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Challenges and techniques for presurgical brain mapping with functional MRI

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ABSTRACT

Functional magnetic resonance imaging (fMRI) is increasingly used for preoperative counseling and planning, and intraoperative guidance for tumor resection in the eloquent cortex. Although there have been improvements in image resolution and artifact correction, there are still limitations of this modality. In this review, we discuss clinical fMRI's applications, limitations and potential solutions. These limitations depend on the following parameters: foundations of fMRI, physiologic effects of the disease, distinctions between clinical and research fMRI, and the design of the fMRI study. We also compare fMRI to other brain mapping modalities which should be considered as alternatives or adjuncts when appropriate, and discuss intraoperative use and validation of fMRI. These concepts direct the clinical application of fMRI in neurosurgical patients.

1. Introduction

Precise preoperative assessment of the individual functional anatomy surrounding a brain lesion is crucial for safe and effective neurosurgery. The operative feasibility, surgical approach, and risk of postoperative functional deficits are essential considerations when planning neurosurgical interventions. As each patient's brain anatomy is unique, and the functional anatomy may present pathology-induced atypical organization or reorganization, brain mapping is not generalizable and must be done in a patient-specific manner (Bates et al., 2003; Duffau, 2005). Currently, intraoperative electrocortical stimulation (ECS) (Ojemann, 1993) and intracarotid amobarbital test (Wada test) (Wada and Rasmussen, 1960) remain the clinical gold-standards for mapping brain functions and determination of dominant hemisphere respectively. However, these techniques are invasive, highly demanding, and unavailable preoperatively with limited information. Numerous non-invasive neuroimaging modalities have been developed for preoperative functional brain mapping, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS), each of which has unique strengths and weaknesses when used for surgical planning (Tharin and Golby, 2007).

In this review, we focus on blood oxygen level-dependent (BOLD) fMRI which was first introduced in the early 1990’s (Kwong et al., 1992; Ogawa et al., 1990). Currently, fMRI is the most commonly used non-invasive neuroimaging modality for surgical planning, and has proven effective in guiding epilepsy and tumor surgery (Petrella et al., 2006; Bartsch et al., 2006; Bookheimer, 2007; Genetti et al., 2013; Hirsch et al., 2000; Rosen and Savoy, 2012; Sunaert, 2006; Orringer et al., 2012; Pillai, 2010). Conventional task-based fMRI uses BOLD signal changes during performance of a particular task vs. a baseline or resting condition to indirectly measure the neuronal activity induced by the task. This effect relies on the coupling of neuronal activity to regional increases in cerebral blood flow, and is thought to represent synaptic activity (Logothetis et al., 2001). During task performance, increased local perfusion via capillary vasodilation exceeds the metabolic demands of the activated brain region, resulting in an increased ratio of oxyhemoglobin to deoxyhemoglobin and an increased T2* signal that can be detected by MR scanners (Ogawa et al., 1990; Fox and Raichle, 1986). Compared with the clinical gold-standard brain mapping techniques, fMRI has the advantages of non-invasiveness, presurgical availability, and capability of mapping the whole brain rather than only those areas exposed by craniotomy. fMRI may also be relatively easily adopted in many medical centers since the basic infrastructure, high field MRI, is already in place at most neurosurgical centers (Rigolo et al., 2011). Additionally, there is a large body of data and experience with fMRI in neuroscience, cognitive science and psychology, which provides a framework to facilitate interpretation of fMRI results in the

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clinical setting.

There are practical barriers to fMRI for its application in surgical planning. fMRI relies on a sufficient signal-to-noise ratio (SNR) to allow detection of BOLD signal increase during task performance vs. baseline conditions, which can be as small as 1–5% (Parrish et al., 2000). Thus, even minor alterations in neurovascular coupling, task execution, or inappropriate data processing can degrade the quality and usefulness of the fMRI results. Patient comorbidities can limit the quality and quantity of data collected, and the BOLD signal can be altered by factors exogenous to the function performed. Numerous factors including task design and selection, data acquisition and analysis can also introduce errors including both false positives and false negatives. Logistically, fMRI brain mapping for surgical planning is inherently limited by certain practical constraints of the clinical setting, namely time and scanner availability. This review aims to provide a structured approach to understand these challenges and the potential solutions for overcoming them. Here we outline the many factors that impact BOLD signal and thus affect the interpretation of fMRI findings, with particular attention given to distinguishing universal from unique barriers, and modifiable from non-modifiable barriers. Intraoperative use and validation of the fMRI results are also discussed in this review.

2. fMRI physics considerations

The limitations related to fMRI physics will occur with every patient's testing and are important to recognize when interpreting fMRI results. One factor that can decrease SNR is signal loss from susceptibility artifacts. In contrast to the dynamic microscopic susceptibility changes that generate the BOLD signal, static macroscopic susceptibility artifacts can cause signal loss and geometric distortions (Farzaneh et al., 1990). The underlying cause of this susceptibility artifact is that during echo-planar imaging, different spin frequencies of different materials within the space of a voxel (such as brain and air or brain and surgical implants) result in dephasing (also called off-resonance) (Farzaneh et al., 1990; Song et al., 1997). Susceptibility artifacts are normally prominent in regions like the inferior temporal and inferior medial frontal regions where adjacent bone or air sinuses generate large field gradients (Ojemann et al., 1997). Devlin et al. found discrepancies in language localization between fMRI and PET due to BOLD signal loss in language-associated temporal regions near air-filled sinuses (Devlin et al., 2000). This susceptibility artifact can be decreased with smaller voxel size at the cost of time as well as increased noise (Bellgowan et al., 2006). Spiral acquisition methods can also diminish susceptibility artifact and improve sensitivity of detection without compromising spatial resolution (Li et al., 2006). Spin echo techniques have also been shown to correct susceptibility artifacts and improve image quality, even at ultra-high field strength (≥ 7 T) (Abduljalil et al., 1999; Yacoub et al., 2001).

