Clinical Challenges of Functional MRI

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Introduction

Functional magnetic resonance imaging (fMRI) has revolutionized clinical brain mapping by allowing a relatively rapid and noninvasive assessment of brain activity. Because of its relative ease, it has become one of the predominant functional neuroimaging techniques—and neuroimaging modality for surgical planning [1]—since its original report by Belliveau and colleagues [2]. The appeal of fMRI is attributable to several advantages that it offers over other functional neuroimaging techniques. Besides widespread accessibility, perhaps the most important advantage, especially in clinical populations, relate to the safety of fMRI: It is noninvasive, in contrast to either the Wada test or electrical stimulation mapping; it does not require exposure to ionizing radiation (as with positron emission tomography [PET]); and because it does not require stimulation of any kind, there is no risk of seizures (as may be the case with transcranial magnetic stimulation [TMS]). The other major advantage of fMRI is that it offers the opportunity for reliable, repeated measurements of the same task to investigate response consistency, compare activations across tasks, and measure change over time. It also allows for mapping the whole brain rather than areas that are accessible on the convexity via noninvasive techniques such as TMS [1]. Above all, fMRI is sufficiently powerful to produce maps of cognitive and motor functions that are reliable and valid at the single-subject level. This made possible the transition of fMRI from a research tool into a practical, approved, and reimbursable clinical procedure.

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Despite its advantages, fMRI presents several unique challenges, especially in the clinical setting. One of these challenges arises from the fact that fMRI does not directly measure neuronal activity. Instead, fMRI detects coupled perfusion-related signals that serve as a proxy for neuronal activity. fMRI analysis typically makes assumptions about the characteristics of neurovascular coupling and, therefore, the significance of fMRI activations; these assumptions are more suspect in a clinical setting when pathology may alter normal coupling mechanisms.

Clinical fMRI is also complicated by factors not normally encountered in a healthy population (Table 25.1). For example, the presence of intracerebral pathologies (e.g., arteriovenous malformations [AVMs] or brain tumors), perilesional edema, and mass effect can induce field inhomogeneities, cause decrease or absent blood-oxygen-level-dependent (BOLD) signal in functionally intact tissue. It may also alter neurovascular coupling mechanisms—all of which may hamper measurement of reliable hemodynamic-based fMRI signals [3]. Surgical clips and hardware from prior craniotomies can also create patches of signal loss, and often these are in the very regions in which mapping is needed.

Other important challenges of clinical fMRI include the ability of patients to comply with imaging protocols and perform cognitive tasks. For example, imaging in clinical populations is often associated with increased head movement. In one study, nearly 30% of subjects with intracranial masses were excluded from the final analysis because of gross motion artifacts [4]. This is a particularly difficult problem if one wishes to study patients with movement disorders, such as Parkinson's disease and Tourette syndrome. Impairments

Table 25.1 Potential limitations of fMRI in clinical populations

Field inhomogeneities in region of interest (ROI)
Movement artifacts
Altered baseline intelligence
Impaired task compliance
Impaired motivation
Sensitivity to certain stimuli (e.g., flickering lights)

S. H. Faro, F. B. Mohamed (eds.), *Functional Neuroradiology*, https://doi.org/10.1007/978-3-031-10909-6_25

in cognition may also alter patients' abilities to complete tasks, both with respect to motivation and task difficulty (i.e., the presumed difficulty of a task may be different in various populations due to differences in baseline skills).

Analytic methods also require special consideration in that clinical brain mapping emphasizes results for the individual rather than for a group—single-subject analyses are inherently different from group analyses. Altered anatomy due to intracerebral lesions may prohibit spatial registration and normalization tools commonly used in group statistics, making it difficult to directly compare patients results with those from a normative sample [5].

This chapter will elaborate on some of the most salient points, including study and task design, data analysis, and reproducibility when considering the use of fMRI for clinical planning. Although there is a large number of clinical fMRI studies being published, few have tackled these challenges fully. Ultimately, our ability to derive clinical benefit from fMRI will depend upon finding appropriate solutions to these challenges. What is clear is that a black box method of using fMRI in clinical populations will produce reliable results. Successful implementation of clinical fMRI requires a dedicated and informed team of psychologists and individuals with detailed knowledge of image analyses and the specific imaging challenges reviewed here.

Mapping Cognitive Function with Activation Versus Disruption

Until the advent of fMRI and other perfusion-based brain mapping techniques, our understanding of the functional organization of the brain largely stemmed from studying the effects of brain lesions. Although brain lesions initially were limited to strokes and other "accidents of nature," Penfield recognized in 1937 that temporary brain lesions could also be induced to study brain function by applying electrical stimulations directly on the cortex [6]. More recently, TMS has been introduced as a means of noninvasively delivering electrical stimulation, which can act as a temporary lesion in some cortices while serving as a noninvasive means of cortical activation in other cortices, such as the primary motor cortex [7]. With respect to lesions, whether permanent or temporary, these disruption-based techniques identify parts of the brain that are essential and critical for executing a given task; in essence, those regions which, when disrupted, result in catastrophic loss of function for which other brain regions cannot compensate. These disruption-based techniques of brain mapping have emerged as the gold standard of clinical brain mapping, especially in the neurosurgical arena.

Functional MRI and all activation-based brain mapping techniques differ fundamentally from the classic lesion-based approach to clinical brain mapping in that instead of only identifying areas of the brain that are essential for performing a task, fMRI reveals all brain areas that demonstrate activity-related changes during a given task, regardless of whether a given brain area is, in fact, critical for task performance, identifying both "essential" and supplemental cortical areas. Because of this fundamental difference in methodology, fMRI maps and lesion maps will inevitably differ. Both maps are probably clinically relevant, but one must be aware of the different data produced, their implications, and the types of conclusions that can be drawn from each.

As discussed in earlier chapters, fMRI offers an indirect measure of brain function: instead of directly measuring neuronal activity, fMRI maps the brain by detecting functional hemodynamic responses that are coupled to neuronal activity. Establishing clinical validity of the instrument assumes both that MRI signal changes reflect underlying neural activity and, assuming we accept this relationship, that a particular patient has a normal fMRI response (e.g., the blood flow response is unaffected by their clinical condition). This complexity can be illustrated by conceptualizing brain mapping as a series of mathematical functions (Fig. 25.1) [8].

Given a stimulus x, there is a given neuronal response $f(x)$, representing the "true" brain map. The neuronal response is coupled to a functional hemodynamic response by a neurovascular coupling function, p. The uncertainty of this neurovascular coupling function introduces one of the biggest challenges and one of the most significant sources of error in interpreting clinical fMRI studies. What ultimately matters about the neurovascular relationship is the degree and precision of spatial coupling between neuronal activity. As discussed later, the spatial coupling between fMRI activation signals and electrophysiologically active cortex may not be as precise as most would like or as may be clinically relevant.

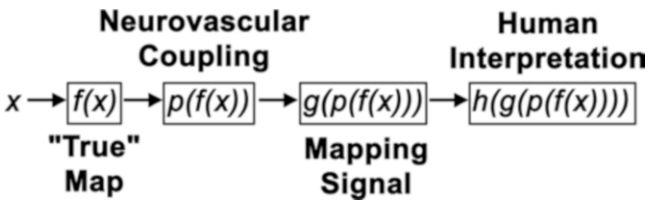

Fig. 25.1 Cascade of functional brain mapping functions. The mapping signal observed and reported is actually not a true map of neuronal activity. Rather, it is a product of a series of complex functions, including, for example, the coupling of neuronal activity and local cerebral perfusion or neurovascular coupling (p). To better understand how functional brain maps relate to underlying true maps, it is critical to characterize the robustness of neurovascular coupling under different stimulus conditions, in different cortices, and in the presence of different pathologies. (Adapted from [8])

Several studies indicate that hemodynamic responses can be significantly different across brain regions, especially when adjacent to major pathology. In a study of 98 patients, Krings and colleagues showed that the distance of a central mass from the motor region significantly influenced the magnitude of activation, even in patients without paresis [3]. Other studies have found similar suppression of the hemodynamic response adjacent to pathology [9, 10]. Conversely, in a study of 14 patients, Schlosser and colleagues suggest that fMRI activation patterns in patients with frontal lobe tumors when mapped using a verbal fluency paradigm were comparable to signals in normal controls [11]. Similarly, Righini and colleagues studied 17 patients with frontoparietal masses and found little difference in motor activations between the affected and unaffected hemispheres [4]. The contradiction in these studies highlights the need to be aware of the possibility that adjacent pathologies may alter cerebral hemodynamics, but that this alteration is most likely pathology and location-dependent and, possibly, task-dependent. Finally, different physiological states (e.g., hypercapnia, hypoxia, and hypertension) and different disease states (e.g., vasculitis, angiopathies) can differentially impact the relationship between neuronal activity and functional perfusion [12, 13]. Schmitz and colleagues have shown, in a rodent model, that brief exposure to hypercapnia may potentiate the hemodynamic response without affecting the underlying electrophysiological response [14, 15]. In fact, hypercapnia can be used in a normal subject as a means of contrast enhancement [16]. The age of the subject may also affect the magnitude of the hemodynamic response and the coupling mechanism itself [3] since increasing age is associated with impaired autoregulation and a loss of vasodilatory response to neural activation [1, 17]. Understanding the underlying coupling dynamics is essential to interpreting fMRI results. This uncertainty continues to motivate continued investigation of neurovascular coupling dynamics.

Assuming neurovascular coupling is intact, several more functions are still applied before arriving at any interpretations of fMRI maps. The functional perfusion response produces a brain mapping signal, g: $g(p(f(x)))$. The function g is determined not only by the physics behind fMRI signals sources (i.e., field strengths, scan sequences), but also by the recording capabilities of the particular scanner, including but not limited to resolution limitations, data filtering, artifacts that may be introduced by different disease processes or medical interventions (e.g., coils, clips, arteriovenous malformations, air cavities after neurosurgical resections), and head movement (which can be significantly more in a patient population).

Finally, yet another function is introduced into the formula, h, for introducing human study design, human interpretation, and statistics. When not quantitative, human interpretation of mapping signals is always susceptible to bias. The bias may be inadvertent and as subtle as in selecting an inappropriate control for comparison or measuring inappropriate signal parameters from which to draw conclusions. However, strict adherence to automated and quantitative analysis has its own problems. For example, the incidence of right hemisphere language in a right-handed individual without a developmental disorder is extremely low—maybe a few percent, based on studies of patients with stroke. An apparent finding of greater right than left hemisphere activation on language tasks in a patient with a space-occupying lesion near the language cortex creates a dilemma: Does one give greater weight to the actual data or the known probability of hemispheric dominance? The statistics and thresholds commonly used in fMRI also introduce error and misinterpretations, presenting yet another challenge to clinical interpretation scans. Where does one set a threshold in a clinical study: strictly, as in typical research studies, or liberally, in order to avoid false negatives? What are the potential implications of making a false-positive versus a false-negative error? In the case of surgical planning, it is probably important to be more inclusive of potentially relevant functional cortical areas rather than be overly restrictive, fail to identify functionally relevant brain regions, and induce a neurological deficit. Simply showing the data may not convey the information necessary to allow surgeons to make an informed decision.

Although many studies compare "blobs" across groups, there are a number of assumptions that underlie those blobs. In order to better understand the underlying map, or $f(x)$, we must deconvolve this complex function by characterizing the factors that influence all of these functions. Alternatively, the investigator can pay special attention to study design and analysis in order to minimize assumptions and strengthen their conclusions. Many of these issues of study design and analysis are discussed as follows.

