Review

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Resting-State Blood Oxygen Level-Dependent Functional MRI: A Paradigm Shift in Preoperative Brain Mapping

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Abstract
Currently, functional magnetic resonance imaging (fMRI) facilitates a preoperative awareness of an association of an eloquent region with a tumor. This information gives the neurosurgeon helpful information that can aid in creating a surgical strategy. Typically, task-based fMRI has been employed to preoperatively localize speech and motor function. Task-based fMRI depends on the patient's ability to comply with the task paradigm, which often is impaired in the setting of a brain tumor. This problem is overcome by using resting-state fMRI (rs-fMRI) to localize function. rs-fMRI measures spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal, representing the brain's functional organization. In a neurosurgical context, it allows noninvasive simultaneous assessment of multiple large-scale distributed networks. Compared with task-related fMRI, rs-fMRI provides more comprehensive information on the functional architecture of the brain and is applicable in settings where task-related fMRI may provide inadequate information or could not be performed. Taken together, rs-fMRI substantially expands the preoperative mapping capability in efficiency, effectiveness, and scope. In this article, a brief introduction into rs-fMRI processing methods is followed by a detailed discussion on the role rs-fMRI plays in presurgical planning.

Introduction

An ongoing challenge in the surgical resection of gliomas is balancing the extent of resection with the preservation of eloquent function. This is especially notable in tumors that are in close proximity to the cortex and white matter connections associated with speech and motor function. In these situations, maximal resection around a tumor generally improves clinical outcomes with regard to survival [1–5]. The benefits of a larger resection, however, must be weighed against the cost of deficits incurred in areas of eloquent cortex, particularly in motor and language areas [5]. Because there is a high degree of individual variability in these areas, presurgical localization and intraoperative cortical mapping are often required to optimize this balance for the best clinical outcome.

In these specific clinical scenarios, functional magnetic resonance imaging (fMRI) has historically provided a supportive role in the preoperative assessment of these pa-

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tients. fMRI measures neuronal activity using the ratio of oxyhemoglobin to deoxyhemoglobin as a contrast mechanism (known as blood oxygen level-dependent, or BOLD, fMRI). In a typical block design application, the subject alternates between a passive resting state and performing a task. Clinical applications of task-based fMRI have commonly focused on identifying areas of activation associated with language and motor function for presurgical planning [6]. In comparative studies, these anatomic areas localized with task-based fMRI have been shown to approximate the functional sites identified with intraoperative electrophysiology [7], Wada testing [8], and prediction of loss of function postoperatively [9]. Despite its utility, task-based fMRI has several disadvantages that limit its application for preoperative functional localization. First, the results depend on the patient's ability to perform the proscribed task. In the setting of a brain tumor, claustrophobia, or baseline cognitive impairment, cooperation and effective participation may be limited due to neurological deficits, inability to hold still, or confusion [10]. Second, because the patient must be awake during the imaging procedure, sedation cannot be used. This often limits effective imaging in pediatric populations for whom conscious sedation or general anesthesia is frequently necessary. Finally, in the setting where multiple functional regions need to be identified, this can require lengthy imaging sessions, further making their acquisition more difficult.

An alternative to task-based fMRI is resting-state fMRI (rs-fMRI). This is an alternative imaging methodology for localizing critical sites independent of patient participation [11]. This approach uses the endogenous brain activity detectable with BOLD to identify areas that are interacting at rest. Spontaneous BOLD fluctuations are low-frequency (<0.1 Hz) oscillations in metabolic activity that are anatomically correlated within distinct functional networks [12]. First reported by Biswal et al. [13], there is strong and reproducible coherence between the left and right somatomotor cortices [13, 14], between language areas [15, 16], and between numerous other functional regions in the absence of task performance. Using spontaneous activity, one can generate resting-state correlation maps that are similar to the functional maps obtained from task activations [17]. This approach has a number of advantages. Most importantly, patient participation is not required. An additional advantage is that these methods are robust; spontaneous fluctuations have been shown to persist under conditions of sleep [16, 17] and anesthesia [18–20], as well as in the presence of tumors [11]. Thus resting state could potentially be widely applied irrespective of age and cognitive status.

In this review, we evaluate the use of rs-fMRI in the context of presurgical mapping. Data collected for this review were approved by the human research protection office at the Washington University School of Medicine, and informed written consent was obtained from each participant. Specifically, the items discussed will include the fundamental networks commonly identified and their functional associations, the analytic methods used to define functional topographies, and the clinical considerations of using these methodological approaches.

Resting-State Networks

The topographies of functionally connected regions across the brain are known as resting-state networks (RSNs; equivalently, intrinsic connectivity networks [21]). rs-fMRI scans are generally acquired while the subject is in a state of quiet wakefulness [12]. The importance of RSNs lies in the fact that their topography closely corresponds to responses elicited by a wide variety of sensory, motor, and cognitive tasks [17]. Intrinsic RSNs persist during sleep [22, 23] or even under sedation and general anesthesia [24]. The robustness of the spontaneous fluctuations during states of reduced consciousness and pharmacological suppression suggests that this intrinsic neuronal activity is fundamental in the maintenance of the brain's functional integrity [25]. Spontaneous BOLD activity has been detected in all mammalian species investigated thus far [26–28], further supporting the importance of this physiological phenomenon. Despite the ubiquitous presence of RSNs, the precise function of these endogenous RSNs remains incompletely understood.

