total power within a specific frequency range (0.01-0.1 Hz),[39] fractional amplitude of low-frequency fluctuations,[40] and regional homogeneity, which is a measure of functional coherence of a given voxel with its nearest neighbors.[41]

NEUROSURGICAL APPLICATIONS OF rs-fMRI

rs-fMRI and Neurooncology

Clinical applications of fMRI in neurooncology have focused on localizing areas of critical function before surgery using task-based methodologies.[42] Although this approach has proven useful and has shown good correspondence with intraoperative electrophysiology for motor areas[43,44] and Wada testing for language lateralization,[45-47] several disadvantages limit its application. The first reported evidence that functional networks can be mapped with rs-fMRI (Table 2) in patients with brain lesions came from Quigley et al.[52] Using seed regions based on activation maps from a task-based experiment, they reported that patterns of functional connectivity remain intact in patients with focal cerebral lesions. This finding was repeated in 2009, when Shimony et al[53] reported that several key functional networks could be identified in patients with brain tumors using rs-fMRI. They followed this study with another that provided evidence that sensorimotor cortex could be reliably delineated with rs-fMRI and that this localization showed good correspondence with cortical stimulation mapping.[49] In 6 patients with brain tumors or epileptic foci near the motor cortex, Liu et al[51] demonstrated that rs-fMRI can differentiate between hand and tongue motor regions. In the 1 patient they tested, results from rs-fMRI functional connectivity analysis were consistent with those from intraoperative cortical stimulation. Using functional connectivity analysis of rs-fMRI data, Otten et al[48] provided evidence that this technique has potential to be used as a prognostic indicator in patients with intra-axial lesions close to eloquent cortex. Specifically, they found differences in functional connectivity in motor networks between patients who had motor weakness and those who did not, suggesting that gross motor function is related to the level of functional connectivity in the sensorimotor network, as revealed by rs-fMRI. They also found that motor performance, measured by performance on the grooved pegboard, was related to functional connectivity in this network. Functional connectivity analysis of magnetoencephalography resting-state data also showed the potential for resting-state neuroimaging to be used in surgical planning and as a prognostic indicator for patients with lesions in or close to eloquent cortex.[54,55] Although the majority of studies looking at RSNs in patients with brain lesions used some form of ROI analysis, Kokkonen et al[50] also showed that using ICA may be feasible for locating sensorimotor networks in neurosurgical populations. There is also early evidence that resting-state neuroimaging can be used to localize language networks in individual subjects and that there is potential to have this process automated.[56] The significance of using rs-fMRI for neuro-oncological applications is not completely clear. However, it is reasonable to suggest that functional connectivity analysis of rs-fMRI may be used preoperatively to localize areas of eloquent cortex, to provide prognostic information by suggesting the degree of morbidity resulting from removal of specific areas of brain tissue, and to inform the surgeon of safe maximal resection boundaries.

rs-fMRI and Epilepsy Surgery

Multiple studies have shown abnormalities in RSNs in patients with epileptic disorders, including medial temporal lobe epilepsy (MTLE),[57-60] idiopathic generalized epilepsy,[61,62] and absence epilepsy.[63,64] For example, Doucet et al[59] found that patients with MTLE may have impaired functional connectivity in a bilateral extratemporal network and that this may be linked to the performance and brain organization of the episodic memory network. Given the evidence linking epileptic disorders to RSNs, it is not surprising that rs-fMRI analysis has the potential to aid in both presurgical planning and prognostication (Table 3). Building on previous work showing abnormalities in basal functional connectivity in epileptogenic networks,[58] Bettus et al[66] have suggested that the presence of basal functional connectivity increases in the nonepileptogenic side could be used as a marker for epileptogenic zone localization in the presurgical assessment of MTLE. Specifically, they showed that this measure had a sensitivity of 64% and a specificity of 91% for localizing the

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

TABLE 2. Review of Studies Using Resting State Functional Magnetic Resonance Imaging for Neurooncological Applications[a]

Reference	Subjects	Method	Analysis	Finding	Clinical Relevance
Otten et al[48]	22 adult, right-handed patients with intra-axial lesions, 22 sex- and handedness-matched control subjects from 1000 Functional Connectomes database	rs-fMRI	Seed approach with hand-motor knobs in primary motor cortex	Control subjects: motor network functional connectivity was observed in PMC, SMA, PMA, and SPL lateralizing to the left. Patients without weakness were similar to control subjects. Patients with motor weakness showed diminished functional connectivity of interhemispheric connections in the motor network. Performance on a grooved pegboard was correlated with connectivity	Motor networks in patients with brain tumors are demonstrable using rs-fMRI and show differences in functional connectivity between patients with and without motor weakness. These networks predict motor performance
Zhang et al[49]	17 healthy control subjects, 4 patients with brain tumors	rs-fMRI, task-based fMRI (block design finger tapping), intraoperative cortical stimulation	Seed-based approach using an ROI in the hand region of sensorimotor cortex. (One patient had to have this ROI adjusted by shifting it until the normal spatial pattern of the sensorimotor network was seen.) ICA also used	Sensorimotor cortex networks in healthy subjects were consistent on an individual basis. Displacement and disruption of sensorimotor network were seen in patients with brain tumors. The resting-state functional mapping in patients showed localization to sensorimotor networks consistent with cortical stimulation mapping. Resting-state measures performed as well as or better than task-based fMRI	Functional localization of eloquent cortex in patients with brain tumors can be assessed noninvasively by rs-fMRI measures
Kokkonen et al[50]	8 patients with brain tumors, 10 healthy subjects	Task-based and rs-fMRI	ICA	The spatial correlation between the task-based– and resting-state–derived sensorimotor networks was 0.27 in the cases, and 0.33 in the controls. This was not significantly different. A main difference was that the task recruited the SMA and cerebellum into the sensorimotor network, whereas the resting state did not	ICA has potential to localize sensorimotor networks in patients with brain tumors. This may provide a complementary method for patients who have difficulty performing motor tasks. In addition, the effect of high-grade gliomas may be more extensive than that of benign lesions