Technical Considerations

Field Strength

Magnetic field strength is an important consideration in clinical fMRI study design. Increasing field strength provides a greater dynamic range of data collection and, ultimately, a greater signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) (e.g., Kruger et al. [18]). This is discussed in detail in Chap. 22. While the greater SNR biases one towards higher field strength, it also poses problems that may prove insurmountable in some brain regions or in some clinical conditions. The most difficult complication arising from increased field strength is the associated increase in susceptibility artifact, especially near tissue interfaces. This is a particular problem in the inferior temporal lobes and the

inferior medial frontal lobes, which are adjacent to the air-filled sinuses. These areas of susceptibility artifact produce both spatial distortion and MR signal loss, which make it difficult or impossible to identify activity-related changes in fMRI. This is particularly important for language mapping, in which investigators expect to find several temporal lobe language areas (e.g., [19, 20]). The lack of signal in these regions does not indicate a lack of activity but may be due to a lack of sensitivity to identify appropriate signals. Devlin and colleagues have proposed alternate strategies when imaging these regions of high susceptibility but also acknowledge that these artifacts can only be partially overcome and that alternative data acquisition paradigms are necessary to address this issue [21]. In some cases, appropriate selection of scan sequence may help overcome some susceptibility artifacts, especially when imaging adjacent to pathology.

Scan Sequence and Susceptibility

The most commonly used fMRI pulse sequence is the gradient-echo echo-planar (EPI) sequence. EPI is the fast scanning technique that acquires all slice locations with a single TR, making fMRI practical [22]. The gradient-echo sequence is optimized to maximize susceptibility because of BOLD contrast. An unfortunate but necessary side effect is that it also maximizes unwanted susceptibility artifacts at tissue interfaces, especially at high fields. The susceptibility artifacts may make imaging these regions impossible in certain brain regions, particularly the amygdala, basal temporal region, and orbitofrontal cortex.

Magnetic susceptibility artifacts—especially at higher field strengths—can also inadvertently highlight draining veins because of the higher deoxyhemoglobin content in the venous system [23, 24]. Veins can generate BOLD signal changes of up to 10%, thereby augmenting activation regions [25]. Some authors speculate that this distortion is responsible for the differences in activation regions detected on PET and fMRI [26].

Clinical fMRI in patients who have had prior brain surgery may be complicated by the presence of implanted devices, such as plates and screws. While most of these devices are considered "magnet compatible"—that is, they are not ferromagnetic and do not pose a safety concern—susceptibility artifacts can generate profound distortions around these objects, including massive signal loss and spatial distortion. It should also be noted that many of these devices have not been tested at high field and could pose a safety risk that does not exist at lower field strength. Typically, these objects will be implanted close to or on top of the precise regions the clinician would like to have mapped.

As ultra-high field (>3 T) MRI becomes more widely available in the clinical setting, some authors have begun investigating what potential diagnostic advantages it may confer for fMRI [27, 28]. While a number of benefits have been observed in higher fields, one important drawback is an increase in susceptibility artifacts [27, 28]. As these technologies begin to supplant 1.5 and 3 T MRI machines in the clinical setting, the importance of limiting susceptibility artifacts will be of even greater importance.

There is a wide variety of simple approaches to reducing susceptibility artifacts at air–tissue interfaces and around objects during functional imaging. Weiskopf et al. describe optimizing BOLD sensitivity (BS) at air–tissue interfaces by adjusting slice tilt, the direction of phase encoding, and the z-shim moment for gradient-echo EPI, and managed to achieve between 30% and 60% increases in BS in brain regions normally affected by air–tissue interface susceptibility [29]. Another solution is to adjust the voxel size. For instance, Merboldt et al. calculated that voxel sizes of 4–8 μL or less are necessary to recover sufficient signal in the amygdala [30]. Fransson et al. used a high-resolution acquisition method to receive the signal in the hippocampus using coronal acquisitions and in-plane resolution of 2 mm^2 and slice thickness of 1 mm [31]. For most centers, this approach is impractical due to a lack of nonstandard sequences on clinically oriented machines and because the associated reduction in the field of view (FOV) is not acceptable for many systems. However, small voxel studies may be appropriate for patients with a focal lesion in which a small FOV is all that is necessary. The loss of contrast-to-noise ratio (CNR) within small voxels may also prohibit the practical use of this approach.

To some extent, the use of alternative pulse sequences can improve, but not wholly overcome, these artifacts. Port et al. performed a series of imaging studies on titanium screws embedded in gel to determine parameters that would decrease susceptibility artifacts in EP images [32]. They reported three factors that can reduce artifacts: reducing the time-to-echo (TE), increasing the frequency matrix, and reducing slice thickness. The latter two approaches are identical to those reported by Merboldt and colleagues [30] for imaging at air-tissue boundaries. However, the effects of reducing TE on susceptibility are controversial. Susceptibility artifacts due to signal loss at air–tissue interfaces are greater with longer TEs. Gorno-Tempini et al. used a double echo EPI sequence to compare susceptibility artifacts and BOLD signal changes at tissue interfaces, comparing TEs of 27 and 40 ms [33]. They used a face-processing task, known to activate the fusiform gyrus in the base of the temporal lobe, an area likely to suffer from susceptibility-induced signal loss. While the lower TE did not change their ability to detect BOLD signals in those regions unaffected by susceptibility artifacts, the lower TE was not sufficient to recover the BOLD signal in the problem areas. Spiral in-out sequences have also shown benefits in reducing artifacts in fMRI [34].

Various pulse sequences have differential effects on susceptibility artifacts. The asymmetric spin echo is one alternative to the commonly used gradient-echo EPI scan. Both spin-echo and gradient-echo sequences base their signals on magnetic susceptibility contrast, as described previously. The spin-echo sequence, however, refocuses the spin dephasing caused by field inhomogeneity. The consequence is that a spin-echo sequence reduces susceptibility artifacts at air-tissue boundaries but will also result in CNR loss due to reduced BOLD contrast. At the high field, this loss may be an acceptable trade-off. Spin-echo sequences tend to recover signal from larger rather than smaller boundaries and thus have been thought to affect unwanted susceptibility artifacts preferentially, including effects in larger blood vessels, while preserving signal changes in the capillaries. The *asymmetric* spin-echo sequence shifts the time differential between the image acquisition and readout, allowing the signal to decay; thus, the amount of reversible dephasing that occurs can be varied by adjusting the length of this shift. The longer the asymmetry, the more the spin-echo images resemble a gradient-echo image. Stables et al. have demonstrated that varying these parameters can optimize for a particular perturbation size (i.e., a small or large blood vessel) [35]. Several fMRI studies have used a spin-echo sequence effectively in high susceptibility areas such as the hippocampus and amygdala (e.g., Stern, Hariri et al., and LaBar et al. [36–38]). Figure 25.2 shows examples of a gradient echo and asymmetric spin-echo EPI images using otherwise identical parameters in the same subject. The recovery of signal in high susceptibility areas, especially around a lesion, is quite apparent, though not complete.

Other modifications to the EPI sequence may reduce susceptibility artifacts. Cordes et al. advocate using a second refocusing gradient in the slice selection orientation to reduce susceptibility artifacts [39]. A more complicated approach offered by Stenger et al. uses three-dimensional (3D) tailored radiofrequency (RF) pulses to refocus regions where the susceptibility is greatest, using a modified spiral *k*-space trajectory [40].

In spiral scanning, *k*-space is traversed in a spiral pattern emanating either from the center to the exterior (spiral-in), the reverse (spiral-out), or in some combination (e.g., dual-echo in-out). Glover and Law reported that a spiral-in trajectory or a combination of in and out trajectories could both increase SNR while reducing susceptibility [41, 42]. Yang et al. developed a reverse spiral scanning technique simultaneous with perfusion imaging with arterial spin labeling [43]. Comparisons of susceptibility artifacts between forward and reverse spiral scanning suggested less susceptibility in the reverse sequence, with adequate BOLD signal in high susceptibility regions. Other techniques to reduce susceptibility artifacts in spiral scans include a sensitivity encoding (SENSE) sequencing [44], which shortens the readout duration, thus minimizing signal loss. However, the effects of BOLD signal recovery were less dramatic.

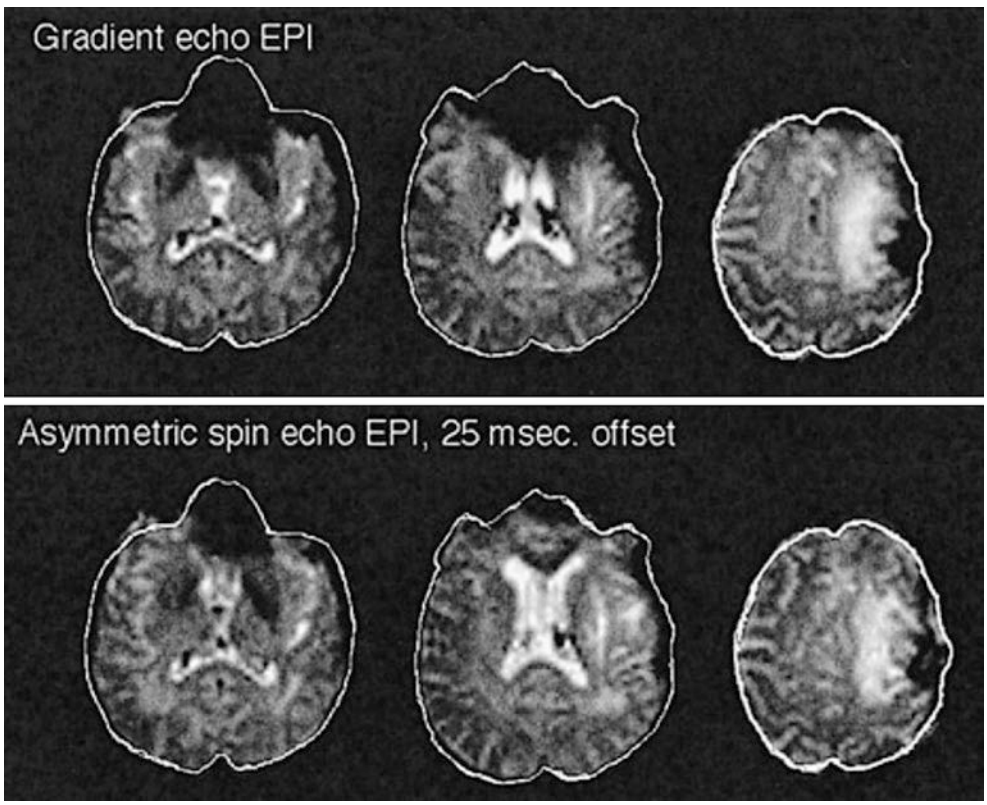

Fig. 25.2 Gradient echo versus asymmetric spin echo (ASE) echo-planar imaging (EPI). Gradient echo (TR = 2.5, TE = 64 × 64 matrix, FOV = 20, 1 NEX) and asymmetric spin echo (TR = 2.5, TE = 45, offset = 25 ms, 64 × 64 matrix, FOV = 20, 1 NEX) EPI scans in two areas of high susceptibility (*left*) at air–tissue interfaces in basal temporal and orbitofrontal cortex (*right*) near the lesion with prior resection. The outlines are derived from a high-resolution spin echo EPI (TR = 4000; TE = 54, 128 × 128 matrix, 20-mm FOV, 5-mm thick, 4 NEX). Note reduced susceptibility in ASE scans in both regions of high susceptibility. *TR* repetition time, *TE* echo time, *FOV* field of view, *NEX* number of excitations

Study and Task Design

Issues in task design, particularly choice of activation and control tasks, as well as difficulty level, are important considerations in all fMRI studies. In the clinical arena, these difficulties take on special significance, as errors in task design can lead to false conclusions that may harm patients. Here we will discuss three issues of particular importance in clinical fMRI: choice of control conditions, the effect of practice on observed fMRI activations, and the appropriate difficulty level given the population to be studied.

Task Selection

Functional MRI activations represent a contrast between two conditions; in the earliest fMRI studies, this contrast was identified by simply subtracting rest or control condition images from those acquired during a task [45, 46]. This simple subtraction approach assumes: (1) a hierarchical organization of brain function, (2) that the investigator can accurately decompose a complex task, and (3) cognitive activity and brain function are insignificant during rest conditions.