Perhaps the most fundamental RSN is the default mode network (DMN; fig. 1a), first identified by a meta-analysis of task-based functional neuroimaging experiments performed with positron emission tomography [29, 30]. The defining property of the DMN is that it is more active at rest than during performance of goal-directed tasks. The DMN was first identified using rs-fMRI by Greicius et al. [31], a finding that has since been replicated many times using a variety of analysis methods [17, 32–38]. Some investigators have hypothesized that there are two large anticorrelated systems in the brain [39, 40], one anchored by the DMN and the other comprised of systems controlling executive and attentional mechanisms. This dichotomy has been variously referred to as 'task positive' versus 'task negative' [34, 38, 39, 41, 42] and 'intrinsic' versus 'extrinsic' [40, 43]. Although the nomenclature associated with the DMN remains controver-

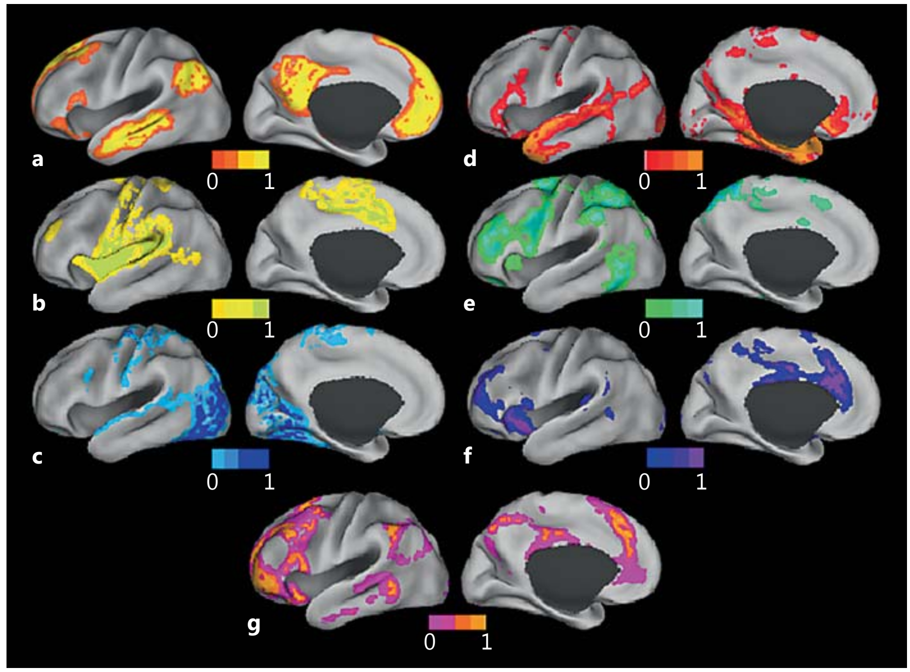

Fig. 1. Surface plots of RSNs as derived from a fuzzy c-means algorithm [38]. **a** DMN. **b** SMN. **c** Visual network. **d** Language network. **e** DAN. **f** VAN. **g** Frontoparietal control network.

sial [44, 45], the topography of the DMN is remarkably consistent across diverse analysis strategies.

Primary sensory and motor RSNs include the somatomotor network (SMN), first identified by Biswal et al. [13], which encompasses primary and higher-order motor and sensory areas (fig. 1b). The visual network (VIS) spans much of the occipital cortex (fig. 1c) [17, 32–35]. The auditory network includes Heschl's gyrus, the superior temporal gyrus, and the posterior insula [17]. The language network includes Broca's and Wernicke's areas but also extends to prefrontal, temporal, parietal, and subcortical regions (fig. 1d) [46–48].

RSNs involved in attentional and cognitive control include the dorsal attention network (DAN) and the ventral attention network (VAN) [21, 34, 35, 49, 50]. The DAN (fig. 1e) includes the intraparietal sulcus and the frontal eye field, and is recruited by tasks requiring control of spatial attention. The VAN (fig. 1f), which includes the temporoparietal junction and ventral-frontal cortex, is involved in the detection of environmentally salient events [49–51]. The frontoparietal control network (fig. 1g), which includes the lateral prefrontal cortex and the inferior parietal lobule, is associated with working memory and control of goal-directed behavior [52, 53]. Finally, the cingulo-opercular network, also known as the salience network [21] or the core control network [54], includes the medial superior frontal cortex, anterior insula, and anterior prefrontal cortex. The cingulo-opercular network is thought to enable the performance of tasks requiring executive control [34, 54, 55].

Overview of Processing Methods

From a neurosurgical perspective, it is important to have an understanding of the methods used in identifying RSNs because they can impact on the interpretation of cortical localization and also impact on the ease of implementation of this imagining in a given clinical environment. The approaches are generally categorized as *supervised* or *unsupervised* classification methods. Below, we present results obtained by two unsupervised methods: spatial independent component analysis (sICA) and c-means clustering, and two supervised methods: conventional seed-based correlation mapping and RSN mapping using a trained multilayer perceptron (MLP) classifier.

Seed-Based Correlation Mapping

Seed-based correlation mapping is one of the most widely adopted techniques for studying cofluctuations in intrinsic neuronal activity or functional connectivity [15, 56]. The high adoption rate of the seed-based approach is partly attributable to its simplicity of implementation, and to the ease with which the results can be interpreted.