(Continues)

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

TABLE 2. *Continued*

Reference	Subjects	Method	Analysis	Finding	Clinical Relevance
Liu et al[51]	6 epileptic patients with tumors or epileptic foci near the motor cortex	Task-based and resting-state fMRI, with 1 patient also undergoing intraoperative cortical stimulation	Anatomic based-seed regions in the hand and tongue regions of healthy motor cortex	The hand motor regions identified by functional connectivity analysis were quite similar to those identified during the task-based analysis. rs-fMRI can differentiate between hand and tongue motor regions. Results from rs-fMRI functional connectivity analysis were consistent with intraoperative cortical stimulation	rs-fMRI may be able to map functional anatomy in patients with epilepsy and brain tumors for use in presurgical planning
Quigley et al[52]	12 patients with focal cerebral lesions	Task-based and rs-fMRI	Seed-based analysis with the ROI selected on the basis of activated voxels in the task paradigm	On average, there was a 40% concurrence between functional networks identified with the task-based paradigm and with rs-fMRI	rs-fMRI has potential to identify a variety of functional networks in patients with a variety of brain lesions

[a]fMRI, functional magnetic resonance imaging; ICA, independent component analysis; PMA, Pre-motor area; PMC, primary motor cortex; ROI, region of interest; rs-fMRI, resting-state functional magnetic resonance imaging; SMA, supplementary motor area; SPL, superior parietal lobe.

epileptogenic zone. Using a different evaluation of local and remote functional connectivity, Stufflebeam et al[68] suggested that rs-fMRI may provide a noninvasive method of localizing epileptic discharges in patients with refractory epilepsy. Interestingly, they found that the loci of disrupted functional connectivity fell within a 5-mm radius of the intraoperative electroencephalography electrodes. Morgan et al[69] used rs-fMRI to identify a region in the ventral lateral nucleus of the thalamus in which connectivity to the hippocampus separated left from right temporal lobe epilepsy patients. Recently, Weaver et al[70] used regional homogeneity analysis of rs-fMRI data in 4 patients with nonlesional focal epilepsy to test the hypothesis that this measure of local connectivity may be used to differentiate epileptogenic zones from normal brain tissue. They showed that local connectivity in the epileptogenic zone was significantly reduced in 3 of the 4 nonlesional focal patients. These early data suggest that regional homogeneity may be used to aid in delimiting the seizure onset zone, which may be particularly important for patients who otherwise have no macroscopic structural abnormalities that can be used to guide surgical planning.

In addition to providing a tool for the localization of epileptogenic zones, resting-state measures have been shown to have the potential to provide an indicator of surgical morbidity in epilepsy surgery. Negishi et al[67] took 18 patients with a wide range of seizure types and epileptogenic locations and found that a specific measure of functional connectivity could differentiate patients who had recurrent seizures postoperatively. Specifically, they found that the laterality indexes (normalized difference between functional connectivity in ipsilateral hemisphere and that of contralateral hemisphere) of the seizure recurrence group were lower than in the seizure-free group using a spike-correlated seed-based approach. This suggests that the laterality of functional connectivity has potential to be used as a predictor of surgical outcome, along with more traditional measures such as febrile seizures, mesial temporal lobe sclerosis, tumors, abnormal MRI, and electroencephalography/MRI correspondence.[71] Another study showed that connectivity in the default mode network may also predict the degree of cognitive impairment after surgery in patients with MTLE.[65] In patients with left MTLE, higher presurgical connectivity between the posterior cingulate cortex and left hippocampus was correlated with greater verbal memory decline after resection of the left temporal lobe, whereas higher connectivity between the posterior cingulate cortex and contralateral hippocampus was associated with less or no postsurgical decline. This same pattern was seen in patients with right MTLE with respect to nonverbal memory.

rs-fMRI and DBS

Resting-state techniques will likely have a large impact on the area of functional neurosurgery, both as a research tool and as a way to optimize surgical outcomes in DBS. One of the biggest challenges that has limited the amount of research done with resting-state fMRI in the investigation of DBS is the safety issue regarding the use of MRI in patients with chronically implanted

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

TABLE 3. Studies Using Resting-State Functional Magnetic Resonance Imaging in Epilepsy Surgery[a]

Reference	Subjects	Method	Analysis	Finding	Clinical Relevance
McCormick et al[65]	20 patients with right MTLE, 20 with left MTLE, 19 healthy control subjects; 9 with left MTLE and 8 with right MTLE underwent epilepsy surgery and were evaluated preoperatively and postoperatively	rs-fMRI	Seed-based approach using PCC and 19 other ROIs based on the DMN and graph analytic analysis	Connectivity between PCC and rHC correlated with nonverbal memory, and PCC-lHC correlated with verbal memory. Connectivity between PCC and epileptogenic HC in MTLE patients correlated with functional decline postoperatively, and PCC-contralateral HC connectivity correlated with less or no postsurgical decline	Connectivity in the DMN may reflect behavioral capacities and has potential to be a biomarker for surgical outcomes in MTLE
Bettus et al[66]	22 patients with MTLE, 36 healthy sex-matched control subjects	rs-fMRI	10 ROIs (Amy, EC, Ant Hip, Post Hip, temporal pole bilaterally) usually involved in epileptogenic networks of MTLE were analyzed	BFC was defined as the normalized correlation coefficients between pairs of ROI signal time courses. BFC decreases were found bilaterally, although the number of decreased links was higher on the epileptogenic side in patients. BFC increases were found almost exclusively in the contralateral lobe, showing a strong test effect for locating the nonepileptogenic lobe	The presence of basal functional connectivity increases in the nonepileptogenic side could be used as a marker for epileptogenic zone localization in the presurgical assessment of MTLE
Negishi et al[67]	18 epilepsy patients with a wide range of seizure types and epileptogenic locations, 14 healthy sex-matched control subjects	Resting EEG and fMRI	Seed-based approach using spike-correlated fMRI and seeds derived from the difference in postsurgical and presurgical anatomic MRIs	Laterality indexes (normalized difference between functional connectivity in ipsilateral hemisphere and that of contralateral hemisphere) of the seizure recurrence group were lower than for the seizure-free group using the spike-correlated seed-based approach	Laterality of functional connectivity has potential to be used as a predictor of surgical outcome
Stufflebeam et al[68]	6 patients with epilepsy, 300 healthy control subjects from an existing functional connectivity database	rs-fMRI and iEEG monitoring	Voxel-wise whole-brain correlation analysis in which the time course of each voxel was correlated with every other voxel at the local (in a 3-mm sphere) and remote (outside of a 25-mm sphere) levels	Statistically significant differences in functional connectivity maps of 5 of the 6 patients were found. These differences fell within a 5-mm radius of the iEEG electrodes. No significant abnormality was seen in 1 patient, despite ictal activity identified by iEEG	rs-fMRI data and the specific method of determining local and remote functional connectivity on a whole-brain level may provide a noninvasive method of localizing epileptic discharges in patients with refractory epilepsy