Magnetic susceptibility artifacts can also accentuate draining veins due to deoxyhemoglobin in the venous system, especially at higher field strengths (Abduljalil et al., 1999; Abduljalil and Robitaille, 1999). Veins can generate BOLD signal changes of 5–10% and can distort activation regions (Alkadhi et al., 2000). Fig. 1 shows false positive activations caused by a large cortical vein. Some studies have attributed discrepancies between activation regions detected by fMRI and PET to nearby draining veins (Kinahan and Noll, 1999). In order to correct for this venous effect, several techniques have been proposed, including data processing that accounts for the delay between the parenchymal and venous BOLD signals (Kinahan and Noll, 1999).

3. Pathophysiological considerations

3.1. Perilesional BOLD changes

In neurosurgery patients, perilesional brain parenchyma may demonstrate anatomic distortion, tumor infiltration, edema, and in some cases marked neuroplasticity, which make interpretation of preoperative fMRI difficult in the context of classical functional neuroanatomy (Alkadhi et al., 2000; Thickbroom et al., 2004). Moreover, perilesional edema and mass effect can cause decreased or absent BOLD signal in functionally intact tissue yielding misleading results (Krings et al., 2002). In addition, hemosiderin deposition from prior hemorrhage can produce susceptibility artifacts that can distort adjacent BOLD signal (Thickbroom et al., 2004; Lehericy et al., 2002). Artifacts may be particularly prominent in patients undergoing re-operation because of effects of hemosiderin deposition, reconstructive materials, or gliotic scarring. Fig. 2 shows BOLD anomalies associated with scarring along the previous craniotomy edges. Paramagnetic surgical objects from previous surgeries such as plates and clips can introduce an additional source of susceptibility artifact, potentially obscuring nearby functional cortex. In such cases, review of the baseline anatomic imaging and the raw BOLD images can demonstrate these potential artifacts when interpreting the fMRI results.

Neurosurgical patients with brain tumors or arteriovenous malformations (AVM) can have altered hemodynamics leading to neurovascular uncoupling (NVU) that undermines the fundamental premise of BOLD fMRI in detection of neuronal activations (Lehericy et al., 2002; Ulmer et al., 2003; Hou et al., 2006; Holodny et al., 2000). Tumor-induced neovascularization in the hypoxic perilesional regions can cause an increased capacity for vascular demand, resulting in a nonlinear response and a ceiling effect on the BOLD signal (Hou et al., 2006). The chronic demand-perfusion mismatch can lead to vasomotor paralysis, loss of local cerebrovascular autoregulation, and subsequent loss of BOLD signal variability. In addition, an increase of deoxyhemoglobin was detected during task performance in brain tumor patients, leading to decreased BOLD signal (Fujiwara et al., 2004). These false negatives are particularly relevant and prevalent in clinical practice. Unlike in research studies where type-I errors (false positives) are more concerning, preoperative fMRI typically aims to reduce type-II errors (false negatives) where genuine functional areas are not demonstrated by the task (Loring et al., 2002). This is because neurosurgical patients are more likely to experience significant harm from mistakenly deeming a region to be functionally uninvolved and subsequently resecting critical tissue than from incorrectly assigning function to an uninvolved region. To detect NVU, approaches have been proposed including a breath-holding cerebrovascular response (CVR) mapping (Zaca et al., 2014; Pillai and Zaca, 2012), as hypercapnia can induce vasodilatation in normal vasculature but has no effect on chronically vasodilated vessels (Hsu et al., 2004; Li et al., 1999). Detection of atypical cerebral blood oxygenation changes (such as increased deoxyhemoglobin) can be accomplished with two-tail testing of the signal changes, which looks for both signal increases and decreases as indicators of functional activation (Fujiwara et al., 2004).

3.2. Patients' physiological state

Neurosurgical patients with systemic diseases may present metabolic, cardiac, and respiratory changes which in turn can affect the BOLD fMRI signal by inducing physiologic noise (Birn et al., 2006). Baseline cerebral blood flow increases with hypercapnia, which increases noise and decreases the magnitude of the BOLD response (Bandettini and Wong, 1997; Cohen et al., 2002). Thus, changes to a patient's respiration during fMRI imaging, including anxiety or sedation, can affect the BOLD response. Efforts have been made to correct for these effects by synchronizing BOLD signal with changes in respiratory and heart rate (Hu et al., 1995).