The assumption that an investigator can accurately decompose a task into its components is a challenge in itself. Not all subjects will always use the same strategy to perform a task, nor can we easily deduce all the cognitive processes that are required to complete a given task function. This challenge may be even more difficult in a clinical population in which there may be subclinical or overt cognitive deficits that may alter the strategies used to perform a task. That is to say, tasks that are suitable for brain mapping in the general healthy population cannot necessarily be applied blindly to a sick population. Finally, this approach assumes cognitive functions linearly summate to produce the observed fMRI signals and that there is no interaction between cognitive functions that may produce a unique output based on the combination of tasks.

To test the assumptions of linearity of hierarchical structure, Sidtis and colleagues compared activation maps using "simple subtraction" (maps were generated by subtracting a rest condition from a task condition), and "complex subtractions" (maps were generated by subtracting two tasks that were presumed to only differ with respect to a single parameter) [47]. The three tasks used were syllable repetition, phonation, and lip closure. Syllable repetition was assumed to be a combination of phonation and lip closure for the purposes of this study. Lip closure maps were generated by "simple subtraction" of the rest condition from the lip closure condition, and "complex subtraction" maps were generated by subtracting the phonation condition from the syllable repetition condition. The simple and complex subtraction maps were different both with respect to signal intensities and distribution, suggesting that the condition of additivity necessary to decompose complex tasks by subtraction was not present in the data, calling into serious question subtraction methodology and the assumption that we can accurately decompose tasks.

Stark and Squire examined activation patterns associated with rest conditions (used as a baseline) to determine if "rest" is necessarily an appropriate control or baseline, with particular attention to memory tasks looking at the medial temporal lobe [48]. The authors measured fMRI signals during seven different tasks: novel pictures, familiar pictures, noise detection, odd/even discrimination, arrow discrimination, moving fixation, and rest. The first two tasks were considered memory tasks, while the last five were considered to be various controls. Not surprisingly, the authors demonstrated that identifying activity in the medial temporal lobe (including hippocampal and parahippocampal structures) varied depending on the control condition used. In fact, the authors reported that activity within these structures was *higher* during the rest condition than during other control conditions. Consequently, identifying activity in the region of interest (ROI) intimately depended on the control condition used. This study highlights two important points. First, fMRI activations represent contrasts between two conditions and do not indicate whether a part of the brain was active. Rather, it means there was not a significant enough change in neuronal activity *relative to the baseline* to evoke a functional hemodynamic response. This highlights the need for careful selection of baseline tasks and even the more careful interpretation of observed activation patterns. Second, "rest" does not mean that the brain is quiescent; the brain is cognitively active even during rest, which has formed the basis for the entire field of resting-state fMRI. Gusnard and Raichle provided an early review of the concept of a "physiological baseline," suggesting that the brain has a high level of activity at baseline and that this must be considered when using rest as a control condition and when interpreting functional activation studies [49]. Importantly, they provide a thorough discussion of task-related *decreases* in activation and argue that while some may represent a task-dependent decrease in cerebral activity, many decreases seem to be task-independent, representing an "organized mode of brain function, which is attenuated during various goal-directed behaviors" [49]. This so-called "default mode network" [50, 51] involves several regions, including medial parietal cortex, hippocampus, and temporal cortex, that typically are reduced in blood flow during task performance across a wide range of tasks. As several of these regions are frequent targets for clinical mapping—the hippocampus and dominant temporal lobe—understanding how they respond during task engagement and how these responses compare to disruption methods are completely unstudied.

Practice Effects

Paradigm design is important not only for selection of tasks but also for task timing. Several studies now indicate that practicing a task can significantly alter activation patterns, revealing different maps that may represent alternative strategies for performing the given task, such as automatization [52–55]. Raichle and associates were the first to report that functional activation patterns can be altered by relatively brief periods of practice [52]. Comparing a novel verbal response selection task with reading visually presented nouns, they found a practice-related decrease in cortical activation of those regions mediating performance at the beginning of the task after only 15 min of practice. Moreover, other brain regions increased activity, such that, with practice, the verbal response task more resembled the reading task. This practice effect was reversed by introducing a novel list of words, allowing the authors to conclude that the activation patterns associated with practice represented a reversible automatization of the task. Van Mier et al. [54] and Petersen et al. [53] report similar findings of shifts in activation patterns, or changes in functional neuroanatomy, from one part of the brain to another with practice, which is thought to represent an activity-dependent shift in effortful task performance to skilled, automatic task performance.

Similarly, Madden and colleagues reported a decrease in functional activation with practice in the two populations they studied: young adults (20–29 years) and older adults (62–79 years) [55]. Using a verbal recognition memory task, this group characterized activation patterns during encoding, baseline, and retrieval and found that activation patterns were different (both increased magnitude and different spatial distribution) between these populations for each task. Interestingly, despite differences initially, both groups demonstrated practice-related effects, showing decreased activation magnitude, although the practice effects were greater in the younger population than in the elderly. The authors concluded that older adults required a more distributive network of brain activation in order to perform the given task. While task performance improved with practice, the smaller practice effect observed in the older group represents a continual recruitment of cognitive processes and attention to support task execution that is not required in the younger population, who can learn and automate more quickly and effectively.

Not all groups, however, have reported activation of additional areas with practice. Garavan and associates argued that if the core task is unchanged by practice, then practice may cause a decreased magnitude of activation but will not necessarily recruit additional areas of the brain [56]. Using a visuospatial working memory (VSWM) task, they reported decreased fMRI activations in the four areas of interest with activation but did not report seeing additional areas of activation with practice. They suggested that their observations were consistent with the fact that the task used continues to tax the VSWM system and cannot be automated completely, regardless of the amount of practice. This raises an interesting consideration that not all cognitive tasks are equally susceptible to practice effects.

The existence of practice effects and relative rapidity of onset is important technical consideration in implementing a functional brain mapping study, especially if one wishes to identify those brain regions that are actively involved in and essential to task performance. Most fMRI studies take approximately 1 h to complete, during which brain activation patterns may be modified secondary to practice. It is therefore critical to plan experiments efficiently and to continually provide novel stimuli and tasks in order to assure that practice-related changes do not taint the results (unless, of course, it is the practice-related effects that are being investigated in the first place).

Task Difficulty

Another important consideration that is intimately related to the concept of practice is task difficulty. It is hypothesized that the changes seen due to practice are largely due to decreases in task difficulty with practice and, therefore, automatization of task performance. If a task is too easy, the task may activate brain areas involved with performing automatic activities without taxing the appropriate cognitively critical areas of interest. In contrast, if a task is too difficult, it may recruit additional attentional and supplementary areas (areas that a task may not normally activate) to help execute a task.

The paradigm of mapping a paretic or plegic patient offers an excellent means of discussing task difficulty and its effects on fMRI activations. For these patients, the effort and difficulty to complete a motor task are undoubtedly greater than for a healthy volunteer. The source of the paresis (i.e., intracerebral versus spinal) will influence the fMRI activation pattern. In a study of patients with central masses near the motor strip, fMRI activations of the primary motor cortex decreased with increasing paresis, independent of the distance of the central mass from the motor strip, although the degree of paresis did not correlate with the magnitude of the observed fMRI signal [3, 5]. The observed decrease in primary motor activation cannot be unambiguously attributed to a decreased number of functional neurons in the motor strip, compression due to mass effect (although the observation was independent of the distance of the mass from the central strip), tumor-mediated changes in local cerebral hemodynamics, changes in global perfusion due to the presence of a neoplasm, or a combination of these factors [5]. It is critically important from the perspective of clinical brain mapping to consider if a better primary motor strip mapping

signal could have been obtained by changing the difficulty level of the given motor task. Could a more significant signal be elicited from the primary motor strip if the motor task is made more complex and drives the remaining primary motor neurons harder? What if the motor task is made simpler, or is assisted, imagined, or uses passive movement (in profoundly impaired patients)? [57, 58]. Could a simpler task induce greater activation by giving the remaining primary motor neurons a task they can execute fully? These may be important points of consideration in interpreting clinical data.

In the same study, the investigators report larger secondary motor activations in patients with paresis than without paresis. This is likely attributable to the difficulty of the task for the paretic patients [5]. Similar to the case of elderly patients recruiting a broader network of neurons than younger controls in order to execute a memory task [56], the paretic patients may be recruiting additional cortical areas in order to execute a task that is relatively difficult for them, given their current medical condition. Krings and colleagues therefore conclude, "With increasing task complexity (or with decreasing motor skills), this network must increase its excitatory output, resulting in a higher neuronal activity, more pronounced regional cerebral blood flow changes" [5].

In tasks of higher cognitive functioning, the problem of task difficulty may be even more complex. For instance, in our work with patients who have a genetic risk for Alzheimer's disease (AD), older volunteers with normal memory but who carried the APO-4 allele (which conveys a strong risk of AD) had an increase in the magnitude and spatial extent of brain activation on fMRI in comparison to age- and memory-matched controls [59]. Among subjects who have mild AD, however, there is a significant decrease in fMRI activation [60, 61]. In parametric studies of memory load in normal volunteers, increased memory load was associated with increased activation that varied parametrically [62]. Thus, the relationship between task difficulty and activation magnitude is complex, and performance level must be considered a critical factor in interpreting fMRI results.

Patients with aphasia due to brain lesions show similar alterations in brain activity. For instance, Sonty et al. showed that patients with primary progressive aphasia had activation like normal in primary language areas but also additional language activation in regions outside language cortices, suggesting the use of compensatory strategies [63]. Kim et al. found that the pattern of reorganization in patients with focal lesions varied across individuals and appeared related to whether the lesions were cortical or subcortical [64]. Calvert et al. found that patterns of fMRI activation during language tasks in a frontal lobe CVA patient depending upon the task; increased right hemisphere Broca's area analog was activated during the most difficult task, whereas the left hemisphere Broca's area was active for a matched control subject [65].

Together, the existing data suggest that patients with deficits tend to utilize compensatory strategies that engage additional brain regions to accomplish the task. The pattern of fMRI activation during compensation may give a false impression about the localization of function. For instance, increased compensatory RH activation may incorrectly suggest the patient has right hemisphere speech dominance. Thus, clinical use of fMRI for localization of function must take into account the patient's level of cognitive performance. Impaired performance can easily lead to false conclusions about functional localization, particularly in language tasks.

Ultimately, it is important to consider whether differences in activation patterns across conditions or groups represent differences in brain organization and function or an artifact of the differential capability to cope with task difficulty. We suggest investigators pay close attention to task difficulty in designing, interpreting, and drawing conclusions from their clinical studies, especially when the general medical condition of one group is significantly different from the comparison group.

Task Choice

In clinical imaging for surgical planning, the functions most commonly mapped are motor and language. Motor mapping is relatively straightforward when the clinical questions center around preserving the motor strip. Language mapping is a more complex evaluation, and there are many approaches to task choice. Early studies focused on a single paradigm: word generation, which has been found to be reliable across sites in indicating frontal language areas in particular (e.g., Ruff et al. [66] Rutten et al. [67]). However, the language system is complex, and different tasks may be best suited to map different brain regions, such as naming for the basal temporal language area, semantic decision tasks for Wernicke's area, and reading for inferior temporal and inferior parietal regions.

An alternative strategy is to assess function using a "panel of tasks." Gaillard and colleagues described using a panel of language tasks (verbal fluency, reading comprehension, and auditory comprehension) to assess hemispheric lateralization rather than a single task [67]. They found that using a panel of tasks resulted in superior inter-rater reliability than relying on a single task, reduced the likelihood of having "nondiagnostic findings," and improved concordance between laterality assessments based of fMRI and Wada testing.