(Continues)

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

TABLE 3. *Continued*

Reference	Subjects	Method	Analysis	Finding	Clinical Relevance
Morgan et al[69]	21 patients with temporal lobe epilepsy (seizure-free group: 7 with left TLE and 7 with right TLE; seizure-recurrence group: 5 with left TLE and 2 with right TLE), 15 healthy control subjects	rs-fMRI	Seed-based using rHC and lHC ROI	The degree of functional connectivity between the ventral lateral nucleus of the right thalamus and the rHC was significantly greater in seizure patients with left TLE than in patients with right TLE. Connectivity values of the seizure recurrence group in this network were more variable, although small subject numbers precluded formal statistics	The quantification of rs-fMRI connectivity in the network identified may be used as a noninvasive indicator of lateralization of TLE and can complement other presurgical MRI assessments
Weaver et al[70]	4 nonlesional focal epilepsy patients who had unknown pathology, 4 sex- and age-matched control subjects selected in specific reference to each of the subjects from the 1000 Connectomes database	rs-fMRI	ReHo analysis comparing ROIs containing seizure focus with control ROIs	The ROI containing the seizure focus for ¾ of the epileptic patients showed low levels of local connectivity as measured by ReHo	ReHo may be used to localize epileptogenic zones in patients with focal epilepsy. This may be particularly important for patients with focal epilepsy who have otherwise no macroscopic structural abnormalities that can be used to guide surgical planning

[a]Amy, amygdala; Ant Hip, anterior hippocampus; BFC, basal functional connectivity; DMN, default mode network; EC, entorhinal cortex; EEG, electroencephalogram; iEEG, intraoperative electroencephalogram; fMRI, functional magnetic resonance imaging; lHC, left hippocampus; MTLE, medial temporal lobe epilepsy; PCC, posterior cingulate cortex; ReHo, regional homogeneity; rHC, right hippocampus; ROI, region of interest; rs-fMRI, resting-state functional magnetic resonance imaging; TLE, temporal lobe epilepsy.

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

TABLE 4. Studies Using Resting-State Functional Magnetic Resonance Imaging With Applications Relevant to Deep Brain Stimulation[a]

Reference	Subjects	Method	Analysis	Finding	Clinical Relevance
Brunenberg et al[79]	12 healthy adults	rs-fMRI	Seed-based approach using the STN	Significant functional connectivity between STN and subcortical structures (thalamus, caudate, putamen, midbrain), as well as cortical structures (PMA, SMA, MFG, cingulated gyrus, STG, PHG, FFG). Functional connectivity was related to measures of structural connectivity. Structural and functional connectivity to motor areas in the STN showed a mediolateral gradient. This study also found evidence of the hyperdirect pathway	Provides evidence that the connectivity of the STN can be assessed noninvasively. Analysis showed functional segregation between different areas of the STN, suggesting that the optimal therapeutic target can be assessed preoperatively. Hyperdirect pathway could be used in electrophysiological studies to target STN motor parts during DBS surgery
Anderson et al[78]	58 healthy adult and adolescent subjects plus an additional healthy adult scanned for a total of 3 h	rs-fMRI	Seed-based approach with ROIs including PMC and bilateral superior cerebellum (from atlas and finger tapping task)	Group correlation results between the thalamus and the 2 ROIs showed a cylindrical volume corresponding to the expected location of the VIM, within a 5-mm distance from the coordinates used for thalamic DBS based on anatomic landmarks. Nearly identical results were obtained in the single subject after a minimum of 3 h of scanning time	Functional connectivity measurements have the potential to be used for individualized targeting of DBS electrode placement in essential tremor. This technique may be more suited to taking into account individual variations in thalamic nuclei locations over standard anatomic landmarks

[a]DBS, deep brain stimulation; FFG, fusiform gyrus; MFG, medial frontal gyrus; PHG, para-hippocampal gyrus; PMA, primary motor area; PMC, primary motor cortex; ROI, region of interest; rs-fMRI, resting-state functional magnetic resonance imaging; SMA, supplementary motor area; STG, superior temporal gyrus; STN, subthalamic nucleus; VIM, ventro-intermediate nucleus.