There are other physiologic limitations to BOLD fMRI. For example, BOLD signal intensity decreases with advancing age due to impaired autoregulation and loss of vasodilatory response to neural activation, which may require more trials to compensate the reduced SNR (Huettel et al., 2001; D'Esposito et al., 1999; Chen et al., 2008). Patients with cerebrovascular disease may have decreased BOLD response in the

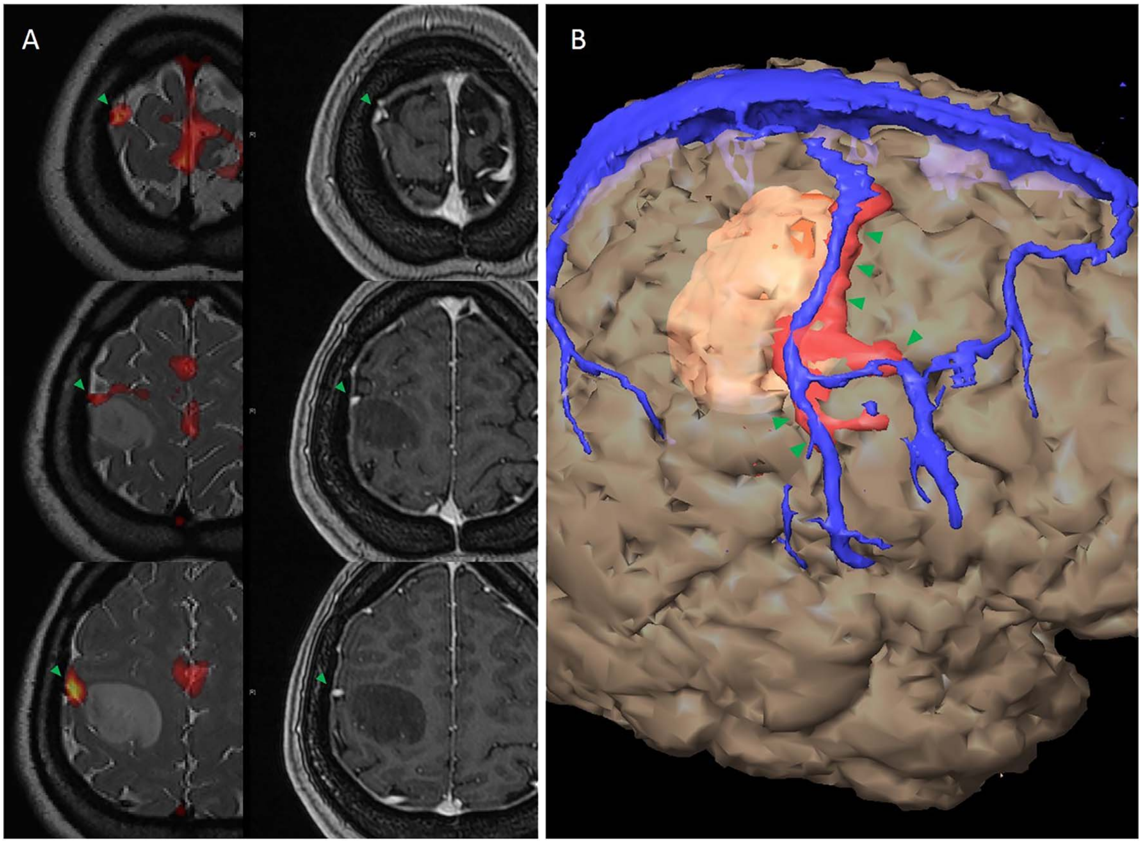

Fig. 1. False positive signal caused by venous effect. (A) fMRI map (left column) of a finger tapping task of a patient with right frontal anaplastic oligodendroglioma. A large cortical vein (highlighted with green arrow heads in the contrast-enhanced T1-weighted structural images shown in the right column) caused false positive activations around the tumor margin (green arrow heads), limiting the interpretation of the fMRI results. (B) 3D rendering of the tumor (orange), fMRI activations (red) and the cortical vein (blue). The false positive activations were confirmed by intraoperative ECS during tumor resection surgery.

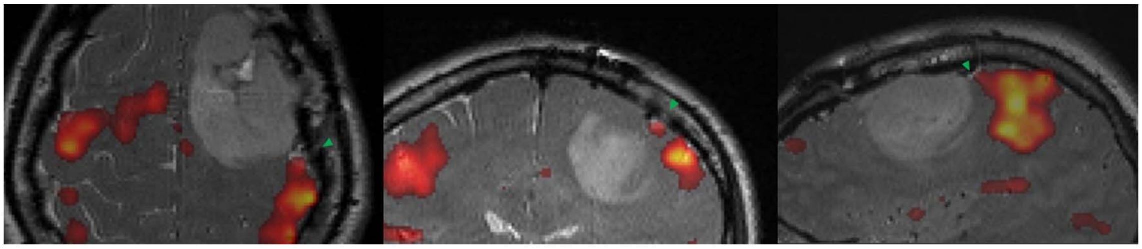

Fig. 2. fMRI results of a hand clenching task of a patient with glioblastoma recurrence. BOLD signal anomalies (green arrow heads) are associated with postoperative scarring along the previous craniotomy edges.

vascular territories of stenotic vessels. In ischemic cerebrovascular disease, hypoperfused vascular territories exhibit diminished cerebrovascular reserve with a ceiling effect that decreases the BOLD response (Carusone et al., 2002). AVMs can generate flow gradients and regions of hypervascularization that can interfere with the BOLD signal (Lin et al., 2016). Therefore, it is important to take into account of these factors when interpreting fMRI results for these patients.