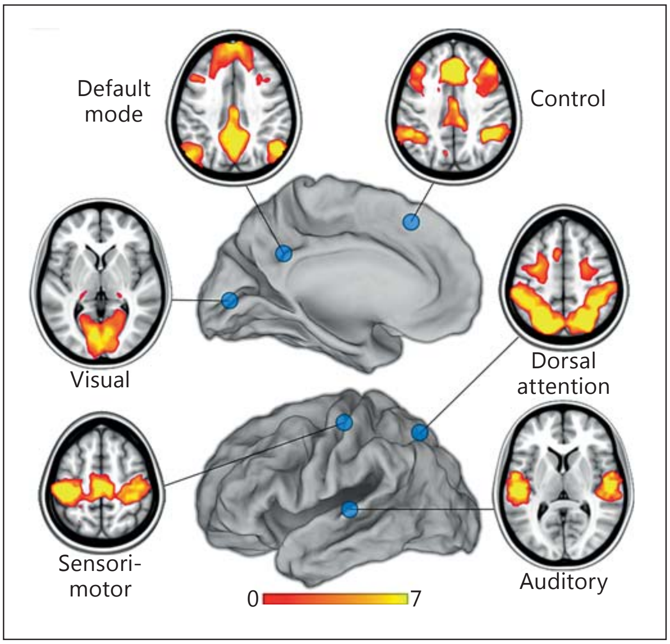

Fig. 2. Examples of multiple RSNs generated using a seed-based approach (blue dots in the figure) [59]. Six of the major networks are illustrated: visual, sensorimotor, auditory, default mode, dorsal attention, and frontoparietal executive control. The scale numbered 0–7 indicates the relative correlation strength.

Biswal et al. [13] used this method to first demonstrate the feasibility of using fMRI in detecting spatially distributed networks.

Pearson's product-moment correlation is the most widely used measure of functional connectivity [13, 15, 31, 39, 57, 58]. Seed-based analysis requires prior knowledge of the locations for regions of interest. They can be obtained from previously determined brain atlas coordinates or from task-based fMRI data. For instance, a simple behavioral motor paradigm may be used to generate data involving the motor network. A subject is asked to move their extremity and the BOLD data are analyzed. The MRI voxel with the strongest activation is used as a 'seed' region to then study the resting-state data. Once the seed region voxel coordinates have been identified, rs-BOLD measurements (over time) between the seed region and the rest of the brain are compared to generate a correlation map. An example of multiple RSNs derived using the seed-based approach is presented in figure 2 [59].

While holding substantial promise, these advanced techniques have not yet entered routine clinical practice due to the high level of technical support necessary to create these resting-state maps. The use of a seed-based approach can be biased by the selection of seed regions and is technically labor intensive. Often multiple regions are tested until the optimal network is identified. While this process is often successful in normal brains using standard atlas coordinates, it becomes more challenging in brains that are distorted due to disease (i.e. brain tumors).

Independent Component Analysis

Unsupervised data-driven approaches are of interest to researchers looking to analyze resting-state data without a priori assumptions. sICA is the most widely used data-driven approach to analyze resting-state data [60–63]. sICA decomposes rs-fMRI data (time × space) into spatial components that are maximally independent. Each spatial component is associated with a particular time course. The components are useful for differentiating noise data from physiological data, as well as identifying statistically independent systems. Comparison studies between seed-based correlation maps and spatial patterns determined by sICA have found similar spatial patterns [32, 64].

Although the sICA approach eliminates the need for a priori seed identification, the user is required to choose the initial number of components as well as to select which components represent noise and which represent functional networks. While some studies have aimed to automate this process and use sICA as a method for identifying and eliminated noise within the BOLD signal [65–67], there remains a substantial need for technical expertise in the deployment and the assignment of networks for them then to be used clinically.

Clustering Algorithms

Another method used to analyze rs-fMRI data makes use of clustering algorithms. Clustering algorithms attempt to group items that are alike on the basis of a set of relevant characteristics to the problem of interest. Voxels can be grouped on the basis of similarity of their BOLD time courses by using some distance metric, such as Pearson's correlation. One example of a clustering algorithm is hierarchical clustering [68, 69], which builds a dendrogram (a treelike structure) of all members. Other examples of clustering algorithms are the k-means [40] and fuzzy c-means [38] clustering algorithms. In these algorithms, all voxels are assigned membership to 1 or more of several clusters on the basis of their distances from the cluster centers, which, in turn, are calculated from an average of their members. Clustering algorithms iteratively update memberships and cluster centers until convergence is achieved (fig. 1) [38]. Other variations in clustering algorithms include spectral-based clustering [70] and