Deciding on the baseline tasks for language has been controversial. While some have argued against using activation controls, which may induce activity in language areas unintentionally (e.g., Bookheimer [68]), others have argued in favor of tailored baseline, sensory activation controls (e.g.,

Binder et al. [69]). In a study examining the magnitude of activation and degree of lateralization during a series of comprehension tasks, Binder et al. found that using a tone control task produced stronger laterality effects than using a rest comparison and argued that semantic processing might occur at rest, obscuring possible LH language areas during language tasks [69]. However, the location of their results is not consistent with the loci of Wernicke's area as reported by other investigators, and their results have not been validated with a gold standard measure of intrahemispheric localization of function. In our view, the potential for false-negative errors is greatest when there are sensory activation controls that may inadvertently activate "eloquent" cortex, or when containing nonlinguistic sensory information, may produce task-related decreases in language areas. In such a scenario, the use of these tasks as controls may falsely indicate task-related activation, which is rather due to the deactivation of the control task. Clearly, the issue of how to choose both activation and control tasks remains of extreme importance, and regardless of theoretical reasons for choosing an approach, any combination of task and control conditions requires confirmation with a gold standard—Wada tests for laterality, electrocortical stimulation mapping (ESM) for intrahemispheric localization—to validate the approach fully.

Special Task Considerations

An additional complication in choosing language tasks concerns whether the patient is bilingual and how (and whether) to map native versus non-native languages. Though results vary depending upon language proficiency and age of second language acquisition, there is consensus that second languages may have unique representations in the brain that can be measured with fMRI and electrocorticography. ESM studies have consistently found areas of unique representations for different languages in bilingual patients (e.g., Lucas et al. [70]) and fMRI studies of normal control; bilingual subjects show differences in language representations based on the age of onset [71] as well as proficiency [72], and language-specific differences in the organization (e.g., reading in phonological- versus pictographic-based languages [73]). Therefore, it is typically necessary to map both native and second languages in bilingual patients.

Head Motion

Excessive head motion is always a problem in fMRI studies but is of particular concern in clinical studies. While in group-average research studies, subjects with too much motion can be removed from the analysis, or at least will just add error; in clinical fMRI examinations, a single valid study, often in a limited time window, may be all that is possible. Further, cognitive compromise makes it more difficult for many patients to stay still voluntarily. Typically, head motion is managed by registration of all images in a time series, or by mathematically removing variance due to motion (e.g., Jenkinson et al. [74]; Grootoonk et al. [75]), or even removing images from the time series that are affected by head motion. Physically minimizing head motion with devices such as bite bars, headbands, or mouth guards is typically uncomfortable for subjects and can introduce an element of distraction, particularly for prolonged studies [76, 77]. Prospective motion correction technologies are currently still of limited utility and can only be applied to certain sequences [77]. Ultimately, there is consensus that too much motion is uncorrectable through such means. Further, the potential effects of head motion may add noise that obscures true signal or may create artifacts that appear as activation, particularly when the motion is correlated with the task (e.g., Desmond et al. [78]). For these reasons, obtaining motion-free, high-quality data from patients is of particular importance, and the raw data must be carefully examined for the presence of motion.

Iatrogenic Considerations

A number of pharmacologic agents have the capacity to interfere with BOLD fMRI responses by uncoupling cerebral blood flow and oxygen consumption. Medications such as acetazolamide or even everyday compounds such as caffeine, ethanol, and nicotine have all been shown to alter BOLD signal and so should be considered prior to commencing fMRI data acquisition [1, 79, 80]. The impact of steroid regimens and anti-epileptic medications remains uncleardespite their common usage in neurosurgical patients [1, 81–83].

Other patient-related factors include sleep deprivation or disturbance (commonly found in neurosurgical patients who are hospitalized on steroid regimens) and fatigue, which have been shown to influence the BOLD signal [84–87]. Moreover, anxiety, fear, and pain, which may be associated with a particular pathology, may interfere with subject attention and task performance and introduce greater activation in the insula and amygdala [88]. Preparing patients appropriately prior to fMRI testing can help promote a "normal" physiologic state to produce reliable fMRI data [1].

Analysis

Adequate study and task design are insufficient to draw strong conclusions from a clinical fMRI study. Careful selection of analysis techniques and attention to the particular

challenges of analysis limitations is necessary in order to accurately interpret mapping data. Analysis in clinical studies differs from other studies most significantly in that analysis is done "within subjects" rather than at a group level. Moreover, one must also be cognizant of the methods used to quantify fMRI activations and the techniques that can be used to optimize the sensitivity and specificity of the derived functional maps.

Within Subject vs. Group Analysis

The vast corpus of data in functional imaging relies almost exclusively on group-averaged data. Early efforts in PET and later fMRI research focused on developing superior tools for registering and ultimately warping brains from different subjects into a common space in order to increase SNR through subject averaging. While these efforts have been extremely useful in making it possible to answer broad questions about human cognition, these approaches have limited clinical utility for the individual patient. Here we differentiate between clinical research studies, which have and will continue to use group averaging procedures, from true clinical fMRI, in which a clinician will attempt to make a diagnosis or decision for an individual based on their fMRI results. First, we consider the broad nature of the question to be answered.

Why will patients be referred for fMRI? Common current applications are to make a decision relevant to surgical intervention, such as: in what hemisphere is language located or where within a hemisphere does a particular functional reside? Future applications may include diagnosis: Does a particular pattern of activation indicate a diagnosis of dyslexia, autism, obsessive-compulsive disorder, or even malingering? The optimal analytic technique will depend upon the specific question being asked and the desired balance between sensitivity and specificity. The derived fMRI maps must also prove to be reliable and reproducible. It is conceivable that in the future, fMRI maps can be used as an imaging biomarker, in which an individual's brain activation pattern could be compared to a probabilistic functional atlas in order to determine the statistical likelihood that a patient belongs to a particular diagnostic class. Here we will focus on the reliability of methods for within-subject analysis in the common current applications.

Given an experimental design that includes at least one activation and one control condition, several approaches to analysis may reveal "active" brain regions. Statistical approaches—including correlation coefficients between MR signal and a predicted response curve; *t*-tests comparing activation versus control voxel intensities; and Kolmogorov-Smirnov tests, which show differences not only in mean but also in variance—produce a statistical value for which an investigator must determine a threshold of statistical significance (often arbitrarily). Current controversies include how to threshold data, whether to use a statistical value or magnitude measure (percent signal change) or to count "volume of activation," i.e., the number of voxels exceeding a statistical threshold as a dependent variable. Each technique has advantages and disadvantages, but few studies have carefully examined the reliability and validity of various approaches.

Dependent Measures

Functional MRI activations can be quantified broadly in two dimensions: spatial extent and magnitude of activation. Calculating activation size by means of voxel counting has become the most common approach to quantifying fMRI activity, especially in the clinical arena. This approach has several limitations, which must be thoroughly understood prior to relying on such data for clinical management. To illustrate these limitations, we will review the application of voxel counting to studies of language lateralization.

When studying language lateralization, the extent of fMRI activation is quantified by counting the number of voxels exceeding a statistical threshold of correlation with a predetermined hemodynamic function. These voxel counts are then used to compute laterality indices (LI), defined as:

$$\left[V_{\mathrm{L}} - V_{\mathrm{R}}\right] / \left[V_{\mathrm{L}} + V_{\mathrm{R}}\right] \times 100$$

where V_{L} and V_{R} are activation volumes for the left and right hemispheres, respectively. A similar index can be calculated for the intracarotid amobarbital procedure (IAP, the Wada test) using the error rates for each hemisphere injected.

In an early study analyzing the concordance of fMRI and Wada testing for determining laterality, Binder and colleagues found a strong correlation between the two procedures despite using a relatively simple single-task whole-brain fMRI design [89]. The high concordance rate reported is striking considering their use of a single language task, the lack of trial-to-trial reliability of voxel counting, and the methodological differences between disruption-based mapping (i.e., Wada testing) and activation-based mapping (i.e., fMRI). While the Wada test identifies areas that are essential for language function, fMRI identifies *all* areas that are involved with language processing (essential or not), including networks that are not specifically related to language such as motor, sensory, and attentional systems. The authors propose that their use of a control paradigm (a perceptual discrimination task) partly controls for these factors, which is probably true, but unlikely to account for all the aforementioned differences. In the subsequent sections, we will explore these limitations and review methodological developments that help overcome these obstacles and make clinical fMRI more reliable.

Despite the common assumption that all voxels exceeding the threshold carry identical weight, studies indicate that fMRI-based LI determinations vary according to the statistical threshold applied [90, 91]. For example, Gaillard and colleagues found in one patient that using a threshold of $t = 2$ resulted in bilateral dominance, whereas using a threshold of $t = 3$ demonstrated left-hemisphere dominance. A potential solution to this problem was proposed by Ramsey and colleagues, who reported that maps created using conjunction analysis (see the discussion that follows) are less susceptible to such thresholding effects [92]. Besides the susceptibility to the threshold applied, maps created using a predefined statistical threshold do not account for differences in activation magnitude (or percent signal change from baseline). It is conceivable that LI (which is based on voxel counts) can be 0, implying equal hemispheric activation, but that the average magnitude of activation in one hemisphere is significantly greater than in the other. In such a scenario, there is clear hemispheric asymmetry, although voxel counts (and LI) do not reflect the underlying differences in activation. Suarez and colleagues have recently proposed a "threshold-independent" method of determining LI that is based upon integrated weighted *t*-scores for all positively correlated voxels [93]. These authors found that using this threshold-independent model produced superior concordance rates between fMRI and Wada testing, although the number of patients studied was modest ($N = 14$).

Determination of LI based on voxel counts is also significantly dependent upon the region-of-interest used for the analysis. In most cases, whole-brain analysis is used to determine LI, which can be problematic because it includes activations in areas that are not normally expected to have lateralized function (e.g., occipital lobe and other midline regions) and excludes the possibility that specific brain regions may be differentially lateralized (e.g., Broca's versus Wernicke's areas). In fact, recent analyses indicate that exclusion of midline structures from fMRI-based LI determinations improves concordance with Wada-based laterality assessments [91]. Likewise, ROI-based analyses of Broca's and Wernicke's area (based on canonical anatomical boundaries) can often demonstrate differential lateralization of distinct language networks, especially in the setting of chronic intracranial pathologies such as arteriovenous malformation (AVMs) [94]. Lehericy and associates similarly reported region-specific concordances [95]. Having employed multiple language tasks, they found that the only statistically significant relationships identified were between the asymmetry of frontal lobe fMRI activations for semantic verbal fluency and covert sentence repetition and Wada asymmetry indices. In contrast, fMRI asymmetry in the temporal lobes (regardless of language task) and fMRI asymmetries noted while story listening did not correlate with Wada asymmetries. By using region-specific analyses, Lehericy and colleagues were trying to address one of the major limitations of current analytic techniques. The weakness of the study was in comparing single-task activations with Wada results rather than looking at conjunction analyses or the entire panel of tasks to create a more robust and reproducible fMRI-based map of laterality.

Reproducibility

Obtaining reproducible and reliable fMRI maps in the clinical setting is complicated by patient-specific and disease-related challenges that are not encountered in the controlled scientific setting. Developing methods to improve the reliability of these maps is of paramount importance, especially now that functional brain mapping is being used increasingly for clinical decision-making [89, 95, 96].

Functional MRI signals can demonstrate marked instability from trial-to-trial [97]. Differences in noise due to artifacts and physiological factors can produce striking differences in *perceived* extent of activation, even though the actual magnitude of activation is likely the same across trials. The noise variance propagates through to statistical calculations and produces various voxels that exceed statistical threshold. Accordingly, the number of significantly activated voxels can vary by up to 750% between trials. In contrast, the slope of the regression line, which is essentially the percent signal change, is much more stable across trials and subjects, with less than 20% variability across trials. Monte Carlo simulations support the assertion that even in very poor CNR conditions, the percent signal change can be determined with relatively good accuracy and precision [97].

A simple approach to improving SNR is to average numerous trials. When using voxel-counting to measure activation size, SNR and activation size only begin to plateau after averaging 150 trials [98]. In most studies, particularly in the clinical setting, the number of trials averaged is usually far less, on the order of 5–10. Therefore, it is critical to be mindful of sources of noise and employ other strategies (both with respect to task design, data acquisition, and analysis) that maximize signal-to-noise and minimize the effect of trial-to-trial variations. One such strategy is to measure response magnitude within a statistically defined ROI across trials or tasks rather than comparing changes in the number of voxels that exceed a statistical threshold.