4. Iatrogenic considerations

Neurosurgical patients often take medications that may interfere with BOLD fMRI response. A patient's pharmacologic state can affect the BOLD signal by uncoupling cerebral blood flow and oxygen consumption (Vorstrup et al., 1984). It has been show that acetazolamide increases baseline cerebral blood flow by promoting vasodilation in response to cerebral hypercapnia, which resulted in decreased BOLD response to visual stimulation (Bruhn et al., 1994). Even chemicals commonly encountered in daily life such as caffeine, alcohol, and tobacco can alter BOLD signal. Similar to acetazolamide, ethanol was shown to decrease BOLD signal by promoting vasodilation (Seifritz et al., 2000). Nicotine has also been shown to increase cerebral blood flow by decreasing vascular resistance, but unlike acetazolamide and ethanol it may not interfere with the coupling of BOLD signal to functional activation (Jacobsen et al., 2002). In contrast, caffeine increases BOLD response by promoting vasoconstriction and decreasing baseline signal (Mulderink et al., 2002). Theophylline, an even more potent adenosine-antagonist than caffeine, has been shown to boost BOLD contrast in rats (Morton et al., 2002), but has not yet been assessed in human fMRI studies. It is not clear that whether peri-operative steroid regimens (despite altering the blood-brain-barrier) or seizure medications (despite effects on neural connectivity) have a significant impact on neurovascular coupling (Kiem et al., 2013; Felix-Ortiz and Febo, 2012; Wandschneider et al., 2014; Wandschneider and Koepp, 2016).

Pre-scan and intra-scan conditions can alter the patient's cognitive state and affect the quality of fMRI. Children frequently undergo practice sessions in a mock scanner to reduce anxiety and improve task performance. It has been shown that sleep deprivation decreased SNR of BOLD signal (Chee and Choo, 2004). However, variable effects of sleep deprivation have been shown to either increase or decrease the activity in frontal and parietal lobes, preventing broader generalizations (Drummond et al., 1999; Drummond et al., 2000; Drummond et al., 2001). For neurosurgical patients, numerous factors such as chronic fatigue, sleep disturbance from steroid regimens and disrupted sleep from hospitalization may result in similar states. Interestingly, fatigue had a greater effect on task execution leading to reduced BOLD response in performing simple tasks than complex tasks (Drummond et al., 2000). In addition, neurosurgical patients may experience anxiety, fear, and pain associated with their pathology, which may interfere with attention and task performance, and may also induce activations in the amygdala, insula, and other brain regions (Ball et al., 2017). Therefore, appropriate patient preparation and education pre-fMRI testing may help reduce stressors and support a normal physiologic state in order to obtain reliable fMRI results.

5. fMRI data acquisition and analysis considerations

5.1. Paradigm design

There are two major task paradigms in the task-based fMRI protocol: blocked and event-related fMRI. In a blocked design fMRI, the patient performs repeated trials of a task during a 20–30 s block, and blocks of different conditions alternate over the run. The longer cognitive engagement and increased BOLD SNR of blocked paradigms improves statistical power and is useful for localizing brain regions activated throughout the course of an executed task (Price et al., 1999). However, blocked design fMRI may miss transiently activated regions. For example, early, transient or biphasic hippocampal activation and later deactivation may not be captured by a blocked design fMRI (Cunnington et al., 2002; Meltzer et al., 2008). In contrast, an event-related design fMRI can capture the transient BOLD response associated with the performance of a single task (Buckner et al., 1996). Despite a lower SNR, event-related design uses temporal associations over many separately spaced repetitions of a task to detect an association between BOLD signal changes and the task. By evaluating individual episodes, this design can detect variations in BOLD signal that occur only transiently during exposure to the task condition. One challenge with event-related design is the complex hemodynamic response to neural activation, including a several second delay between task execution and BOLD response (Buxton et al., 1998; Glover, 1999). fMRI has a low temporal resolution since BOLD signal changes begin within 2–3 s, peak approximately 5–10 s after neuronal firing and may last 30 s, thus event-related fMRI may be more affected by perilesional hemodynamic changes than blocked design fMRI. The inter-stimulus-interval of event-related design is an important parameter and can be randomized to reduce expectation effects from the patients (Buckner et al., 1996; Liu et al., 2001). Compared with blocked-design, event-related design has been shown to produce language maps with more sensitive localization in brain tumor patients (Tie et al., 2009). Another advantage of event-related fMRI is the decreased sensitivity to motion artifact (Birn et al., 1999). Hybrid paradigms that combine blocked and event-related designs have also been proposed (Petersen and Dubis, 2012), with an advantage of measuring both sustained and transient functional activation. Currently, blocked design fMRI is more widely adopted in the clinical settings, likely due to its high detection power, relatively easier design and implementation, and better patient participation (Tie et al., 2009).

5.2. Task selection

The complexity of mapping motor, language, vision, and other functions helps explain the immense diversity of tasks that have been proposed and used to optimize fMRI brain mapping for surgical planning. As an example, language lateralization using fMRI demonstrates drastically different reliability depending on task selection. Pillai and Zaca showed that the expressive tasks of silent word generation and rhyming are more efficacious for language lateralization than receptive tasks such as passive listening or reading comprehension (Pillai and Zaca, 2011). While this may be explained by bilateral involvement of the theorized receptive pathways, the variability in effectiveness among language tasks highlights the importance of choosing tasks that have been validated with gold standard techniques. In fact, given the importance of task selection for the reliability of fMRI in language mapping, efforts have been made to standardize language tasks across institutions by developing paradigm algorithms for both adult and pediatric patient populations (Black et al., 2017).