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

electrodes. However, a recent large case series suggests that the use of MRI in patients with chronically implanted electrodes can be safe with strict safety measures.[72] Many neurological and neuropsychiatric diseases are being characterized by dysfunction of large-scale networks,[8,73-75] and DBS can be used as a tool for probing and modulating specific circuits.[76] rs-fMRI can be used in this context to investigate dysfunctional circuits, thus providing information for novel DBS targets. Functional connectivity analysis may have a role in following treatment response,[77] as demonstrated by positron emission tomography, and in individualizing electrode placement.[78] Brunenberg and colleagues[79] (Table 4) used rs-fMRI, in combination with diffusion tensor imaging, to noninvasively map out the structural and functional connectivity of the subthalamic nucleus, providing evidence of the hyperdirect pathways and confirming the functional segregation of the subthalamic nucleus in humans. Functional segregation of the human cingulate cortex has been confirmed with rs-fMRI,[80] and the structural and functional connectivity of human thalamocortical circuits has been investigated with the combination of diffusion tensor imaging and rs-fMRI.[81] These provide excellent examples of how resting-state neuroimaging can be used to map out functional connectivity of important brain areas targeted by neurosurgeons for DBS. An early example of using resting-state neuroimaging to track the neural and clinical response to DBS comes from a recent study of 5 patients with electrodes implanted in the fornix for Alzheimer disease.[77] Using serial [^{18}F]-2-deoxy-2-fluoro-D-glucose positron emission tomography scans, the authors showed increased functional connectivity in networks associated with memory and cognition after 1 year of DBS treatment. It is interesting to note that 1 of the ROIs used in this analysis was the precuneus, which is commonly associated with the default mode network. A case study of 1 patient undergoing chronic pedunculopontine nucleus stimulation for gait dysfunction in the context of Parkinson disease showed a normalization of pathological connectivity between the pedunculopontine nucleus and cerebellum.[82] Structural connectivity was assessed with a diffusion tensor imaging analysis technique known as probabilistic tractography, which calculates the likelihood of white matter connectivity between selected voxels.[83] This result suggests that changes in functional connectivity may also be expected with long-term stimulation of pathological circuits. Further research into the long-term effects of DBS on dysfunctional circuitry with rs-fMRI will likely yield important insight into the pathophysiology of many neuropsychiatric disorders and into the mechanism through which DBS exerts its efficacious effects.

LIMITATIONS AND CHALLENGES OF RESTING-STATE NEUROIMAGING IN NEUROSURGERY

Despite the promise offered by the increasing use of resting-state neuroimaging for neurosurgical applications, there are significant limitations that must be taken into consideration. The largest issue thus far has been the small sample sizes and the lack of standardization used in the above-mentioned studies. With respect to fMRI technology, one of the biggest limitations is the current lack of understanding of how changes in baseline physiological parameters, pharmacological interventions, or disease-related vascular changes affect the BOLD signal (for a review, see the work by Lindauer et al[84]). Of particular relevance to neurooncology, it is known that increased intracranial pressure has a strong influence on cerebrovascular dynamics,[85] and the influence of increased intracranial pressure on the BOLD signal has not yet been directly studied. Fuchtemeier et al[86] found that increased intracranial pressure in a rat model led to decoupling of the neurovascular response, specifically with a decrease and eventual reverse in the normal stimulus-induced deoxyhemoglobin response in somatosensory cortex. Schreiber et al[87] found that a glial tumor reduced the ipsilateral BOLD activity, whereas a nonglial tumor did not cause a significant change. Changes in baseline blood flow[88] and blood oxygenation[89] have also been implicated in decoupling of the neurovascular response. It is possible that impaired vascular reactivity resulting from aging, vascular dementia, and Alzheimer disease may change cerebral blood flow responses and alter blood oxygenation changes without affecting neuronal activation. Interestingly, Leithner et al[90] found that cyclooxygenase-2 inhibitors had an effect on cerebral blood flow response during functional activation. Other common pharmacological agents that can act as confounding variables during rs-fMRI are caffeine,[91-93] nicotine,[94,95] and propofol.[96] For an overview of other potential procedural and participant related confounds for neuroimaging of the resting state, see the work by Duncan and Northoff.[6] Another potentially significant issue with using rs-fMRI for neurosurgical applications arises from the current methods used to analyze the data. Seed-based approaches have the significant limitation of being based on an a priori ROI. Some patients will have mass-distorting lesions that make the use of atlas-derived ROIs difficult. Other patients may have undergone lesion-induced functional reorganization of cortical architecture, which will also affect proper ROI identification.[97,98] To overcome this limitation, some authors have suggested using data-driven approaches such as ICA.[50,56] Although this approach has yielded some promising data, ICA has its own limitations. Foremost among these is that visual identification is often used to determine specific functional networks of interest, which may introduce variability and uncertainty with respect to which network is actually being chosen. De Martino et al[99] have proposed an automatic determination of component content based on expected spatial activation or by filtering the components based on expected frequency characteristics (ie, between 0.1 and 0.01 Hz), which may prove useful for clinical translation. Another issue relevant to resting-state neuroimaging in neurosurgery is the test-retest reliability of rs-fMRI in identifying functional networks on an individual level. Kristo et al[100] provide evidence that rs-fMRI may be less reliable that task-based fMRI with respect to

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

reproducing functional connectivity maps of the motor network. However, using a different approach, Mannfolk et al[101] found that resting-state measures and task-based measures had comparable test-retest reliability with respect to mapping the sensorimotor network of healthy individual subjects. Because the ability to identify RSNs accurately and reliably in individual subjects will be crucial to the translation of rs-fMRI to clinical practice, this is an area that demands further investigation.

FUTURE DIRECTIONS

As mentioned, it will be imperative to more fully understand how the diseased brain affects the BOLD signal and how this may affect our ability to study RSNs with fMRI. Validation of rs-fMRI with electrophysiological techniques such as intraoperative electroencephalography and local field potentials will strengthen the evidence toward using resting-state measures as a clinical tool in neurosurgery. Standardization of methodology will greatly help our ability to compare studies, and the development of simple, easily adoptable tools for analyzing RSNs will be essential for translation into clinical practice. An early step in this direction has been taken by Bottger et al,[102] who developed an interactive software tool for the exploration of functional connectivity. Tie et al[56] have also made a step in this direction by proposing a semiautomated language component identification procedure. A recent study by Mitchell et al[103] demonstrated that a novel neural network approach to rs-fMRI analysis could independently identify cortical networks in patients undergoing surgery either for epilepsy or for resection of a brain tumor. This study is interesting for not only overcoming an important limitation of ICA but also showing that rs-fMRI may be able to identify RSNs in patients with distorted anatomy and that the identified language and somatomotor networks show strong concordance with electrocortical stimulation. Combining measures of structural connectivity with functional connectivity,[70] integrating multiple measures of the resting state, and correlating these values with clinical variables such as pre-existing neurological deficits and postoperative outcomes may prove valuable for neurosurgical applications. Resting-state studies using methodologies such as magnetoencephalography, which is more suited to directly measuring neuronal activity, will likely also have an important impact on clinical neurosurgery.