Conjunction Analysis

Considering the intrinsic noise associated with fMRI data acquisition (both physiological and equipment-related), strategies such as conjunction analysis have been devised to extract mapping signals that are clinically significant and

consistent across tasks [67, 89, 96] (see Fig. 25.3). Conjunction analysis identifies all voxels that consistently exceed the statistical threshold for two or more independent yet related tasks. By Bayes theorem, the probability of observing significant voxels by chance on multiple scans is equal to the product of the prior probability of chance for each. By using a low statistical threshold for each individual scan, the probability of eliminating functionally significant voxels is minimized, effectively reducing the chance of a false-negative result. Conversely, this analysis minimizes false-positive results by requiring that the same voxel be active across multiple tasks.

The power of this technique was demonstrated by Pouratian and colleagues in a study comparing language-related fMRI activations with intraoperative ESM [96]. The authors created conjunction fMRI maps of expressive language (conjunction of two out of three expressive language tasks: visual object naming, word generation, and auditory response naming) and

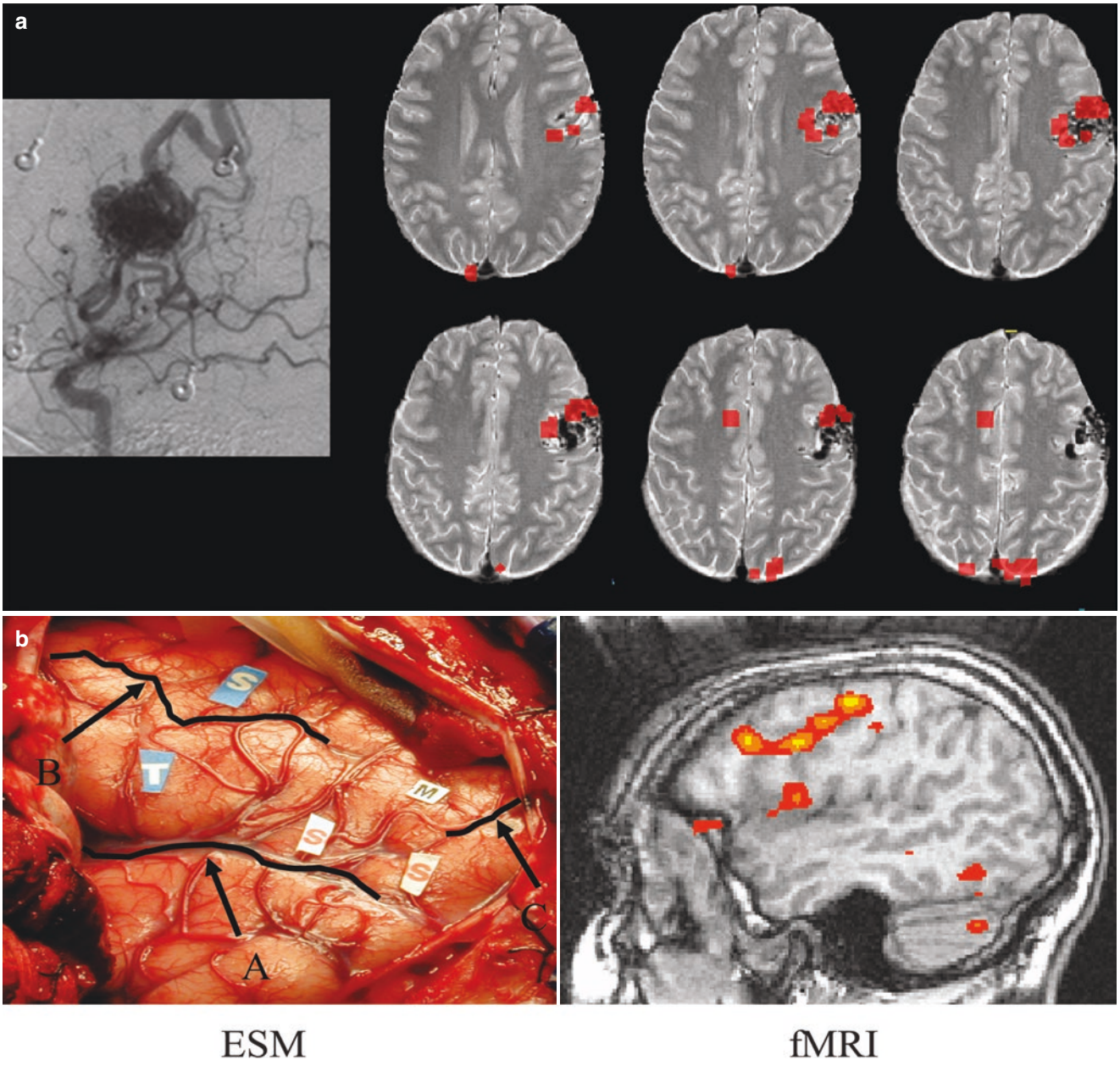

Fig. 25.3 (**a**) Functional MRI activations adjacent to arteriovenous malformation (AVM). Significant fMRI activations are commonly identified adjacent to a left frontal lobe AVM. In this image, fMRI activations of language expression (created by conjunction analysis) are seen adjacent to a frontal AVM, identifying Broca's Area. Note that activations are not identified within the vascular malformation. Functional MRI activations were both qualitatively and quantitatively similar to the intraoperative electrocortical stimulation maps (ESM) (**b**). (Adapted from [96])

receptive language (conjunction of visual responsive naming and sentence comprehension). They compared these fMRI activations with intraoperative ESM (Fig. 25.3). For the population studied, the authors report sensitivity and specificity values of expression fMRI activations of up to 100% and 66.7%, respectively, in the frontal lobe and of comprehension fMRI activations of up to 96.2% and 69.8%, respectively, in the parietal/temporal lobes [96].

Conjunction analysis also has been shown to improve the concordance between fMRI assessment of laterality and Wada testing [89, 91]. Ramsey and colleagues initially reported that in contrast to mapping responses to a single language task, conjunction analysis yields a high LI, which paralleled the neuropsychological assessment of hemispheric dominance [92]. Moreover, they found that conjunction analysis results in LI are more consistent across statistical thresholds than individual task analysis. To better understand the reliability of fMRI to assess language laterality, Arora and colleagues performed a comprehensive comparison of fMRI and Wada testing for laterality assessment [91]. The authors investigated the effect of language tasks employed, varying statistical thresholds, and other analytic techniques such as conjunction analysis. By using conjunction analysis, the authors found the concordance between fMRI and Wada-based assessment of laterality increased from 77% to 83% to 91% [91].

Based on methodological differences between ESM and fMRI, false positives (i.e., imperfect specificity) are expected. Functional MRI is an activation-based technique and will therefore identify all activated brain regions regardless of whether they are "essential" or supplementary. On the other hand, ESM and the Wada test will only identify areas essential to language processing. Conjunction analyses minimize the discrepancy between these techniques by only identifying areas consistently activated across language tasks.

Applying fMRI to Clinical Planning

Significance of Signal Localization

The precise relationship between observed fMRI signals and the underlying electrophysiological activity of the brain is still not well defined. The relationship is even more uncertain in the setting of intracranial pathology (especially vascular pathology), further complicating the interpretation of fMRI studies in the clinical setting. Depending on the scan sequence used, the BOLD fMRI signals can even center in adjacent sulci [99–101] and be up to 1 cm away from the electrophysiologically active cortex [101]. Despite the imprecision, fMRI mapping signals demonstrate a consistent spatial relationship with cortical-stimulation-based maps and are therefore still clinically relevant (see Giussani et al. [102] for a comprehensive review) [96, 102]. In most cases, in order to achieve clinically useful levels of sensitivity and specificity (up to 100% and ~70%, respectively), a "sphere of influence" of fMRI activity of approximately 0.5–1.0 cm must be assumed, and multiple tasks must be mapped and interpreted using a conjunction analysis [96, 100, 101, 103, 104]. Because of the spatial imprecision of fMRI, especially when doing whole head imaging, it is important not to overinterpret small differences in spatial extent or lack of difference in spatial extent as representing a clear difference in activation patterns or a lack of difference in activation patterns, respectively.

Reliability of Signal Adjacent to Pathology

The reliability of fMRI signals in the setting of intracranial pathology is often questioned because of the introduction of susceptibility artifacts into the intracranial space (e.g., arteriovenous malformations, cavernous angiomas, and surgical clips) and because of the uncertain impact of the intracranial pathology on the normal physiology of the brain.

Susceptibility artifact due to intracranial pathology such as an arteriovenous malformation prevents mapping within the area of susceptibility. Therefore, physicians must be cognizant of areas of signal "drop-out" in which the lack of mapping signal may be due to an inability to detect activity-related MR signal changes rather than lack of activity. The question remains, however, as to whether reliable signals can be obtained from adjacent to the pathologies. In a study of 14 patients, Schlosser and colleagues report that fMRI signals in patients with frontal lobe tumors were comparable to signals in normal controls [11]. Similarly, Righini and colleagues found little difference in motor activations between the affected and unaffected hemispheres in 17 patients with frontoparietal masses [4]. Pouratian and colleagues also reported that functional activations, which correlate with intraoperative cortical stimulation mapping, can consistently and reliably be measured adjacent to vascular malformations (i.e., AVMs and cavernous hemangiomas) [96]. These reports are consistent with our findings at UCLA, in which we regularly and successfully map motor and language cortices near eloquent cortices in patients scheduled for neurosurgical intervention (Fig. 25.4 [96]).

Reports of abnormal fMRI activations adjacent to pathology likely represent cases in which the pathology has infiltrated the cortex of interest and altered normal cortical function, cerebral hemodynamics, or both. Because of the importance of preserving eloquent function, if fMRI maps are used for neurosurgical guidance, it is imperative to verify preoperative fMRI maps intraoperatively with intraoperative direct cortical stimulation mapping in order to ensure the preservation of eloquent function.

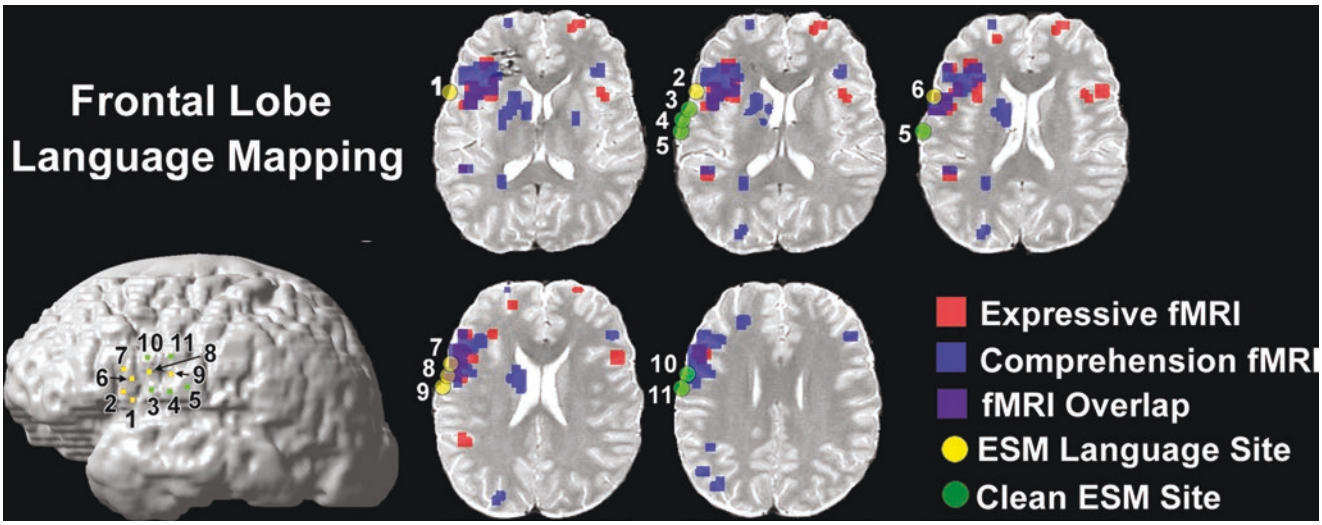

Fig. 25.4 Frontal lobe language mapping using fMRI with conjunction analysis. Yellow circles are areas essential for language as determined by electrocortical stimulation mapping (ESM). Green circles are areas that, when stimulated, did not disrupt language function. Red activations are conjunction fMRI maps of language expression. Blue activations are conjunction fMRI maps of language comprehension. Electrocortical stimulation map sites are shown with a 5-mm radius (determined to produce the highest sensitivity with the least cost to specificity) and parietal/temporal. Red (expression) activations tend to overlap with or are adjacent to essential (yellow) ESM sites but avoid non-essential (green) ESM sites. Blue activations in the frontal lobe also appear predictive but with lower specificity in this subject than the expression fMRI activations. (Adapted from [96])