The choice of baseline task can dramatically affect function localization. Compared with a resting condition, an active baseline can more precisely identify critical brain regions by eliminating background signal associated with the task, but not specific to the precise function of interest. This is because cognitive tasks can coactivate other functions such as attention and visual processing, and an appropriate active baseline condition can help to account for signal changes resulting from attentional or sensory processing. For example, a reading task involving button press in response to visual presentation of real word vs. nonsense string of letters would benefit from a button press during the control task to mask the resultant hand motor activations.

It can be challenging to interpret fMRI results by breaking down the task into components. For example, normal motor function depends on sensory feedback, such as haptic, proprioceptive, and visual sensory information. This sensory feedback can increase activation in the motor task region as well as in confounding sensory regions (Noble et al., 2013). It may be difficult to control for subtle environmental variables like force or visual feedback during a motor task, yet activation regions are highly sensitive to their influence (Noble et al., 2013; Haller et al., 2009).

5.3. Motion artifact

Although all imaging modalities encounter motion artifact limitations, fMRI is particularly susceptible to motion due to long acquisition times. fMRI is based on the premise of detecting change in an image over time, and head motion is a type of change that can falsely be interpreted as relevant. Unlike healthy control subjects, patients with brain lesions and neurological deficits may have greater difficulty keeping their heads still inside the scanner (Seto et al., 2001; Bullmore et al., 1999). Motion artifacts are more common among children, with nearly one-third of fMRI testing in children being non-diagnostic due to motion (Afacan et al., 2016). Active patient participation in performing the various tasks needed for data acquisition can introduce motion artifacts as well, even with tasks as minimal as finger motor testing (Hajnal et al., 1994).

Excessive head motion can be reduced by pre-scan coaching, attention to patient comfort, prioritization of key tasks, and short scanning sessions. Prospective head constraint approaches, such as bite bars, mouth guards, and head bands, are often uncomfortable and can distract the patient during a prolonged fMRI study (Lueken et al., 2012; Maclaren et al., 2013). Head-tracking prospective motion correction has been under development for 20 years but can still only be applied to certain sequences and is limited by delayed tracking updates and cannot correct field distortions from movement (Maclaren et al., 2013). Motion artifact may also be minimized by task selection. For example, toe wiggling and lip pursing are small movements used to map motor cortex with minimal recruitment of muscles unrelated to the task. In addition, higher field strength and multi-channel coils can shorten acquisition time thus reduce fatigue-associated motion artifacts (Bellgowan et al., 2006). Task correlated motion artifact is particularly challenging and should be assessed if suspected. Correlating fMRI data with positional information or applying motion-detection on the images can allow for post-processing motion correction of the images to further reduce motion artifacts, however, the effectiveness of these methods are generally limited (Hajnal et al., 1994; Morgan et al., 2007). Retrospective correction of motion should be performed when motion is recognized. However, if excessive motion or image quality degradation has occurred, the data should be discarded. Centers should establish benchmarks for acceptable motion parameters.

5.4. Patient cooperation

Compared with healthy controls subjects, neurosurgical patients have decreased attention, verbal memory, and executive function based on neurocognitive and neuropsychological testing and resting-state fMRI studies (Noll et al., 2015; Noll et al., 2016; Maesawa et al., 2015; Habets et al., 2014). These deficits limit their ability to understand and complete the tasks sufficiently, resulting in incomplete or unreliable fMRI results, because the reliability of task-based fMRI depends critically on task performance.

Patients undergoing preoperative fMRI may have neurological deficits resulting from the pathologic lesion. For example, a tumor abutting the precentral gyrus may cause paresis or plegia, making some motor tasks impractical or impossible. BOLD signal changes have been shown to be less reliable for motor tasks involving paretic body parts (Mazzetto-Betti et al., 2010). These may limit the functions that can be evaluated with fMRI, particularly in the most severely affected cortex. Modification of study design accounting for each individual patient's abilities and cooperation, and his/her cognitive function and endurance may help to optimize preoperative fMRI. For example, in patients who have motor deficits, assisted motor tasks or substitution of imagined tasks can activate the primary motor area and supplementary motor area (SMA) (Mizuguchi et al., 2013). Passive-movement tasks can be elicited in patients with profound motor impairment with the help of manipulandum devices that reliably activate motor cortex with less motion artifact compared to healthy controls (Shriver et al., 2013). Similarly, stimulus presentation (visual vs. auditory) must account for sensory deficits in patients with lesions of the sensory pathways. For example, auditory presentation should be used in patients who have vision deficits that interfere with visual presentation of the tasks. Language mapping in non-English speakers requires the development of specific paradigms in the native language, though some stimulus presentations such as picture naming can be used regardless of language. There is no data on the optimum sequence of tasks, but there may be a learning curve to participation in an fMRI study that is limited by fatigue and attention, resulting in a potential optimum sequence for task complexity. Furthermore, the study workflow should focus on the most important tasks to identify critical functional areas to minimize acquisition time and maximize degree of patient cooperation. Separate study sessions may be better tolerated if the patient is unable to complete multiple tasks in one session.