CONCLUSION

It is our opinion that resting-state neuroimaging will complement current presurgical investigations and will likely provide important information on surgical planning and prognosis. Specifically, in neurooncology, rs-fMRI may be especially useful for patients with neurological deficits that preclude participation in task-based fMRI. In epilepsy surgery, rs-fMRI has shown promise as a tool for diagnosis and surgical planning and as a prognostic indicator. Finally, rs-fMRI has significant potential in the area of DBS. With the ability to noninvasively map out functional circuits and therefore gain insight into dysfunctional circuits, this technique can be useful in the search for appropriate surgical targets. rs-fMRI may also have a role in individualized target selection, providing a marker of treatment response, and giving insight into the mechanisms of DBS.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med.* 1995;34(4):537-541.
2. Raichle M, MacLeod A, Snyder A, Powers W, Gusnard D, Shulman G. A default mode of brain function. *Proc Natl Acad Sci U S A.* 2001;98(2):676-682.
3. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A.* 2003;100(1):253-258.
4. De Luca M, Beckmann C, De Stefano N, Matthews P, Smith S. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage*. 2006;29(4):1359-1367.
5. Power JD, Cohen AL, Nelson SM, et al. Functional network organization of the human brain. *Neuron*. 2011;72(4):665-678.
6. Duncan N, Northoff G. Overview of potential procedural and participant-related confounds for neuroimaging of the resting state. *J Psychiatry Neurosci.* 2013;38(2):84-96.
7. Raichle ME. A paradigm shift in functional brain imaging. *J Neurosci.* 2009;29(41):12729-12734.
8. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev.* 2009;33(3):279-296.
9. Van den Heuvel MP, Mandl RCW, Kahn RS, Hulshoff Pol HE. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Hum Brain Mapp.* 2009;30(10):3127-3141.
10. Hagmann P, Cammoun L, Gigandet X, et al. Mapping the structural core of human cerebral cortex. *PLoS Biol.* 2008;6(7):e159.
11. Honey CJ, Sporns O, Cammoun L, et al. Predicting human resting-state functional connectivity. *Proc Natl Acad Sci U S A.* 2009;106(6):2035-2040.
12. Skudlarski P, Jagannathan K, Calhoun VD, Hampson M, Skudlarska B, Pearlson G. Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. *Neuroimage*. 2008;43(3):554-561.
13. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex.* 2009;19(1):72-78.
14. Beckmann C, Smith S. Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging.* 2004;23(2):137-152.
15. Duncan N, Wiebking C, Tiret B, et al. Glutamate concentration in the medial prefrontal cortex predicts resting-state cortical-subcortical functional connectivity in humans. *PLos One.* 2013;8(4):e60312.
16. Deco G, Jirsa V, McIntosh A. Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat Rev Neurosci.* 2011;12(1):43-56.
17. Van den Heuvel M, Hulshoff Pol H. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol.* 2010;20(8):519-534.
18. Lee M, Smyser C, Shimony J. Resting-state fMRI: a review of methods and clinical applications. *AJNR Am J Neuroradiol.* 2013;34(10):1866-1872.
19. Rosazza C, Minati L. Resting-state brain networks: literature review and clinical applications. *Neurol Sci.* 2011;32(5):773-785.
20. Yousry T, Schmid U, Alkadhi H, et al. Localization of hand motor area to a knob on the precentral gyrus. *Brain*. 1997;120:141-157.
21. Lehericy S, Duffau H, Cornu P, et al. Correspondence between functional magnetic imaging somatotopy and individual brain anatomy of the central