Value of Resting-State fMRI (rs-fMRI)

Resting-state fMRI (rs-fMRI), which measures spontaneous fluctuations in brain activity while patients are not performing tasks (i.e., while in a state of quiet wakefulness [105]), offers an opportunity to improve the acquisition process without relying so heavily on patient cooperation for particular tasks [106, 107]. In rs-fMRI, endogenous neuronal activity of functional neural networks produces low-frequency BOLD signal changes, which can be analyzed to identify large-scale distributed networks and specific functional territories [105, 108–112]. That rs-fMRI does not require generation, testing, or calibration of a specific task has made it a recent focus for preoperative fMRI mapping, even for language and motor areas [112–117]. Compared with task-related fMRI, rs-fMRI provides greater insight into the functional architecture of the brain (as it can map multiple regions and functional networks simultaneously) [118, 119] and can be applied in those settings where subjects are otherwise impaired or unable to perform a given task [112]. In addition, the measured BOLD signal from spontaneous fluctuations is more robust than those obtained in task-related fMRI in that it has been shown to persist even in patients who are asleep [111, 120] under anesthesia [121–123] or whose anatomy is distorted by tumors [112, 114]. Given that it may be implemented regardless of age or cognitive status, if the value of the maps can be validated with respect to underlying functional anatomy, its applicability may eventually become more widespread than task-related fMRI [112]. Many of the same limitations of task-related fMRI (susceptibility artifacts, head motion, neurovascular uncoupling) persist in rs-fMRI [124].

Relationship to Outcomes

Although many studies have investigated the relationship between fMRI and electrophysiological maps [100, 101, 103, 125–127], very few studies have quantified the sensitivity and specificity of fMRI activations relative to electrophysiological maps, and no studies have rigorously assessed the relationship between fMRI maps and clinical outcomes. While it is helpful to understand the relationship between fMRI and ESM (the gold standard), the relationship between fMRI maps, the extent of resection, and clinical outcomes is ultimately the most important determinant of the clinical utility and reliability of fMRI.

To date, ESM remains the gold standard with respect to intraoperative brain mapping because it is the only functional brain mapping technique that has been rigorously evaluated with respect to clinical outcomes. Haglund and colleagues, who were the first to characterize postoperative clinical outcomes relative to the distance of resection from ESM-defined language sites, reported that maintenance of a 1 cm margin around ESM-defined language sites prevents postoperative dysphasia [128]. Sanai and colleagues published a follow-up study reporting a 1.6% rate of dysphasia when tumor resections were restricted to greater than 1 cm away from cortical

areas where intraoperative stimulation produced language disruption [129]. Besides confirming the original report, they demonstrate that ESM is also reliable in patients with gliomas and not only in epilepsy patients (who were the subject of Haglund and colleagues' report).

Outcomes studies such as these need to be done better to understand the clinical utility and reliability of fMRI, especially as an increasing number of centers have begun to build sufficient confidence in fMRI mapping to obviate the need for intraoperative mapping in some patients [130]. Existing data on this effect remains scarce, and to our knowledge, only retrospective results have been published documenting the link between presurgical fMRI mapping and patient outcomes [131]. In light of mounting evidence that extensive tumor removal imparts a survival and quality-of-life advantage, there is a growing need and demand to develop superior and more reliable mapping methods to aid physicians and surgeons in providing safe avenues to resect intracranial pathologies [132].

Conclusion

Functional MRI is a powerful brain mapping tool whose use has grown exponentially over the last two decades. Despite formal approval of fMRI as a clinical tool for presurgical planning, there remains no single, established, and accepted protocol for task presentation, analysis, or interpretation of results. Further, there remain few studies that have carefully validated a consistent fMRI approach with objective and quantitative measures in established gold-standard techniques (Table 25.2), particularly intraoperative corticogra-

Table 25.2 Summary of key literature

Authors	Article title	Summary
Ojemann G, et al. (1989) [19]	Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989; 71:316–326.	Substantial individual variability in the exact location of language function among the patients showed that language could not be reliably localized on anatomic criteria alone.
Stark CEL, et al. (2001) [48]	When zero is not zero: The problem of ambiguous baseline conditions in fMRI. Proc Natl Acad Sci U S A 2001; 98:12760–12765.	Periods of rest are associated with significant cognitive activity and provide a nonoptimal baseline for memory tasks. The findings have important implications for the designing and interpreting a wide range of fMRI studies of cognition.
Greicius MD, et al. (2003) [51]	Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A. 2003 Jan 7;100(1):253–8.	Functional imaging studies have shown that certain brain regions, including the posterior cingulate cortex (PCC) and ventral anterior cingulate cortex (vACC), consistently show greater activity during resting states than during cognitive tasks. This finding led to the hypothesis that these regions constitute a network supporting a default mode of brain function.
Gaillard WD, et al. (2004) [90]	fMRI language task panel improves determination of language dominance. Neurology. 2004 Oct 26;63(8):1403–8.	A panel of fMRI language paradigms may be more accurate for evaluating partial epilepsy patients than a single task.
Ruff IM, et al. (2008) [66]	Assessment of the language laterality index in patients with brain tumor using functional MR imaging: effects of thresholding, task selection, and prior surgery. AJNR Am J Neuroradiol. 2008 Mar; 29(3):528–35. Epub 2008 Jan 9.	The study sought to determine whether changing the statistical threshold for different language tasks influences the language laterality index (LI) for a group of controls, patients with tumors without prior surgery, and patients with tumors and prior surgery. The resulting data suggest that the LI may be threshold- and task-dependent.
Binder JR, et al. (2008) [69]	A comparison of five fMRI protocols for mapping speech comprehension systems. Epilepsia 2008 Dec;49(12):1980–97.	Brain regions involved in semantic processing were identified only when an active, nonlinguistic task was used as a baseline, supporting the notion that semantic processing occurs whenever attentional resources are not controlled. Identification of these lexical-semantic regions is particularly important for predicting language outcomes in patients undergoing temporal lobe surgery.
Sanai N, et al. (2008) [129]	Mapping the horizon: techniques to optimize tumor resection before and during surgery. Clin Neurosurg. 2008;55:14–9.	The article reviews current and future imaging modalities as well as state-of-the art intraoperative techniques that can facilitate the extent of tumor resection while minimizing the associated neurological morbidity profile.
Giussani C, et al. (2010) [102]	DTI fiber tracking to differentiate demyelinating diseases from diffuse brain stem glioma. Neuroimage. 2010 Aug 1;52(1):217–23.	Diffuse brainstem tumors and demyelinating diseases share common clinical and radiological features, sometimes making diagnosis difficult. DTI fiber tracking of the pyramid tracts in patients with suspected intrinsic brainstem tumor or demyelinating disease presents two clearly different patterns that may help differentiate these two pathologies when conventional MRI and clinical data are inconclusive.
Leuthardt E et al. (2015) [112]	Resting-state blood oxygen level-dependent functional MRI: a paradigm shift in preoperative brain mapping. Stereotact Funct Neurosurg. 2015;93(6):427–39	Resting-state fMRI measures spontaneous fluctuations in BOLD signal, representing the brain's functional organization, which allows for non-invasive 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 can be applied in settings where task-related fMRI cannot be performed.

phy. Of particular concern is the use of fMRI "packages" that present experiments and analyze data blindly, without careful review of image quality, artifacts, subject performance, and individual patient need and deficits.

As fMRI becomes more widely available in clinical settings lacking experienced staff in functional imaging, it is important to acknowledge and address many of the limitations that continue to challenge this modality. Moreover, as with any clinical test, it will be important to quantify its sensitivity, specificity, and relationship to outcomes in the future. Different clinical applications, experimental paradigms, analysis approaches, and even equipment can produce different results; valid applications of fMRI to clinical cases will have to demonstrate reliability and validity for each application separately.

The field should move rapidly toward developing uniform approaches to clinical fMRI that are valid, reliable, and replicable across centers while establishing professional standards for clinicians who wish to perform these studies. Currently, no such standards exist. We believe that clinical decisions should not rest solely on fMRI results for most applications. Instead, fMRI may augment existing clinical tools as validation of the techniques continues.