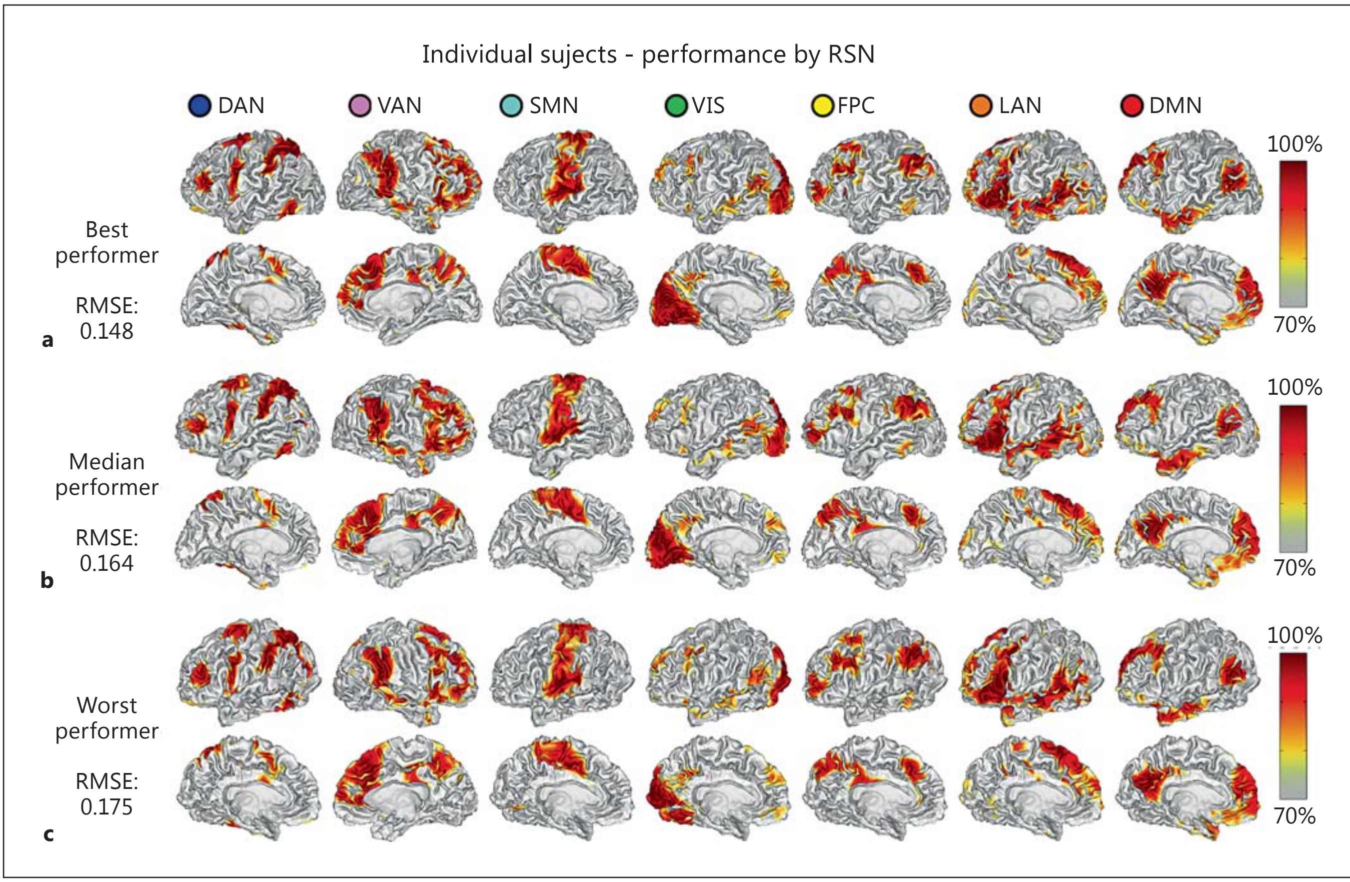

Fig. 3. Single-subject voxel estimation of RSNs using the trained MLP in 3 subjects. The results are from the best, median, and worst performers as determined by root-mean-square error (RMSE) for the DAN, VAN, SMN, VIS, frontoparietal control network (FPC), language network (LAN), and DMN. MLP output was converted to a percentile scale and sampled onto each subject's cortical surface [48].

graph-based clustering [37]. While automated, the clustering algorithm, because it is an unsupervised classifier, suffers from similar constraints as sICA, in that after the clusters are generated they must then be assigned to a particular network by an expert.

Trained MLP

We recently described a technique for mapping the topography of known RSNs in individuals using MLP [48]. Perceptrons are machine learning algorithms that can be trained to associate arbitrary input patterns with discrete output labels [71]. 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 figure 3. It is critical to note that our MLP assigns RSN membership to rs-fMRI correlation maps. This is a critical difference from unsupervised methods where the components or clusters must subsequently be assigned as a network by an expert. Here, the assignment of RSN (e.g. somatomotor/language) is automatic and thus does not require expert input through the analytic process.

It is also important to note that while unsupervised methods have good utility in performed segregation of RSNs across data across subjects, they perform more poorly on individual subject data. MLP methods, however, perform very robustly in individual subjects. Figure 4 demonstrates the degree to which the MLP captures individual variability, by showing that, in each normal subject, the location of the central sulcus in the cortical surface segmented using FreeSurfer [72] is highly correlated

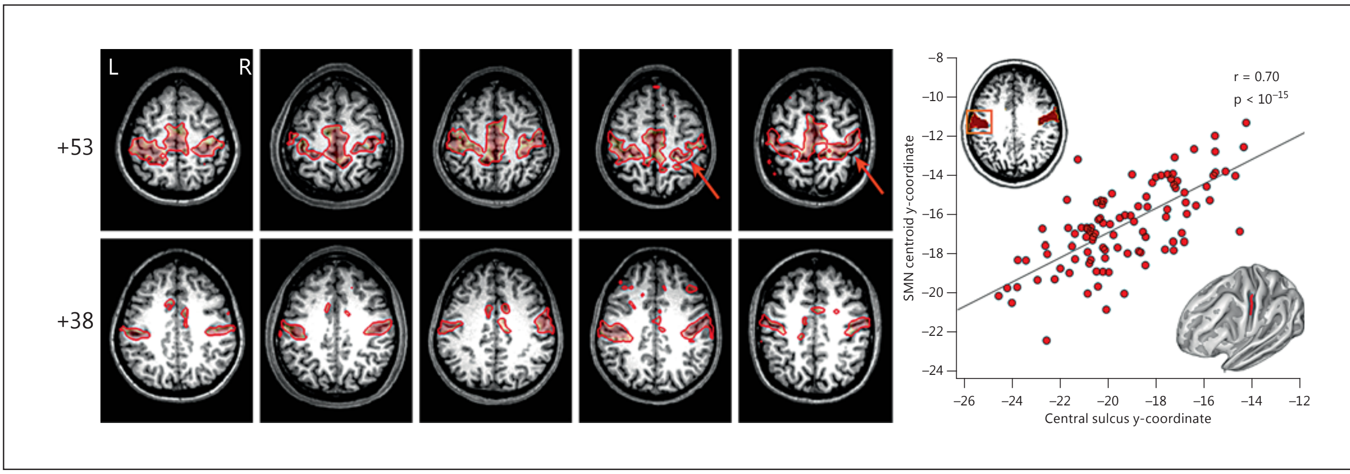

Fig. 4. MLP SMN validation results. The figures are of 5 individuals selected to represent the correspondence between SMN variability and anatomic variability in the central sulcus. The plot shows the correlation between the Talairach y-coordinate of the centroid of the MLP SMN and the y-coordinate centroid of the central sulcus traced over the anatomy (as determined by the FreeSurfer program) in a large validation data set [48].