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

region: comparison with intraoperative stimulation in patients with brain tumours. *J Neurosurg.* 2000;92:589-598.
22. Krainik A, Duffau H, Capelle L, Cornu P, Boch A, Mangin J. Role of the healthy hemisphere in recovery after resection of the supplementary motor area. *Neurology*. 2004;62(8):1323-1332.
23. FitzGerald D, Cosgrove G, Ronner S, et al. Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. *Am J Neuroradiol.* 1997;18(8):1529-1539.
24. Roux F, Boulanouar K, Lotterie J, Mejdoubi M, LeSage J, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery*. 2003;52(6):1335-1347.
25. Rutten G, Ramsey N, van Rijen P, Alpherts W, van Veelen C. FMRI determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. *Neuroimage*. 2002;17(1):447-460.
26. Dagli MS, Ingeholm JE, Haxby JV. Localization of cardiac-induced signal change in fMRI. *Neuroimage*. 1999;9(4):407-415.
27. Lund TE, Madsen KH, Sidaros K, et al. Non-white noise in fMRI: does modelling have an impact? *Neuroimage*. 2006;29(1):54-66.
28. Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage*. 2012;59(1):431-438.
29. Murphy K, Rasmus B, Handwerker D, Jones T, Bandettini P. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage*. 2009;44(3):893-905.
30. Chai X, Castanon A, Ongur D, Whitfield-Gabrieli S. Anticorrelations in resting state networks without global signal regression. *Neuroimage*. 2012;59(2):1420-1428.
31. Lindquist M. The statistical analysis of fMRI data. *Stat Sci.* 2008;23(4):439-464.
32. Margulies D, Bottger J, Long X, et al. Resting developments: a review of fMRI post-processing methodologies for spontaneous brain activity. *Magn Reson Mater Phy.* 2010;23(5-6):289-307.
33. Fox M, Synder A, Zacks J, Raichle M. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci U S A.* 2006;103(26):10046-10051.
34. Cordes D, Haughton VM, Arfanakis K, et al. Mapping functionally related areas of the brain with functional connectivity MR imaging. *AM J Neuroradiol.* 2000; 21(9):1636-1644.
35. Beckmann C, De Luca M, Delvin J, Smith S. Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci.* 2005;360(1457):1001-1013.
36. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci.* 2009;10(3):186-198.
37. Zeng LL, Shen H, Liu L, et al. Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain*. 2012;135(pt 5): 1498-1507.
38. van den Heuvel M, Mandl R, Hulshoff Pol H. Normalized cut group clustering of resting-state fMRI data. *PLoS One.* 2008;3(4):e2001.
39. Yang H, Long XY, Yang YH, et al. Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. *Neuroimage*. 2007; 36(1):144-152.
40. Zou QH, Zhu CZ, Yang Y, et al. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J Neurosci Methods.* 2008;172(1):137-141.
41. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. *Neuroimage*. 2004;22(1):394-400.
42. Rutten G, Ramsey N. The role of functional magnetic resonance imaging in brain surgery. *Neurosurg Focus.* 2010;28(2):1-14.
43. Roessler K, Donat M, Lanzenberger R, et al. Evaluation of preoperative high magnetic field motor functional MRI (3 Tesla) in glioma patients by navigated electrocortical stimulation and postoperative outcome. *J Neurol Neurosurg Psychiatry.* 2005;76(8):1152-1157.
44. Bizzi A, Blasi V, Falini A, et al. Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. *Radiology*. 2008;248(2):579-589.
45. Janecek JK, Swanson SJ, Sabsevitz DS, Hammeke TA, Rozman M, Binder JR. Language lateralization by fMRI and WADA testing in 229 epilepsy patients: rates and predictors of discordance. *Epilepsia*. 2013;54(2):314-322.
46. Dym RJ, Burns J, Freeman K, Lipton ML. Is functional MR imaging assessment of hemispheric language dominance as good as the Wada test? *Radiology*. 2011; 261(2):446-455.
47. Binder JR, Swanson SJ, Hammeke TA, et al. Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology*. 1996;46(4):978-984.
48. Otten M, Mikell C, Youngerman B, et al. Motor deficits correlate with resting state network connectivity in patients with brain tumours. *Brain*. 2012;135 (pt 4):1017-1026.
49. Zhang D, Johnston JM, Fox MD, et al. Preoperative sensorimotor mapping in brain tumor patients using spontaneous fluctuations in neuronal activity imaged with fMRI: Initial experience. *Neurosurgery*. 2009;65(suppl 6):226-236.
50. Kokkonen S, Nikkinen J, Remes J, et al. Preoperative localization of the sensorimotor area using independent component analysis of resting-state fMRI. *Mag Res Imag.* 2009;27(6):733-740.
51. Liu H, Buckner R, Talukdar T, Tanaka N, Madsen J, Stufflebeam S. Task-free presurgical mapping using functional magnetic resonance imaging intrinsic activity. *J Neurosurg.* 2009;111(4):746-754.
52. Quigley M, Cordes D, Wendt G, et al. Effect of focal and nonfocal cerebral lesions on functional connectivity studied with MR imaging. *Am J Neuroradiol.* 2001;22(2):294-300.
53. Shimony JS, Zhang D, Johnston JM, Fox MD, Roy A, Leuthardt EC. Resting-state spontaneous fluctuations in brain activity: a new paradigm for presurgical planning using fMRI. *Acad Radiol.* 2009;16(5):578-583.
54. Tarapore PE, Martino J, Guggisberg AG, et al. Magnetoencephalographic imaging of resting-state functional connectivity predicts postsurgical neurological outcome in brain gliomas. *Neurosurgery*. 2012;71(5):1012-1022.
55. Martino J, Honma SM, Findlay AM, et al. Resting functional connectivity in patients with brain tumors in eloquent areas. *Ann Neurol.* 2011;69(3):521-532.
56. Tie Y, Rigolo L, Norton IH, et al. Defining language networks from resting-state fMRI for surgical planning: a feasibility study. *Hum Brain Mapp.* 2014;35(4): 1018-1030.
57. Waites AB, Briellmann RS, Saling MM, Abbott DF, Jackson GD. Functional connectivity networks are disrupted in left temporal lobe epilepsy. *Ann Neurol.* 2006;59(2):335-343.
58. Bettus G, Guedj E, Joyeux F, et al. Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. *Hum Brain Mapp.* 2009;30(5):1580-1591.
59. Doucet G, Osipowicz K, Sharan A, Sperling M, Tracy J. Extratemporal functional connectivity impairments at rest are related to memory performance in mesial temporal epilepsy. *Hum Brain Mapp.* 2013;34(9):2202-2216.
60. Holmes M, Folley B, Sonmezturk H, et al. Resting state functional connectivity of the hippocampus associated with neurocognitive function in left temporal lobe epilepsy. *Hum Brain Mapp.* 2014;35(3):735-744.
61. Maneshi M, Moeller F, Fahoum F, Gotman J, Grova C. Resting state connectivity of the sustained attention network correlates with disease duration in idiopathic generalized epilepsy. *PLoS One*. 2012;7(12):e50359.
62. Kay B, DiFrancesco M, Privitera M, Gotman J, Holland S, Szaflarski J. Reduced default mode network connectivity in treatment-resistant idiopathic generalized epilepsy. *Epilepsia*. 2013;54(3):461-470.
63. Fang T, Fang F, Zhu H, Zhang G, Liu Z, Li Y. Functional connectivity changes in patients with absence epilepsy studied using resting-state functional MRI. *J Clin Neurosci.* 2013;20(3):413-418.
64. Luo C, Li Q, Lai Y, et al. Altered functional connectivity in default mode network in absence epilepsy: a resting state fMRI study. *Hum Brain Mapp.* 2011;32(3): 438-449.
65. McCormick C, Quraan M, Cohn M, Valiante T, McAndrews M. Default mode network connectivity indicates episodic memory capacity in mesial temporal lobe epilepsy. *Epilepsia*. 2013;54(5):809-818.
66. Bettus G, Bartolomei F, Confort-Gouny S, et al. Role of resting state functional connectivity MRI in presurgical investigation of mesial temporal lobe epilepsy. *J Neurol Neurosurg Psych.* 2010;81(10):1147-1154.
67. Negishi M, Martuzzi R, Novotny EJ, Spencer DD, Constable RT. Functional MRI connectivity as a predictor of the surgical outcome of epilepsy. *Epilepsia*. 2011;52(9):1733-1740.
68. Stufflebeam S, Liu H, Sepulcre J, Tanaka N, Buckner R, Madsen J. Localization of focal epileptic discharges using functional connectivity magnetic resonance imaging. *J Neurosurg.* 2011;114(6):1693-1697.
69. Morgan VL, Sonmezturk HH, Gore J, Abou-Khalil B. Lateralization of temporal lobe epilepsy using resting state functional magnetic resonance imaging connectivity of hippocampal networks. *Epilepsia*. 2012;53(9):1628-1635.