The advent of resting-state fMRI (rs-fMRI), which measures spontaneous brain activity while patients are at rest without performing any tasks, may expedite the acquisition process and diminish the reliance on patient cooperation (Lang et al., 2014; Lee et al., 2013). This is particularly useful for patients who cannot perform a certain task due to neurologic deficits. In rs-fMRI, low frequency BOLD signal changes are associated with spontaneous neuronal activity of inherent functional neural networks (Auer, 2008; Fox and Raichle, 2007), and thus can be used to identify regions associated with particular functions (Binder et al., 1999; Fox et al., 2005; Hampson et al., 2002; Cordes et al., 2000). Rs-fMRI has the additional advantage of simultaneously mapping multiple regions (Damoiseaux et al., 2006; Mitchell et al., 2013). The task-free nature of rs-fMRI and minimal requirements for paradigm design and test administration have found traction and interest in preoperative fMRI mapping for surgical planning, including mapping of motor and language areas (Rosazza et al., 2014; Zhang et al., 2009; Liu et al., 2009; Tie et al., 2014; Sair et al., 2016; Leuthardt et al., 2015). Recent data has demonstrated particularly promising results for the use of rs-fMRI for motor mapping, though this is not yet common clinical practice (Dierker et al., 2017; Schneider et al., 2016).

Rs-fMRI may be more susceptible to head motion artifact than task-based fMRI (Huijbers et al., 2017), therefore, patient compliance remains a primary concern. Furthermore, rs-fMRI is affected by susceptibility artifact and NVU in the same manner as task-based fMRI (Agarwal et al., 2016; Agarwal et al., 2017a; Agarwal et al., 2017b).

In addition to rs-fMRI, other approaches to decrease the demand on patients and simplify image acquisition have been proposed. For example, fMRI recording during movie watching can capture passively stimulated selective language responses, and may serve as a less-demanding addition to task-based fMRI for patients who have difficulty completing language tasks (Tie et al., 2015). Although the use of less-demanding or task-free paradigms are easier for patients to perform and technicians to administer, fMRI data analysis of these paradigms is more complex than task-based fMRI, and thus automatic workflows for deriving functional maps based on this kind of paradigms are needed to make such approaches applicable in clinical settings.

5.5. Data analysis

The core principle of neurovascular coupling forms the foundation for modeling changes in BOLD signal between the task and baseline conditions and establishing statistical significance. The general linear model (GLM) is the most commonly used method for processing fMRI data, and relies on hypothesis-driven statistical testing to capture task-related activation (Friston et al., 1995). However, fMRI data may not conform to the GLM assumptions, which can introduce bias into estimates of the data variance, affecting test statistics, power and false positive rate (Monti, 2011). The current practice of choosing a cut-off of the statistical threshold to show active/inactive regions further complicates the validity of fMRI statistical inference. To address this thresholding issue, approaches have been developed such as threshold-independent approaches to infer dominant hemisphere information which take into account activations at different thresholds (Pillai and Zaca, 2011; Suarez et al., 2008; Branco et al., 2006). Alternative approaches have been proposed for better inference-making with GLM, such as non-parametric approaches (Nichols and Holmes, 2002) and Bayesian inference (Friston et al., 2002). Other than GLM, a data-driven approach, independent component analysis (ICA), has been applied to analyze fMRI data. ICA can separate BOLD time series into spatially independent components that are regarded as functional networks or noise components, without prior knowledge of the time course of the networks (McKeown et al., 1998). It has been shown that ICA can improve the sensitivity and specificity of task-based language fMRI maps (Tie et al., 2008). ICA is more useful in analyzing rs-fMRI as there is no task timing information in the resting-state scans (Tie et al., 2014).

fMRI results also depend on appropriate preprocessing procedure. Spatial smoothing is a controversial but important preprocessing technique that can increase SNR. Smoothing improves the sensitivity of detecting activation in certain brain regions (Molloy et al., 2014; Mikl et al., 2008). Additionally, it increases SNR of lower resolution images to decrease the need to acquire time-intensive high resolution images (Molloy et al., 2014). However, spatial smoothing can decrease spatial resolution (Haller and Bartsch, 2009), and excessive smoothing can suppress activation signal. Conceptually, since the size of cortical representation varies for different anatomic regions and sensory modalities, the ideal spatial smoothing depends on the stimulus size or task size as well as the brain region. For example, primary sensory cortical representation of the lip is geometrically greater than that of the great toe, and thus spatial smoothing which maximizes SNR of the lip activations may extinguish the signal from the great toe. Smoothing may also cause edge artifact by smoothing non-brain voxels with brain voxels and blurring across sulcal boundaries (Maisog and Chmielowska, 1998).