with the location of the SMN centroid calculated by the MLP. Detailed quantitative evaluation of the MLP performance has been specified previously [48]. MLP performance was also compared to 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, MLP is the leading approach from an analytic standpoint for clinical application. MLP accurately generates RSN topography estimates in individuals consistent with previous studies, even in brain regions not represented in the training data, and can be used for generating individual patient RSN maps. These findings are important to future applications because they demonstrate that this approach can reliably and effectively map multiple RSNs across individual subjects. At the Washington University School of Medicine, this methodology has been deployed as a clinical radiology imaging option at the Barnes Jewish Hospital, and has been rapidly adopted and widely used by neurosurgeons (fig. 5).

Application of rs-fMRI to Presurgical Planning

Currently, fMRI enables a 'preoperative anatomic awareness' of the proximity of an eloquent region to a given tumor. This information gives the neurosurgeon helpful, but nondefinitive, information that can facilitate a surgical strategy (e.g. regions to avoid or areas that will require intraoperative cortical mapping, should surgery be done awake). The most common types of eloquent cortex that utilize preoperative mapping are the cortical regions subserving motor and language function. With task-based MRI, localization requires that the patient be conscious, attentive, and capable of participating in the given cognitive paradigm. In the setting of a brain tumor, effective participation may be impaired due to a neurological deficit or confusion. Additionally, because the patient must be awake during the imaging procedure, sedation cannot be used, thus eliminating pediatric or claustrophobic patients. Because RSNs are task independent and have been shown to be present despite the level of consciousness (i.e. sleep or anesthesia), the limitations of task-based fMRI do not apply and thus makes this approach substantially more widely applicable. Several authors report rs-fMRI mapping in patients with brain tumors (table 1). In this section, we review some of the previously published works demonstrating the feasibility and provide some examples of unique capabilities of rs-fMRI.

Preoperative Sensorimotor Mapping in Brain Tumor Patients Using Seed-Based Methods

Zhang et al. [11] described their initial experience in using rs-fMRI brain mapping for presurgical planning of tumor resections in 4 tumor patients (table 1). The tu-

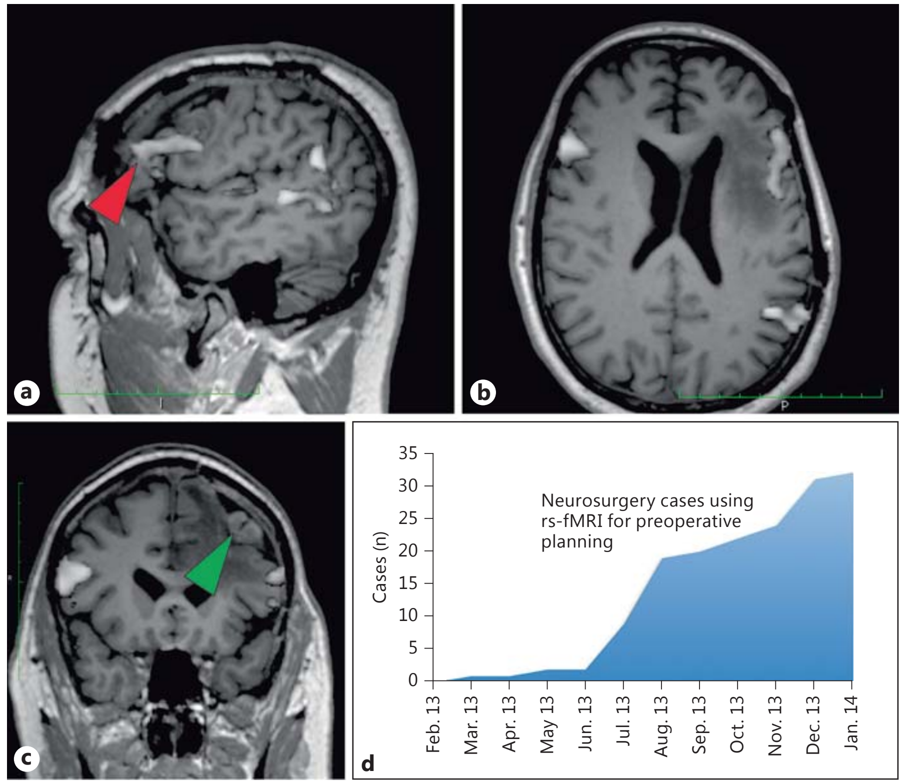

Fig. 5. Example of clinical utilization and adoption curve at the Washington University School of Medicine. **a–c** Language RSN map using MLP analysis in an expressively aphasic patient with recurrent high-grade glioma (green arrowhead). The red arrowhead highlights the clinically relevant resting-state speech site. **d** Clinical utilization of MLP analysis in the previous year.

mors in all 4 patients were adjacent to the motor and sensory cortices, thus necessitating accurate localization prior to surgery to minimize postoperative deficits. Each of the patients was scanned using rs-fMRI and again using task-based fMRI while performing a block design finger-tapping task. fMRI in each patient included four 7-min runs (28 min in total). rs-fMRI data previously acquired from a group of normal controls (n = 17) were also used for comparison. Standard processing of the BOLD fMRI data was used for both the resting-state and task-induced data [73]. Electro-cortical stimulation (ECS) mapping was performed on 3 of 4 tumor patients, and these data, in addition to the task-based fMRI, were used for comparisons with the resting-state data.