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

70. Weaver KE, Chaovalitwongse WA, Novotny EJ, Poliakov A, Grabowski TG, Ojemann JG. Local functional connectivity as a pre-surgical tool for seizure focus identification in non-lesion, focal epilepsy. *Front Neurol.* 2013;4(43): 1-14.
71. Tonini C, Beghi E, Berg AT, et al. Predictors of epilepsy surgery outcome: a meta-analysis. *Epilepsy Res.* 2004;62(1):75-87.
72. Zrinzo L, Yoshida F, Hariz MI, et al. Clinical safety of brain magnetic resonance imaging with implanted deep brain stimulation hardware: large case series and review of the literature. *World Neurosurg.* 2011;76(1-2):164-172.
73. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A.* 2004;101(13):4637-4642.
74. Zhang D, Raichle ME. Disease and the brain's dark energy. *Nat Rev Neurol.* 2010;6(1):15-28.
75. Poston KL, Eidelberg D. Functional brain networks and abnormal connectivity in the movement disorders. *Neuroimage*. 2012;62(4):2261-2270.
76. Lozano A, Lipsman N. Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron*. 2013;77(3):406-424.
77. Smith G, Laxton A, Tang-Wai D, et al. Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. *Arch Neurol.* 2012;69(9): 1141-1147.
78. Anderson J, Dhatt H, Ferguson M, et al. Functional connectivity targeting for deep brain stimulation in essential tremor. *Am J Neuroradiol.* 2011;32(10): 1963-1968.
79. Brunenberg E, Moeskops P, Backes W, et al. Structural and resting state functional connectivity of the subthalamic nucleus: identification of motor STN parts and the hyperdirect pathway. *PLoS One.* 2012;7(6):1-14.
80. Yu C, Zhou Y, Liu Y, et al. Functional segregation of the human cingulate cortex is confirmed by functional connectivity based neuroanatomical parcellation. *Neuroimage*. 2011;54(4):2571-2581.
81. Zhang D, Snyder AZ, Shimony JS, Fox MD, Raichle ME. Noninvasive functional and structural connectivity mapping of the human thalamocortical system. *Cereb Cortex.* 2010;20(5):1187-1194.
82. Schweder P, Joint C, Hansen P, Green A, Quaghebeur G, Aziz T. Chronic pedunculopontine nucleus stimulation restores functional connectivity. *Neuro-Report*. 2010;21(17):1065-1068.
83. Behrens E, Woolrich M, Jenkinson M, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med.* 2003;50(5): 1077-1088.
84. Lindauer U, Dirnagl U, Fuchtemeier M, et al. Pathopysiological interference with neurovascular coupling: when imaging based on hemoglobin might go blind. *Front Neuroenerg.* 2010;2(25):1-9.
85. Kety SS, Shenkin HA, Schmidt CF. The effects of increased intracranial pressure on cerebral circulatory functions in man. *J Clin Invest.* 1948;27(4): 493-499.
86. Fuchtemeier M, Leithner C, Offenhauser N, et al. Elevating intracranial pressure reverses the decrease in deoxygenated hemoglobin and abolishes the post-stimulus overshoot upon somatosensory activation in rats. *Neuroimage*. 2010;52 (2):445-454.
87. Schreiber A, Hubbe U, Ziyeh S, Hennig J. The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement. *Am J Neuroradiol.* 2000;21(6):1055-1063.
88. Huppert TJ, Allen MS, Diamond SG, Boas DA. Estimating cerebral oxygen metabolism from fMRI with a dynamic multi-compartment Windkessel model. *Hum Brain Mapp.* 2009;30(5):1548-1567.
89. Lindauer U, Gethmann J, Khl M, Kohl-Bareis M, Dirnagl U. Neuronal activity-induced changes of local cerebral microvascular blood oxygenation in the rat: effect of systemic hyperoxia or hypoxia. *Brain Res.* 2003;975(1-2):135-140.
90. Leithner C, Royl G, Offenhauser N, et al. Pharmacological uncoupling of activation induced increases in CBF and CMRO2. *J Cereb Blood Flow Metab.* 2010;30(2):311-322.
91. Liu TT, Liau J. Caffeine increases the linearity of the visual BOLD response. *Neuroimage*. 2011;49(3):2311.
92. Griffeth V, Perthen J, Buxton R. Prospects for quantitative fMRI: investigating effects of caffeine on baseline oxygen metabolism and the response to a visual stimulus in humans. *Neuroimage*. 2011;57(3):809-816.
93. Liu TT, Behzadi Y, Restom K, et al. Caffeine alters the temporal dynamics of the visual BOLD response. *Neuroimage*. 2004;23(4):1402-1413.
94. Brody AL. Functional brain imaging of tobacco use and nicotine dependence. *J Psychiatr Res.* 2006;40(5):404-418.
95. Tanabe J, Nyberg E, Martin LF, et al. Nicotine effects on default mode network during resting state. *Psychopharmacology*. 2011;216(2):287-295.
96. Boveroux P, Vanhaudenhuyse A, Bruno M, et al. Breakdown of within- and between-network resting state during propofol-induced loss of consciousness. *Anesthesiology*. 2010;113(5):1038-1053.
97. Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol.* 2005;4(8): 476-486.
98. Goldmann RE, Golby AJ. Atypical language representation in epilepsy: implications for injury-induced reorganization of brain function. *Epilepsy Behav.* 2005;6(4):473-487.
99. De Martino F, Gentile F, Esposito F, et al. Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers. *Neuroimage*. 2007;34(1):177-194.
100. Kristo G, Rutten G, Raemaekers M, Gelder B, Rombouts S, Ramsey N. Task and task-free fMRI reproducibility comparison for motor network identification. *Hum Brain Mapp.* 2011;35(1):340-352.
101. Mannfolk P, Nilsson M, Hansson H, et al. Can resting-state functional MRI serve as a complement to task-based mapping of sensorimotor function? A test-retest reliability study in healthy volunteers. *J Magn Reson Imaging.* 2011;34(3): 511-517.
102. Bottger J, Margulies D, Horn P, et al. A software tool for interactive exploration of intrinsic functional connectivity opens new perspective for brain surgery. *Acta Neurochir.* 2011;153(8):1561-1572.
103. Mitchell T, Hacker C, Breshears J, et al. A novel data driven approach to preoperative mapping of functional cortex using resting-state functional magnetic resonance imaging. *Neurosurgery*. 2013;73(6):969-983.