References

1. Silva MA, See AP, Essayed WI, Golby AJ, Tie Y. Challenges and techniques for presurgical brain mapping with functional MRI. Neuroimage Clin. 2017;17:794–803. https://doi.org/10.1016/j.nicl.2017.12.008.
2. Belliveau JW, Kennedy DN, McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, et al. Functional mapping of the human visual cortex by magnetic resonance imaging. Science. 1991;254(5032):716–9.
3. Krings T, Reinges MHT, Willmes K, Nuerk HC, Meister IG, Gilsbach JM, et al. Factors related to the magnitude of T2* MR signal changes during functional imaging. Neuroradiology. 2002;44(6):459–66.
4. Righini A, De Divitiis O, Prinster A, Spagnoli D, Appollonio I, Bello L, et al. Functional MRI: primary motor cortex localization in patients with brain tumors. J Comput Assist Tomogr. 1996;20(5):702–8.
5. Krings T, Töpper R, Willmes K, Reinges MHT, Gilsbach JM, Thron A. Activation in primary and secondary motor areas in patients with CNS neoplasms and weakness. Neurology. 2002;58(3):381–90.
6. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 1937;60(4):389–443.
7. Jahanshahi M, Rothwell J. Transcranial magnetic stimulation studies of cognition: an emerging field. Exp Brain Res. 2000;131:1–9.
8. Villringer A, Dirnagl U. Coupling of brain activity and cerebral blood flow: basis of functional neuroimaging. Cerebrovasc Brain Metab Rev. 1995;7(3):240–76.
9. Holodny AI, Schulder M, Liu WC, Wolko J, Maldjian JA, Kalnin AJ. The effect of brain tumors on BOLD functional MR imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. Am J Neuroradiol. 2000;21(8):1415–22.
10. 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):1055–63.
11. Schlösser R, Hunsche S, Gawehn J, Grunert P, Vucurevic G, Gesierich T, et al. Characterization of BOLD-fMRI signal during a verbal fluency paradigm in patients with intracerebral tumors affecting the frontal lobe. Magn Reson Imaging. 2002;20(1):7–16.
12. Chen JJ, Pike GB. Global cerebral oxidative metabolism during hypercapnia and hypocapnia in humans: implications for BOLD fMRI. J Cereb Blood Flow Metab. 2010;30(6):1094–9.
13. An H, Liu Q, Chen Y, Lin W. Evaluation of MR-derived cerebral oxygen metabolic index in experimental hyperoxic hypercapnia, gypoxia, and ischemia. Stroke. 2009;40(6):2165–72.
14. Schmitz B, Böttiger BW, Hossmann KA. Brief hypercapnia enhances somatosensory activation of blood flow in rat. J Cereb Blood Flow Metab. 1996;16(6):1307–11.
15. Bock C, Schmitz B, Kerskens CM, Gyngell ML, Hossmann KA, Hoehn-Berlage M. Functional MRI of somatosensory activation in rat: effect of hypercapnic up-regulation on perfusion- and BOLD-imaging. Magn Reson Med. 1998;39(3):457–61.
16. Bandettini PA, Wong EC. A hypercapnia-based normalization method for improved spatial localization of human brain activation with fMRI. NMR Biomed. 1997;10(4–5):197–203.
17. Chen CM, Hou BL, Holodny AI. Effect of age and tumor grade on BOLD functional MR imaging in preoperative assessment of patients with glioma. Radiology. 2008;248(3):971–8.
18. Krüger G, Kastrup A, Glover GH. Neuroimaging at 1.5 T and 3.0 T: comparison of oxygenation-sensitive magnetic resonance imaging. Magn Reson Med. 2001;45(4):595–604.
19. Ojemann GA, Lettich E, Berger M, Ojemann J. Cortical language localization in left, dominant hemisphere: an electrical stimulation mapping investigation in 117 patients. J Neurosurg. 1989;71(2):316–26. https://pubmed.ncbi.nlm.nih.gov/18240946/.
20. Ojemann JG, Akbudak E, Snyder AZ, McKinstry RC, Raichle ME, Conturo TE. Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. NeuroImage. 1997;6(3):156–67.
21. Devlin JT, Russell RP, Davis MH, Price CJ, Wilson J, Moss HE, et al. Susceptibility-induced loss of signal: comparing PET and fMRI on a semantic task. NeuroImage. 2000;11(6 I):589–600.
22. Cohen MS, Weisskoff RM. Ultra-fast imaging. Magn Reson Imaging. 1991;9:1–37.
23. Abduljalil AM, Kangarlu A, Yu Y, Robitaille PML. Macroscopic susceptibility in ultra high field MRI. II: Acquisition of spin echo images from the human head. J Comput Assist Tomogr. 1999;23(6):842–4.
24. Abduljalil AM, Robitaille PML. Macroscopic susceptibility in ultra high field MRI. J Comput Assist Tomogr. 1999;23(6):832–41.
25. Alkadhi H, Kollias SS, Crelier GR, Golay X, Hepp-Reymond MC, Valavanis A. Plasticity of the human motor cortex in patients with arteriovenous malformations: a functional MR imaging study. Am J Neuroradiol. 2000;21(8):1423–33.
26. Kinahan PE, Noll DC. A direct comparison between whole-brain PET and BOLD fMRI measurements of single-subject activation response. NeuroImage. 1999;9(4):430–8.
27. van der Zwaag W, Francis S, Head K, Peters A, Gowland P, Morris P, et al. fMRI at 1.5, 3 and 7 T: characterising BOLD signal changes. NeuroImage. 2009;47(4):1425–34.
28. Beisteiner R, Robinson S, Wurnig M, Hilbert M, Merksa K, Rath J, et al. Clinical fMRI: evidence for a 7T benefit over 3T. NeuroImage. 2011;57(3):1015–21.
29. Weiskopf N, Hutton C, Josephs O, Deichmann R. Optimal EPI parameters for reduction of susceptibility-induced BOLD sensitivity losses: a whole-brain analysis at 3 T and 1.5 T. NeuroImage. 2006;33(2):493–504.

30. Merboldt KD, Fransson P, Bruhn H, Frahm J. Functional MRI of the human amygdala? NeuroImage. 2001;14(2):253–7.
31. Fransson P, Merboldt KD, Ingvar M, Petersson KM, Frahm J. Functional MRI with reduced susceptibility artifact: high-resolution mapping of episodic memory encoding. Neuroreport. 2001;12(7):1415–20.
32. Port JD, Pomper MG. Quantification and minimization of magnetic susceptibility artifacts on GRE images. J Comput Assist Tomogr. 2000;24(6):958–64.
33. Gorno-Tempini ML, Hutton C, Josephs O, Deichmann R, Price C, Turner R. Echo time dependence of BOLD contrast and susceptibility artifacts. NeuroImage. 2002;15(1):136–42.
34. Glover GH, Thomason ME. Improved combination of spiral-in/out images for BOLD fMRI. Magn Reson Med. 2004;51(4):863–8.
35. Stables LA, Kennan RP, Gore JC. Asymmetric spin-echo imaging of magnetically inhomogeneous systems: theory, experiment, and numerical studies. Magn Reson Med. 1998;40(3):432–42.
36. Stern CE, Corkin S, González RG, Guimaraes AR, Baker JR, Jennings PJ, et al. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci U S A. 1996;93(16):8660–5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC38729/.
37. Hariri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses. Neuroreport. 2003;11(1):43–8.
38. LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron. 1998;20(5):937–45.
39. Cordes D, Turski PA, Sorenson JA. Compensation of susceptibility-induced signal loss in echo-planar imaging for functional applications. Magn Reson Imaging. 2000;18(9):1055–68.
40. Stenger VA, Boada FE, Noll DC. Three-dimensional tailored RF pulses for the reduction of susceptibility artifacts in T2/(*)-weighted functional MRI. Magn Reson Med. 2000;44(4):525–31.
41. Glover GH, Law CS. Spiral-in/out BOLD fMRI for increased SNR and reduced susceptibility artifacts. Magn Reson Med. 2001;46(3):515–22.
42. Glover GH. Spiral imaging in fMRI. NeuroImage. 2012;62:706–12.
43. Yang Y, Gu H, Zhan W, Xu S, Silbersweig DA, Stern E. Simultaneous perfusion and BOLD imaging using reverse spiral scanning at 3T: characterization of functional contrast and susceptibility artifacts. Magn Reson Med. 2002;48(2):278–89.
44. Weiger M, Pruessmann KP, Österbauer R, Börnert P, Boesiger P, Jezzard P. Sensitivity-encoded single-shot spiral imaging for reduced susceptibility artifacts in BOLD fMRI. Magn Reson Med. 2002;48(5):860–6.
45. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci U S A. 1992;89(12):5675–9. https://doi.org/10.1073/pnas.89.12.5675.
46. Ogawa S, Tank D, Menon R, Ellermann J, Kim S, Merkle H, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci U S A. 1992;89(13):5951–5. https://pubmed.ncbi.nlm.nih.gov/1631079/.
47. Sidtis JJ, Strother SC, Anderson JR, Rottenberg DA. Are brain functions really additive? NeuroImage. 1999;9(5):490–6.
48. Stark CEL, Squire LR. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. Proc Natl Acad Sci. 2001;98(22):12760–6.
49. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci. 2001;2(10):685–94. https://www.nature.com/articles/35094500.
50. Fox MD, Zhang D, Snyder AZ, Raichle ME. The global signal and observed anticorrelated resting state brain networks. J Neurophysiol. 2009;101(6):3270–83.
51. 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. 2003;100(1):253–8.
52. Raichle ME, Fiez JA, Videen TO, Macleod A, Mary K, Pardo JV, Fox PT, et al. Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex. 1994;4(1):8–26.
53. Petersen SE, van Mier H, Fiez JA, Raichle ME. The effects of practice on the functional anatomy of task performance. Proc Natl Acad Sci. 2002;95(3):853–60.
54. van Mier H, Tempel LW, Perlmutter JS, Raichle ME, Petersen SE. Changes in brain activity during motor learning measured with PET: effects of hand of performance and practice. J Neurophysiol. 1998;80(4):2177–99. https://journals.physiology.org/doi/full/10.1152/jn.1998.80.4.2177.
55. Madden DJ, Turkington TG, Provenzale JM, Denny LL, Hawk TC, Gottlob LR, et al. Adult age differences in the functional neuroanatomy of verbal recognition memory. Hum Brain Mapp. 1999;7(2):115–35.
56. Garavan H, Kelley D, Rosen A, Rao SM, Stein EA. Practice-related functional activation changes in a working memory task. Microsc Res Tech. 2000;51(1):54–63.
57. Mizuguchi N, Nakata H, Hayashi T, Sakamoto M, Muraoka T, Uchida Y, et al. Brain activity during motor imagery of an action with an object: a functional magnetic resonance imaging study. Neurosci Res. 2013;76(3):150–5.
58. Shriver S, Knierim KE, O'Shea JP, Glover GH, Golby AJ. Pneumatically driven finger movement: a novel passive functional MR imaging technique for presurgical motor and sensory mapping. Am J Neuroradiol. 2013;34(1):E5.
59. Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziota JC, et al. Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med. 2000;343(7):450–6.
60. O'Brien JL, O'Keefe KM, Laviolette PS, Deluca AN, Blacker D, Dickerson BC, et al. Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. Neurology. 2010;74(24):1969–76.
61. Rombouts SARB, Barkhof F, Veltman DJ, Machielsen WCM, Witter MP, Bierlaagh MA, et al. Functional MR imaging in Alzheimer's disease during memory encoding. Am J Neuroradiol. 2000;21(10):1869–75.
62. Jaeggi SM, Seewer R, Nirkko AC, Eckstein D, Schroth G, Groner R, et al. Does excessive memory load attenuate activation in the prefrontal cortex? Load-dependent processing in single and dual tasks: functional magnetic resonance imaging study. NeuroImage. 2003;19(2):210–25.
63. Sonty SP, Mesulam MM, Thompson CK, Johnson NA, Weintraub S, Parrish TB, et al. Primary progressive aphasia: PPA and the language network. Ann Neurol. 2003;53(1):35–49.
64. Kim DS, Duong TQ, Kim SG. High-resolution mapping of iso-orientation columns by fMRI. Nat Neurosci. 2000;3(2):164–9.
65. Calvert GA, Brammer MJ, Morris RG, Williams SCR, King N, Matthews PM. Using fMRI to study recovery from acquired dysphasia. Brain Lang. 2000;71(3):391–9.
66. Ruff IM, Petrovich Brennan NM, Peck KK, Hou BL, Tabar V, Brennan CW, et al. Assessment of the language laterality index in patients with brain tumor using functional MR imaging: effects of thresholding, task selection, and prior surgery. Am J Neuroradiol. 2008;29(3):528–35.
67. Rutten GJM, Ramsey NF, Van Rijen PC, Van Veelen CWM. Reproducibility of fMRI-determined language lateralization in individual subjects. Brain Lang. 2002;80(3):421–37.
68. Bookheimer SY, Zeffiro TA, Blaxton T, Malow BA, Gaillard WD, Sato S, et al. A direct comparison of PET activation and electrocortical stimulation mapping for language localization. Neurology. 1997;48(4):1056–65.