The 17 control brains were mapped using the seed region in the left sensorimotor cortex. The correlations of resting-state activity to the seed region were recorded for each of the other voxels in the brain. The group average was used as a control to show the distribution of the sensorimotor network in a healthy brain. To confirm the reproducibility of this method in individual subjects, the full rs-fMRI data set in each subject (28 min) was divided into four separate scans (7 min), and a separate analysis was performed on each segment. The somatomotor cortex was consistently seen in the same region over the four scans in all control subjects. The four tumor patients were also mapped individually following the placement of the seed regions on the contralateral side of the brain.

An exemplar is taken from this series. A 64-year-old man developed focal motor seizures secondary to mass in the left hemisphere (fig. 6a). Finger-tapping fMRI showed atypical response topography including activation in the right parietal cortex in addition to the expected activation of the somatomotor area (fig. 6b). Seed-based (fig. 6c) correlation mapping rs-fMRI showed the somatomotor RSN without parietal involvement. Correlation mapping with a seed in the right parietal cortex matched the topography of the DAN (fig. 6d). The interpretation of these findings are that during the task fMRI, the patient had to strongly focus his attention in order to complete the task, which accounts for the activation in the attentional network. This case illustrates the potential increased specificity of the rs-fMRI method. Also of note, the motor localization of the rs-fMRI was consistent with the intraoperative ECS.

The findings illustrated by Zhang et al. [73] have been corroborated by other studies evaluating the efficacy of seed-based rs-fMRI network mapping in brain tumor pa-

Table 1. Preoperative mapping for brain tumor patients using rs-fMRI: literature review

Authors [Ref.]	Year	Tumor patients	Controls	Tumor locations	rs-fMRI	Other mapping methods	Results
Quigley et al. [74]	2001	11[a]	1	Near eloquent cortices; details not reported	Seed-based	Task-based fMRI	40% concurrence between rs-fMRI and task-based fMRI
Zhang et al. [11]	2009	4	17	Pre-/postcentral gyri	Seed-based	Task-based fMRI ECS	SMN locations determined by rs-MRI were mapped to expected locations in normal subjects; rs-fMRI accurately mapped SMN as confirmed by other mapping methods
Kokkonen et al. [76]	2009	8	10	F (3), P (1), T (3), O (1)	ICA	Task-based fMRI	Correlation between rs-fMRI mapping and task-based fMRI is similar for normal controls and brain tumor patients
Liu et al. [20]	2009	6[b]	None	Near motor cortex; details not reported	Seed-based	Task-based fMRI ECS	rs-fMRI, task-based fMRI, and ECS mapping are similar to one another; rs-fMRI mapping shows selectivity for hand and tongue motor regions
Otten et al. [75]	2012	22	22	F (7), T (9), FT (1), FP (1), O (2), C (1), CC (1)	Seed-based	None	SMN abnormalities are present in brain tumor patients and can predict weakness
Mitchell et al. [77]	2013	7	6[c]	F (2), P (1), T (1), FP (2), FT (1)	MLP	ECS	MLP identified all RSNs in tumor and seizure groups; high degree of overlap between MLP and ECS; MLP can be used to identify 'no-cut' regions of cortex

F = Frontal; P = parietal; T = temporal; O = occipital; FT = frontotemporal; FP = frontoparietal; C = cerebellum; CC = corpus callosum. [a] Cerebral tumors, cysts, or vascular malformations. [b] Tumors or epileptic foci. [c] Epilepsy.

tients. Quigley et al. [74] found 40% concurrence between tasked-based fMRI and rs-fMRI in 11 patients with cerebral tumors, cysts, and malformations. Liu et al. [20] found that rs-fMRI mapping shows selectivity for hand and tongue motor regions, and similar to task-based fMRI and ECS. Otten et al. [75] showed that rs-fMRI abnormalities present in brain tumor patients correlate with predicted weakness. These seed-based fMRI methods parallel similar findings using ICA methods [76]. Together these studies support a role for the rs-fMRI method to localize cortical networks in brain tumor patients.

Neurological deficits correlate with resting-state motor network connectivity in patients with brain tumors. Otten et al. [75] used rs-fMRI methods to measure motor networks in patients with brain tumors, and they showed reduced connectivity in patients with pre- and postoperative motor deficits. They found that postoperative deficits correlated with preoperative RSN networks. Furthermore, clinical recovery of motor function was accompanied by reconstitution of the RSN motor network. Future studies evaluating the role of RSNs in the prediction of postoperative deficits will be necessary.

Comprehensive Network Mapping of the Functional Cortex Using MLP

Mitchell et al. [77] reported application of MLP-based RSN mapping to presurgical planning in 6 patients with intractable epilepsy and 7 patients with brain tumors. Epilepsy patients underwent electrocorticographic monitoring to localize the epileptogenic zone of seizure onset and to perform functional mapping with ECS mapping. Patients with tumors underwent intraoperative ECS mapping prior to resection of the tumor mass. Lesions were manually segmented using T1- and T2-weighted images. The MLP was trained and applied de novo in each tumor patient, omitting tumor voxels. Additionally, for the patients with implanted grid electrodes, the electrodes were coregistered via CT scan with the anatomic and functional MRI for statistical comparison of stimulation-positive and -negative sites. Motor regions were defined by the presence of induced involuntary motor movements. Language sites were defined by speech arrest during the stimulation.

An electrode was classified as positive or negative in the MLP results according the probability of its belonging to the appropriate RSN (motor or language). These probabilities were then plotted against the ECS results to generate receiver operating characteristic (ROC) curves. These ROC curves were averaged, and the area under the averaged curve (AUC) was used as a measure of the agreement between the MLP and the ECS method.