6. Intraoperative use of fMRI results

The effectiveness of presurgical fMRI is ultimately measured by achieving intended operative goals and preservation of neurological function during surgery. Importantly, fMRI is useful for mapping the cortical surface, but does not aid with the mapping of subcortical structures (for which techniques such as diffusion tensor imaging (DTI) and subcortical stimulation mapping are designed). Currently, fMRI imaging is integrated with frameless stereotactic systems (i.e., neuronavigation systems) in what has been termed functional neuronavigation (Roessler et al., 1998a). After preoperative review and interpretation of the fMRI results, the fMRI maps are registered to the high-resolution anatomical imaging which is registered via the neuronavigation system to the patient. The neuronavigation system typically uses cutaneous facial features or fiducial markers which are delineated by the surgeon in reference to an optical reference frame or electromagnetic reference point which has been fixed in relation to the head. During the operation, a sensor triangulates position relative to the reference frame as well as the position of a surgical instrument or the surgical microscope. Compatible operating microscopes also provide focus distance information to the neuronavigation system. The location information allows the display of appropriate imaging data with fMRI map as well as other types of imaging data such as DTI derived from diffusion MRI (Archip et al., 2007). Fig. 3 shows a brain tumor patient's 3D rendering of the arcuate fasciculus with language fMRI results, where fMRI helped to validate the DTI findings and plan the safest route for tumor resection.

Accuracy of the imaging in the radiology setting may not correlate to accuracy of guidance intraoperatively. Error can arise from registration of the preoperative fMRI maps with preoperative anatomic imaging or from fiducial or surface registration techniques (Roessler et al., 1998b). Anatomic registration based on surface landmarks may not correlate with the operative anatomy, most significantly from brain shift due to craniotomy, durotomy, and tissue retraction and resection. However, since cortical mapping is usually performed immediately after dural opening, minimal brain shift has occurred at the time of capture. Three approaches have been proposed to account for perioperative changes. First, awake craniotomy with intraoperative ECS mapping has long been the gold-standard for intraoperative functional localization and surgical guidance (Ojemann, 1993; Sanai et al., 2008). This requires continued patient cooperation during potentially long procedure and may not be tolerated by some patients. Preoperative fMRI can aid ECS to improve its efficiency by guiding the region to be tested, making it shorter and better tolerated. Second, despite the difficulty of understanding the physical dynamics of the intracranial components, computational models have been proposed to predict brain shift and adjust preoperative imaging for intraoperative guidance (Kyriacou et al., 2002; Onofrey et al., 2013). Although these models were developed from clinical images, they have yet to be validated in clinical practice. Third, perhaps the most promising approach is to correlate intraoperative structural MRI or ultrasound images with preoperative fMRI to measure and compensate for brain shift occured during the procedure (Archip et al., 2007; Clatz et al., 2005). Rather than trying to predict the degree of brain deformation during a procedure, intraoperative imaging can be fused to preoperative fMRI to adjust for brain deformation in real-time and improve image guidance (Warfield et al., 2005). Intraoperative 3D image guidance used concurrently with fMRI can help ensure alignment of the preoperative fMRI data with the brain by examining sulcal and vascular anatomy to further improve the reliability of preoperative fMRI (Berntsen et al., 2010). This may provide more dynamic localization of the lesion, particularly since 3D ultrasound, like intraoperative DTI, can be updated throughout the procedure whereas structural MRI and cortical mapping are typically done at few discrete time points during surgery (Ozawa et al., 2009; Xiao et al., 2017). However, these techniques are unable to demonstrate subcortical structures and thus complementary to DTI and subcortical stimulation techniques. An interesting application of rs-fMRI is its intraoperative use where functional mapping could be obtained with the patients either under general or awake anesthesia (Qiu et al., 2017). While it has been shown to be safe and effective in glioma patients, it is not yet widely used.

7. Validation of fMRI results against gold-standard brain mapping techniques

Validation of the non-invasive fMRI against the invasive gold-standard brain mapping techniques such as ECS and Wada test is crucial for assessing the effectiveness of fMRI for surgical planning. However, there exists a fundamental difference between fMRI and the gold-standard tests. Unlike ECS or Wada tests which are inhibition techniques, task-based fMRI is an activation technique which is able to identify all functional brain regions associated with performance of a certain task, but unable to distinguish essential from participating areas. In surgical planning, the essential areas are the most important to preserve during surgery as their damage will result in permanent neurologic deficits. This fundamental difference may explain the mixed results among the studies that have assessed the validity of fMRI against gold-standard tests. Estimates of concordance between fMRI and ECS vary widely depending on patient characteristics and task selection, with reports ranging from 67% to 100% (Bizzi et al., 2008; Kapsalakis et al., 2012; Yetkin et al., 1997). For language lateralization, studies have demonstrated a strong correlation between fMRI and Wada test (Binder, 2011; Binder et al., 1996). According to one meta-analysis, fMRI may be as reliable as Wada test for language lateralization in patients with clear evidence of left-lateralized language function, while Wada test may be necessary when lateralization is less conclusive (Bauer et al., 2014). However, another meta-analysis found a sensitivity of 83.5% and specificity of 88.1% for fMRI for atypical language dominance determination, suggesting that fMRI may be sufficiently reliable for language lateralization in all patients (Dym et al., 2011). Additionally, Janecek et al. found that fMRI was superior to Wada test in predicting postoperative language function in patients for whom fMRI and Wada test were discordant (Janecek et al., 2013). A most recent guideline by the American Academy of Neurology suggested that