69. Binder JR, Swanson SJ, Hammeke TA, Sabsevitz DS. A comparison of five fMRI protocols for mapping speech comprehension systems. Epilepsia. 2008;49(12):1980–97.
70. Lucas TH, McKhann GM, Ojemann GA. Functional separation of languages in the bilingual brain: a comparison of electrical stimulation language mapping in 25 bilingual patients and 117 monolingual control patients. J Neurosurg. 2009;101:449–57.
71. Bloch C, Kaiser A, Kuenzli E, Zappatore D, Haller S, Franceschini R, et al. The age of second language acquisition determines the variability in activation elicited by narration in three languages in Broca's and Wernicke's area. Neuropsychologia. 2009;47(3):625–33.
72. Chee MWL, Hon N, Lee HL, Soon CS. Relative language proficiency modulates BOLD signal change when bilinguals perform semantic judgments. NeuroImage. 2001;13(6):1155–63.
73. Tan LH, Spinks JA, Feng CM, Siok WT, Perfetti CA, Xiong J, et al. Neural systems of second language reading are shaped by native language. Hum Brain Mapp. 2003;18(3):158–66.
74. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage. 2002;17(2):825–41.
75. Grootoonk S, Hutton C, Ashburner J, Howseman AM, Josephs O, Rees G, et al. Characterization and correction of interpolation effects in the realignment of fMRI time series. NeuroImage. 2000;11(1):49–57.
76. Lueken U, Muehlhan M, Evens R, Wittchen HU, Kirschbaum C. Within and between session changes in subjective and neuroendocrine stress parameters during magnetic resonance imaging: a controlled scanner training study. Psychoneuroendocrinology. 2012;37(8):1299–308.
77. Maclaren J, Herbst M, Speck O, Zaitsev M. Prospective motion correction in brain imaging: a review. Magn Reson Med. 2013;69(3):621–36.
78. Desmond JE, Atlas SW. Task-correlated head movement in fMR imaging: false activations can contaminate results despite motion correction. Am J Neuroradiol. 2000;21(8):1370–1.
79. Bruhn H, Kleinschmidt A, Boecker H, Merboldt KD, Hänicke W, Frahm J. The effect of acetazolamide on regional cerebral blood oxygenation at rest and under stimulation as assessed by MRI. J Cereb Blood Flow Metab. 1994;14(5):742–8.
80. Seifritz E, Bilecen D, Hänggi D, Haselhorst R, Radü EW, Wetzel S, et al. Effect of ethanol on BOLD response to acoustic stimulation: implications for neuropharmacological fMRI. Psychiatry Res Neuroimaging. 2000;99(1):1–13.
81. Kiem SA, Andrade KC, Spoormaker VI, Holsboer F, Czisch M, Sämann PG. Resting state functional MRI connectivity predicts hypothalamus-pituitary-axis status in healthy males. Psychoneuroendocrinology. 2013;38(8):1338–48.
82. Wandschneider B, Koepp MJ. Pharmaco fMRI: determining the functional anatomy of the effects of medication. Neuroimage Clin. 2016;12:691–7.
83. Wandschneider B, Stretton J, Sidhu M, Centeno M, Kozák LR, Symms M, et al. Levetiracetam reduces abnormal network activations in temporal lobe epilepsy. Neurology. 2014;83(17):1508–12.
84. Chee MWL. Functional imaging of working memory after 24 hr of total sleep deprivation. J Neurosci. 2004;24(19):4560–7.
85. Drummond SP, Brown GG, Stricker JL, Buxton RB, Wong EC, Gillin JC. Sleep deprivation-induced reduction in cortical functional response to serial subtraction. Neuroreport. 1999;10(18):3745–8. http://journals.lww.com/neuroreport/Abstract/1999/12160/Sleep_deprivation_induced_reduction_in_cortical.4.aspx.
86. Drummond SPA, Brown GG, Gillin JC, Stricker JL, Wong EC, Buxton RB. Altered brain response to verbal learning following sleep deprivation. Nature. 2000;403(6770):655–7.
87. Drummond SPA, Gillin JC, Brown GG. Increased cerebral response during a divided attention task following sleep deprivation. J Sleep Res. 2001;10(2):85–92.
88. Ball TM, Knapp SE, Paulus MP, Stein MB. Brain activation during fear extinction predicts exposure success. Depress Anxiety. 2017;34(3):257–66.
89. Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, et al. Determination of language dominance using functional MRI: a comparison with the Wada test. Neurology. 1996;46(4):978–84.
90. Gaillard WD, Balsamo L, Xu B, McKinney C, Papero PH, Weinstein S, et al. fMRI language task panel improves determination of language dominance. Neurology. 2004;63(8):1403–8.
91. Arora J, Pugh K, Westerveld M, Spencer S, Spencer DD, Todd CR. Language lateralization in epilepsy patients: fMRI validated with the Wada procedure. Epilepsia. 2009;50(10):2225–41.
92. Ramsey NF, Sommer IEC, Rutten GJ, Kahn RS. Combined analysis of language tasks in fMRI improves assessment of hemispheric dominance for language functions in individual subjects. NeuroImage. 2001;13(4):719–33.
93. Suarez RO, Whalen S, Nelson AP, Tie Y, Meadows ME, Radmanesh A, et al. Threshold-independent functional MRI determination of language dominance: a validation study against clinical gold standards. Epilepsy Behav. 2009;16(2):288–97.
94. Lee DJ, Pouratian N, Bookheimer SY, Martin NA. Factors predicting language lateralization in patients with perisylvian vascular malformations. J Neurosurg. 2010;113:723–30.
95. Lehéricy S, Cohen L, Bazin B, Samson S, Giacomini E, Rougetet R, et al. Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. Neurology. 2000;54(8):1625–33.
96. Pouratian N, Bookheimer S, Rex D, Martin N, Toga A. Utility of preoperative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. J Neurosurg. 2002;97(1):21–32. https://pubmed.ncbi.nlm.nih.gov/12134916/.
97. Cohen MS, DuBois RM. Stability, repeatability, and the expression of signal magnitude in functional magnetic resonance imaging. J Magn Reson Imaging. 1999;10(1):33–40.
98. Huettel SA, McCarthy G. The effects of single-trial averaging upon the spatial extent of fMRI activation. Neuroreport. 2001;12(11):2411–6.
99. Cannestra AF. Temporal spatial differences observed by functional MRI and human intraoperative optical imaging. Cereb Cortex. 2002;11(8):773–82.
100. Martin R, Brinkley JF, Keith S, Poliakov A, Ojemann GA, Mulligan K, et al. Correspondences between language cortex identified by cortical stimulation mapping and fMRI. NeuroImage. 2004;11(5):S295.
101. Lurito JT, Lowe MJ, Sartorius C, Mathews VP. Comparison of fMRI and intraoperative direct cortical stimulation in localization of receptive language areas. J Comput Assist Tomogr. 2000;24(1):99–105.
102. Giussani C, Poliakov A, Ferri RT, Plawner LL, Browd SR, Shaw DWW, et al. DTI fiber tracking to differentiate demyelinating diseases from diffuse brain stem glioma. NeuroImage. 2010;52(1):217–23.
103. Roux FE, Boulanouar K, Ranjeva JP, Manelfe C, Tremoulet M, Sabatier J, et al. Cortical intraoperative stimulation in brain tumors as a tool to evaluate spatial data from motor functional MRI. Investig Radiol. 1999;34(3):225–9.
104. Pouratian N, Sicotte N, Rex D, Martin NA, Becker D, Cannestra AF, et al. Spatial/temporal correlation of BOLD and optical intrinsic signals in humans. Magn Reson Med. 2002;47(4):766–76.

105. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8:700–11.
106. Lang S, Duncan N, Northoff G. Resting state fMRI: review of neurosurgical applications. Neurosurgery. 2014;74(5):453–65. http://www.ncbi.nlm.nih.gov/pubmed/24492661.
107. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. Am J Neuroradiol. 2013;34(10):1866–72.
108. Auer DP. Spontaneous low-frequency blood oxygenation level-dependent fluctuations and functional connectivity analysis of the "resting" brain. Magn Reson Imaging. 2008;26(7):1055–64.
109. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC. The human brain is intrinsically organized in to dynamic, anticorrelated functional networks. J Phys Org Chem. 2005;102(27):9673–8.
110. Binder JR, Frost JA, Hammeke TA, Bellgowan PSF, Rao SM, Cox RW. Conceptual processing during the conscious resting state: a functional MRI study. J Cogn Neurosci. 1999;11(1):80–93.
111. Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC. Detection of functional connectivity using temporal correlations in MR images. Hum Brain Mapp. 2002;15(4):247–62.
112. Leuthardt EC, Allen M, Kamran M, Hawasli AH, Snyder AZ, Hacker CD, et al. Resting-state blood oxygen level-dependent functional MRI: a paradigm shift in preoperative brain mapping. Stereotact Funct Neurosurg. 2015;93(6):427–39.
113. Rosazza C, Aquino D, D'Incerti L, Cordella R, Andronache A, Zacà D, et al. Preoperative mapping of the sensorimotor cortex: comparative assessment of task-based and resting-state fMRI. PLoS One. 2014;9(6):e98860.
114. Zhang D, Johnston JM, Fox MD, Leuthardt EC, Grubb RL, Chicoine MR, et al. Preoperative sensorimotor mapping in brain tumor patients using spontaneous fluctuations in neuronal activity imaged with functional magnetic resonance imaging: initial experience. Neurosurgery. 2009;65(6 Suppl 1):226.
115. Liu H, Buckner RL, Talukdar T, Tanaka N, Madsen JR, Stufflebeam SM. Task-free presurgical mapping using functional magnetic resonance imaging intrinsic activity. J Neurosurg. 2009;111(4):746–54. http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19361264&retmode=ref&cmd=prlinks%5Cnpapers3://publication/doi/10.3171/2008.10.JNS08846.
116. Tie Y, Rigolo L, Norton IH, Huang RY, Wu W, Orringer D, et al. Defining language networks from resting-state fMRI for surgical planning - a feasibility study. Hum Brain Mapp. 2014;35(3):1018–30.
117. Sair HI, Yahyavi-Firouz-Abadi N, Calhoun VD, Airan RD, Agarwal S, Intrapiromkul J, et al. Presurgical brain mapping of the language network in patients with brain tumors using resting-state fMRI: comparison with task fMRI. Hum Brain Mapp. 2016;37(3):913–23.
118. Damoiseaux JS, Rombouts SARB, Barkhof F, Scheltens P, Stam CJ, Smith SM, et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci. 2006;103(37):13848–53.
119. Mitchell TJ, Hacker CD, Breshears JD, Szrama NP, Sharma M, Bundy DT, et al. A novel data-driven approach to preoperative mapping of functional cortex using resting-state functional magnetic resonance imaging. Neurosurgery. 2013;73(6):969–83.
120. Mackay CE, Fox PT, Miller KL, Toro R, Filippini N, Fox PM, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci. 2009;106(31):13040–5.
121. Birbaumer N, Elbert T, Canavan AG, Rockstroh B. Slow potentials of the cerebral cortex and behavior. Physiol Rev. 2017;70(1):1–41.
122. Mitzdorf U. Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. Physiol Rev. 2017;65(1):37–100.
123. Medical HH, Chase C, Liu H, Buckner RL, Talukdar T, Tanaka N, et al. Task-free presurgical mapping using functional magnetic resonance imaging intrinsic activity. J Neurosurg. 2009;111(4):746–54. http://www.ncbi.nlm.nih.gov/pubmed/19361264.
124. Agarwal S, Sair HI, Pillai JJ. Limitations of resting-state functional MR imaging in the setting of focal brain lesions. Neuroimaging Clin N Am. 2017;27(4):645–61.
125. Mueller WM, Yetkin FZ, Hammeke TA, Morris GL, Swanson SJ, Reichert K, et al. Functional magnetic resonance imaging mapping of the motor cortex in patients with cerebral tumors. Neurosurgery. 1996;39(3):515–21.
126. Roux FE, Boulanouar K, Ranjeva JP, Tremoulet M, Henry P, Manelfe C, et al. Usefulness of motor functional MRI correlated to cortical mapping in Rolandic low-grade astrocytomas. Acta Neurochir. 1999;141(1):71–9.
127. Rutten GJM, Van Rijen PC, Van Veelen CWM, Ramsey NF. Language area localization with three-dimensional functional magnetic resonance imaging matches intrasulcal electrostimulation in Broca's area. Ann Neurol. 1999;46(3):405–8.
128. Haglund MM, Berger MS, Shamseldin M, Lettich E, Ojemann GA. Cortical localization of temporal lobe language sites in patients with gliomas. Neurosurgery. 1994;34(4):567–76.
129. Sanai N, Berger MS. Mapping the horizon: techniques to optimize tumor resection before and during surgery. Clin Neurosurg. 2008;55:14–9.
130. Cannestra AF, Pouratian N, Forage J, Bookheimer SY, Martin NA, Toga AW, et al. Functional magnetic resonance imaging and optical imaging for dominant-hemisphere perisylvian arteriovenous malformations. Neurosurgery. 2004;55(4):804–14.
131. Benjamin CFA, Li AX, Blumenfeld H, Constable RT, Alkawadri R, Bickel S, et al. Presurgical language fMRI: clinical practices and patient outcomes in epilepsy surgical planning. Hum Brain Mapp. 2018;39(7):2777–85.
132. Asthagiri AR, Pouratian N, Sherman J, Ahmed G, Shaffrey ME. Advances in brain tumor surgery. Neurol Clin. 2007;25:975–1003.