Across all patients, MLP demonstrated a robust ability to identify all seven canonical functional networks. This was true for both structurally normal (i.e. epilepsy) brains and anatomically distorted brains (i.e. tumors; fig. 7). For networks in which no direct clinical comparison was possible, the acquired maps were in good agreement with published results. These included the VIS [32, 36], DAN and VAN [21, 50], frontoparietal control network [34, 52, 78], and DMN [31, 79]. For the motor and language networks, which were compared to the clinical findings using ECS, there was a high degree of qualitative overlap between the two methods. Quantitative comparisons were performed with an ROC analysis. Findings yielded an average AUC of 0.89 for the motor network and an average AUC of 0.76 for the language network.

Loci in MLP maps outside the appropriate RSN but eloquent as determined by ECS were defined as MLP false negatives. Minimization of MLP false negatives is critical to reduce surgical morbidity, since resection of a false-negative area could lead to a clinical deficit. An assessment of the anatomic limits of MLP false negatives demonstrated that the probability of an MLP false negative could be reduced to less than 2% by expanding the 'no-cut' zone by 15 mm around the contour corresponding to 85% likelihood of belonging to the motor RSN.

In summary, MLP-based RSN mapping robustly identified all networks in all patients, including those with distorted anatomy attributable to a mass effect, and showed

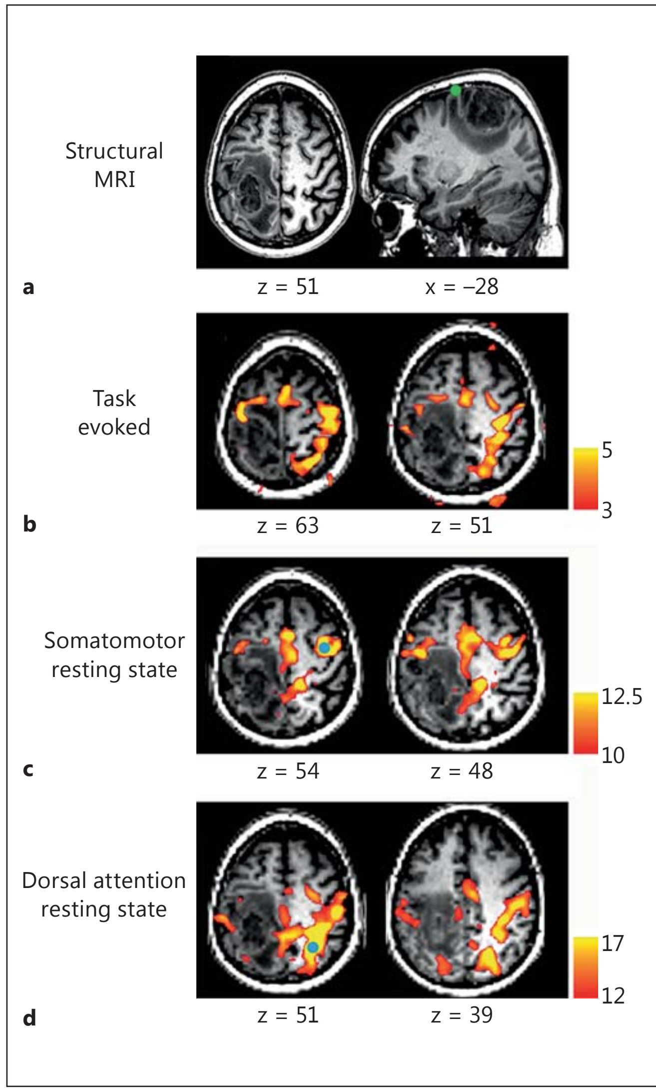

Fig. 6. MRI of a 64-year-old man who presented with focal motor seizures (case 2). **a** Structural MRI revealed a tumor in the left parietal cortex that invades the territory near the central sulcus (neurologic convention). The green dot represents the location of ipsilateral hand response to cortical stimulation. **b** Task-related activity was seen bilaterally in the frontal lobe. In addition, a large band of activity appeared in the right parietal cortex, not consistent with the pattern of activity from the sensorimotor network. **c** Resting-state correlation mapping using a seed in the right (unaffected) hemisphere (blue dot) showed ipsilateral correlations anterior to the tumor as well as a region of activity in the midline parietal cortex. Note the absence in the correlation mapping results of parietal activity seen in the task-related map. **d** Parietal activation seen during task-evoked imaging is revealed to be a separate RSN, the DAN, which is normally dissociated from the sensorimotor network (seed: blue dot). All images are displayed left on left (neurologic convention) [11].

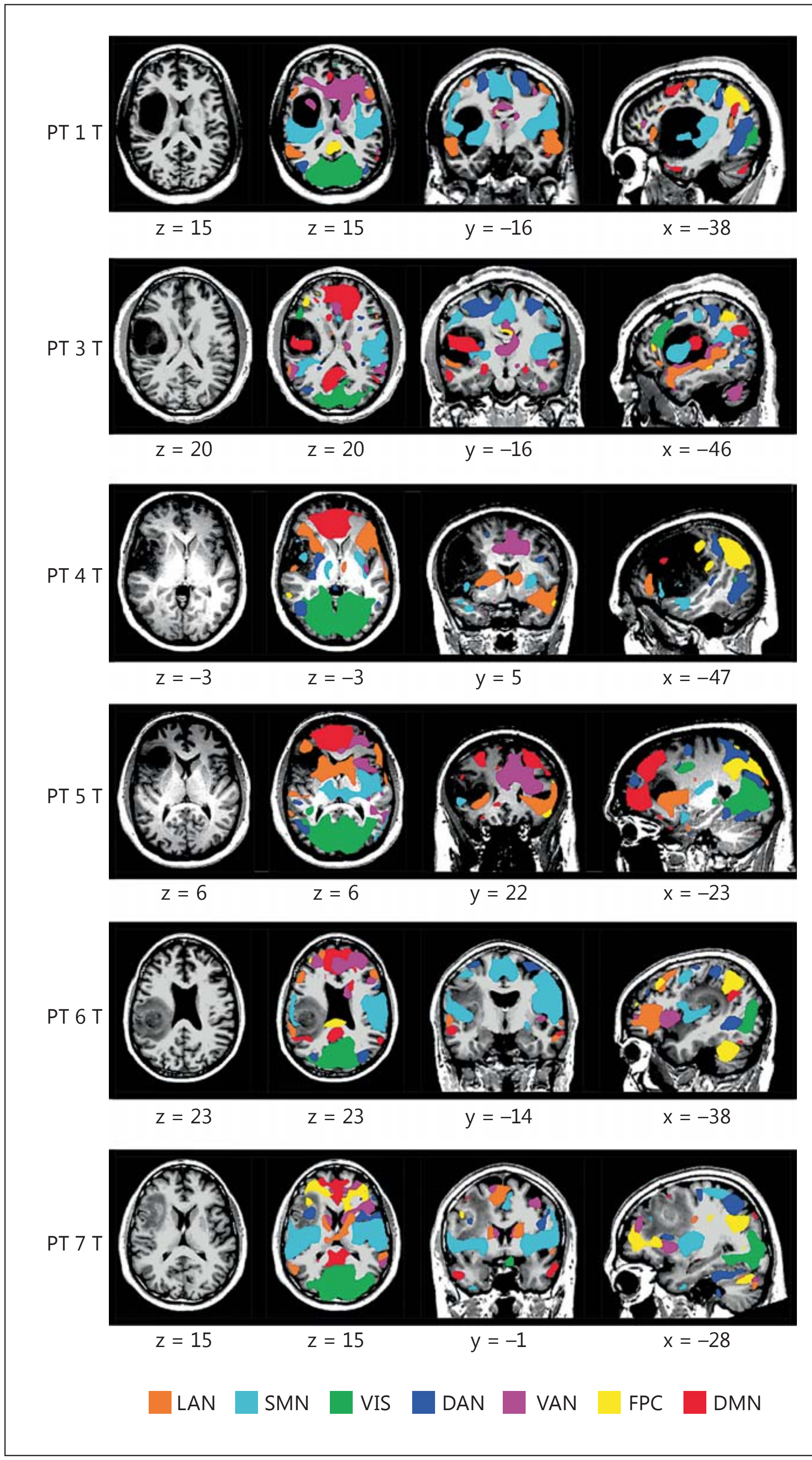

Fig. 7. RSN maps produced by MLP for 7 tumor patients. The seven networks language (LAN), SMN, VIS, DAN, VAN, frontoparietal control (FPC), and DMN were mapped in the area of the tumor using the winner-take-all format [77]. PT = Patient; T = tumor.

a strong correlation with stimulation. These findings demonstrate that the MLP-defined RSNs are able to identify eloquent cortex.

Future Applications

Mapping beyond Motor and Speech

In addition to broadening the patient population that can be preoperatively mapped, the use of rs-FMRI for the identification of multiple cortical networks also broadens the capability of what cognitive operations can be assessed, and can potentially redefine what regions are considered 'eloquent'. The previously reported correlations between stimulation mapping and the somatomotor and speech RSNs supports that the other cortical networks identified are also functionally relevant. Other cognitive operations of attention, executive control, and sensory perception are challenging if not impossible to screen pre- and intraoperatively in a comprehensive fashion. Either the number of tasks needed to identify all these functionally relevant regions would simply be too long to test in an MRI, or there are no ways of eliciting or interrupting these complex cognitive operations in the operating room in a reliable way. Although the current standard for care is that a surgeon does his or her utmost to preserve a patient's ability to move and speak after surgery, these other cognitive operations and their associated networks may also play a role in long-term clinical outcomes which are harder to test. The use of automated methods, such as MLP, to rapidly identify all these networks with a single brief scan may provide an important tool to enable a more subtle appreciation for how these patients will cognitively perform clinically beyond simple motor and speech tasks. As an example, insights into the location of the attentional networks may aid in preventing a neglect or avoiding the frontoparietal control network in a high-functioning professional to avoid compromise of his/her decision making would both be highly clinically relevant.

Integration with Stereotactic Imaging

By providing real-time *anatomic* information to the neurosurgeon, stereotactic neuronavigation has been shown to improve the extent of tumor resection [80] and, as a result, to improve survival statistics [4]. That said, it is *not* routine during resections to make use of similar neuronavigation displays that reflect the *functional* organization of the brain. Hence, the neurosurgeon often has very little insight into what cognitive functions may be compromised by the operative procedure. Task-based fMRI has been employed as a means of preoperatively localizing function [81], but it is not routinely integrated with standard neuronavigation. Because, rs-fMRI provides a much more complete functional map of the brain and does so in a much more reliable and highly time-efficient manner, this could become a natural adjunct to preoperative stereotactic imaging. Thus, every patient would both have their anatomy and their functionally relevant data available for every surgical case. While the impact of surgery on these various networks needs to be explicitly tested before any clinical recommendations can be made, this combined approach would at least provide the necessary tools to address such important questions.

Conclusion

The mapping of RSNs defined by rs-fMRI offers a new method for preoperative planning. These techniques not only localize motor and speech regions classically understood to be eloquent, but also enable the identification of all the canonical functional networks. Taken together, because this approach is task independent and can identify a multitude of networks simultaneously, these findings stand to fundamentally alter preoperative imaging by substantially expanding the patients that can be mapped and by better interrogating all regions of function in the human brain.

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Disclosure Statement

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