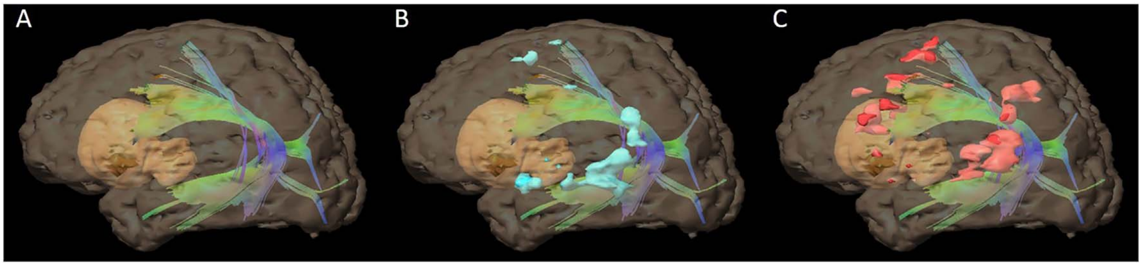

Fig. 3. 3D rendering of the arcuate fasciculus and language fMRI results for surgical planning for a patient with fronto-insular tumor. (A) Overlay of arcuate fasciculus fibers and the tumor (orange). (B) Overlay of auditory naming task-based fMRI results (blue) and DTI. (C) Overlay of antonym generation task-based fMRI results (red) and DTI. fMRI results helped to validate the DTI findings and allowed selection of the safest surgical route.

fMRI may be considered as a replacement of Wada test in epilepsy patients (Szaflarski et al., 2017).

However, for language localization, studies have suggested that the discordance of fMRI and ECS does not allow fMRI to replace ECS yet (Rutten et al., 2002; Petrovich et al., 2005; Roux et al., 2003). For example, Roux et al. correlated fMRI and ECS in 14 patients, and found sensitivities of $< 50\%$ for language fMRI (Roux et al., 2003). Kapsalakis et al. showed that language localization with fMRI exhibits lower concordance rates with ECS than sensory-motor and visual area localization (Kapsalakis et al., 2012). Interestingly, they found an association between patients' functional condition and language concordance rates, suggesting a possible role for patient participation and selection in influencing the reliability of fMRI for language mapping (Kapsalakis et al., 2012). These findings also suggest that poor baseline function can lead to spurious intraoperative ECS results. Motor mapping with fMRI has demonstrated reasonable association with ECS, with higher correlation than language mapping, but may also be too discordant to replace ECS (Bizzi et al., 2008; Kapsalakis et al., 2012; Yetkin et al., 1997). One study of intraoperative rs-fMRI for motor mapping reported sensitivity and specificity as 61.7% and 93.7%, respectively (Qiu et al., 2017).

fMRI may be sufficiently reliable to replace Wada test for mapping of memory function, according to the American Academy of Neurology's recommendations for patients with medial temporal lobe epilepsy (Szaflarski et al., 2017). However, this guideline specifically addresses laterality in epilepsy surgeries within the temporal lobe, and thus may not be generalizable to focal localization relevant in tumor surgeries.

fMRI has been used to map human visual system including the retinotopic organization of the visual cortex (Wandell and Winawer, 2011), and for presurgical planning in patients with tumors or seizure foci in the occipital lobe (DeYoe et al., 2015). Visual fMRI has proven to be particularly reliable, with near complete concordance with ECS and other gold-standard techniques (Hirsch et al., 2000; Kapsalakis et al., 2012).

Ultimately, some cases may benefit from alternative brain mapping techniques such as navigated TMS (nTMS) or MEG (Juenger et al., 2009; Makela et al., 2013). As discussed previously, alterations in neurovascular coupling can lead to errors in fMRI localization, while nTMS may have improved localization accuracy although it also involves significant variability in quality depending on the technical execution (Weiss Lucas et al., 2017; Picht et al., 2012). Compared with fMRI which is an observational study, TMS involves a component of minimally invasive intervention and associated risk, similar to intraoperative ECS mapping. MEG represents another non-invasive adjunctive functional imaging modality. MEG reflects neuronal electrical activity and is therefore one step more directly related to the function than the neurovascular changes assessed with fMRI, and may have higher temporal resolution than fMRI (Burianova et al., 2013). However, it is not clear how temporal resolution of functional imaging would impact surgical planning, and some MEG techniques are dependent on inferences hypothesis driven analysis; these models are modified to account for tumors and results are dependent on the subjectivity of model selection (Hyder et al., 2015).

8. Conclusions

fMRI is an increasingly used preoperative planning tool that has shown effectiveness for mapping brain functions in neurosurgical patients with lesions in the eloquent cortex. When applying fMRI in clinical settings, maximizing its benefits and mitigating its limitations requires an understanding of the fundamental aspects of this technique, which is critical to appropriately use and interpret fMRI mapping results. To derive accurate conclusions, the patient must be imaged under optimal conditions specifically catered to the individual patient's cognitive and physiologic state to allow proper detection of cerebrovascular change related to relevant neurologic activity. Patient cognitive, psychological, and physiologic states can magnify or dampen these changes, and protocol design can be used to overcome these obstacles. Data processing provides an opportunity to optimize the sensitivity and specificity of fMRI, especially in the context of patient-specific and task-related disruptions to BOLD signal changes. While the data on the concordance of fMRI with clinical gold-standard brain mapping techniques (such as ECS and Wada) is mixed, fMRI is widely adopted for surgical planning as it can provide functional information non-invasively and prior to undertaking a surgical procedure.

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