COMMENT

The present article reviews technical and practical aspects of the application of resting functional magnetic resonance imaging (r-fMRI) to neurosurgery. The authors are to be commended for the detailed way they have described the advantages and limitations of this technique. Neurosurgeons will likely wonder, Can this help me in the operating room? Will it help distinguish eloquent from noneloquent brain? r-fMRI has shown some promise in a number of preclinical settings, including distinguishing frontotemporal dementia from Alzheimer disease[1] and prediction of the outcome of coma after cardiac arrest.[2] These findings are preliminary, and there have been few attempts to use r-fMRI to guide surgical decision making. It should be emphasized that the short acquisition time (usually <10 minutes) and lack of complex task design are the features most attractive to clinicians; however, there is little agreement in the neuroimaging community about what the best approach to the acquired data is. Independent component analysis, amplitude of low-frequency fluctuations, seed-based, and graph techniques are all mentioned in the article as options, but it is not clear which would be best for neurosurgical applications. Mass lesions present a special problem for resting fMRI because it is usually dependent on registration to a standard brain. However, some recent attempts have been made to use both independent component analysis[3] and seed-based techniques[4] in anatomically abnormal brains.

Once a technique has been identified for identification of functional tissue with r-fMRI, a suitably designed clinical trial will need to be performed. Ideally, this trial would combine multiple techniques for mapping, including task-based fMRI, cortical stimulation mapping and "high gamma" mapping.[5] Some concordance has been previously described between cortical stimulation mapping and resting connectivity, as the authors point out. A recent publication in *Neurosurgery* describes an

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited

exciting candidate technique for data-driven r-fMRI analysis that should be tested in a larger trial.[6]

Neurosurgeons have always been at the cutting edge of technical developments in neuroscience research, and the authors are to be commended for bringing these advances to the readers of *Neurosurgery*. It is our hope that in the future r-fMRI can be used to maximize patient safety during tumor surgery.

Charles Mikell
Guy McKhann
New York, New York

1. Zhou J, Greicius MD, Gennatas ED, et al. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain*. 2010;133(pt 5):1352-1367.
2. Norton L, Hutchison RM, Young GB, Lee DH, Sharpe MD, Mirsattari SM. Disruptions of functional connectivity in the default mode network of comatose patients. *Neurology*. 2012;78(3):175-181.
3. Soddu A, Vanhaudenhuyse A, Bahri MA, et al. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. *Hum Brain Mapp*. 2012;33(4):778-796.
4. Otten ML, Mikell CB, Youngerman BE, et al. Motor deficits correlate with resting state motor network connectivity in patients with brain tumours. *Brain*. 2012;135 (pt 4):1017-1026.
5. Sinai A, Bowers CW, Crainiceanu CM, et al. Electrocorticographic high gamma activity versus electrical cortical stimulation mapping of naming. *Brain*. 2005;128 (pt 7):1556-1570.
6. Mitchell TJ, Hacker CD, Breshears JD, et al. A novel data-driven approach to preoperative mapping of functional cortex using resting-state functional magnetic resonance imaging. *Neurosurgery*. 2013;73(6):969-983.

CME Questions:

1. What is the main advantage of resting-state fMRI (rs-fMRI) over the traditional task-based fMRI?
   A. Rs-fMRI can be used in patients with neurological deficits that preclude participation in task-based fMRI.
   B. Region of interest in rs-fMRI is not confounded by pathology.
   C. Only a single functional network can be derived from the same data set.
   D. Institutional rs-fMRI protocols are well standardized.

2. Which MRI sequence is used to non-invasively assess the structural connectivity of the brain?
   A. FIESTA
   B. DTI
   C. FLAIR
   D. DWI
   E. T2

3. In the assessment of mesial temporal lobe epilepsy, what is the sensitivity of identifying increases in basal functional connectivity as a marker for epileptogenic zone localization?
   A. 50-60%
   B. 60-70%
   C. 70-80%
   D. 80-90%
   E. 90-100%

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited