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Clinical Challenges of fMRI

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Introduction

Functional magnetic resonance imaging (fMRI) has revolutionized clinical brain mapping and has become the predominant functional neuroimaging technique since its original report by Belliveau and colleagues.[1] The appeal of fMRI is attributable to several advantages that it offers over other functional neuroimaging techniques. Functional MRI is non-invasive; it is a rapid technique that offers the opportunity for repeated measurements of the same task to investigate response consistency, to compare activations across tasks, and to measure change over time.

Despite its advantages, fMRI presents several unique challenges, especially in the clinical setting (Table 5.1). Many of these challenges arise from the fact that fMRI does not directly measure neuronal activity. Instead, fMRI detects perfusion-related signals that are coupled to neuronal activity. Many studies make 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; for example, the presence of intracerebral pathologies [e.g., arteriovenous malformations (AVMs)] can induce field inhomogeneities and also may alter neurovascular coupling mechanisms, both of which may hamper measurement of reliable hemodynamic-based fMRI signals. Another challenge of clinical fMRI includes the inability of patients to comply with imaging protocols. One study[2] showed that nearly 30% of subjects with intracranial masses were excluded from the final analysis due to gross motion artifact. This may be a particularly difficult problem if one wishes to study patients with known movement disorders. Impairments in cognition also may alter patients abilities to complete tasks, both with respect to motivation and task difficulty.

Finally, clinical brain mapping emphasizes results for an individual rather than for a group, impacting strongly on choice of analysis methods. Moreover, altered anatomy due to intracerebral lesions may prohibit spatial registration and normalization tools commonly used in

Table 5.1. Potential Limitations of fMRI in Clinical Populations

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

group statistics, making it difficult to directly compare results from patients with those from a normative sample.[3] This chapter will elaborate on the challenges of fMRI in clinical populations, including issues of field strength and sequence selection, study and task design, and data analysis.

A Brief History of Clinical Brain Mapping

Until the advent of fMRI and other perfusion-based brain mapping techniques, such as positron emission tomography (PET),[4] optical imaging of intrinsic signals (OIS),[5] and near-infrared spectroscopy (NIRS),[6] 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 also could be induced to study brain function by applying electrical stimulations directly on the cortex.[7] Most recently, transcranial magnetic stimulation (TMS) has been introduced as a means of inducing temporary lesions non-invasively.[8] By mapping the effects of lesions, these disruption-based techniques identify parts of the brain that are essential and critical for executing a given task. These disruption-based techniques of mapping the brain have emerged as the gold standard of clinical brain mapping, especially in the neurosurgical arena.

Functional MRI differs 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 indicates 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 (i.e., both essential and supplementary cortical areas). Because of the differences 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.

Hemodynamic Basis of fMRI Maps

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. The clinical challenges of fMRI stem,

in part, from the fact that the fMRI map is an indirect measure of brain activity. To establish 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 (Figure 5.1).[9]

Given a stimuluxs x, there is a given neuronal response $f(x)$, which represents 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 below, the spatial coupling between fMRI activation signals and electrophysiologically active cortices may not be as precise as most would like.

Several recent studies have indicated 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 within patients without paresis.[10] Other studies have found similar suppression of the hemodynamic response adjacent to pathology.[11,12] Conversely, in a study of 14 patients, Schlosser and colleagues suggested that fMRI activation patterns within patients with frontal lobe tumors, when mapped using a verbal fluency paradigm, were comparable to signals in normal controls.[13] Similarly, Righini and colleagues studied 17 patients with frontoparietal masses and found little difference in motor activations between the affected and unaffected hemispheres.[2] The contradiction in these studies highlight 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, hypertension) and different disease states (e.g., vasculitis, angiopathies) can impact differentially the relationship between neuronal activity and functional perfusion. Schmidt and

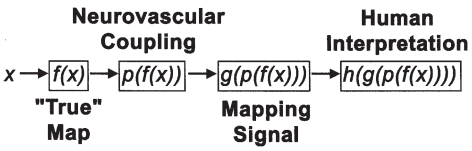

Figure 5.1. Cascade of functional brain mapping functions. The mapping signal observed and reported is actually not a true map of neuronal activity. Rather, it is a product of a series of complex functions, including, for example, the coupling of neuronal activity and local cerebral perfusion, or neurovascular coupling (p). In order 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.

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, highlighting the effect that hypercapnia may have on signals in normal subjects, hypercapnia can be used in normal subject as a means of contrast enhancement.[16] The age of the subject also may affect the magnitude of the hemodynamic response and the coupling mechanism itself.[10] Understanding the underlying coupling dynamics is essential to interpreting fMRI results. It is this uncertainty that continues to motivate continued investigation of neurovascular coupling dynamics.

Assuming neurovascular coupling is intact, several more functions are still applied before arriving at any conclusions from fMRI data. 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. This includes, but is not limited to, resolution limitations, data filtering, and artifacts that may be introduced by different disease processes or medical interventions (e.g., coils, clips, arteriovenous malformations, air cavities after neurosurgical resections).

Finally, yet another function is introduced into the formula, h, for the introduction of human study design, human interpretation, and statistics. Human interpretation of mapping signals, when not quantitative, is always susceptible to bias. The bias may be inadvertent and may be as subtle as in selecting an inappropriate control for comparison or measuring inappropriate signal parameters from which to draw conclusions. The statistics commonly used in fMRI also introduce error and misinterpretations, presenting yet another challenge to clinical interpretation scans.

Although many studies compare blobs across groups, there are a number of assumptions that underlie those blobs. To better understand the underlying map, or $f(x)$, this complex function must be deconvolved 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 to strengthen their conclusions. Many of these issues of study design and analysis are discussed below.

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).[17] Increased SNR and CNR improve study power and decrease Type II errors. Presumably, increased CNR can reduce the scanning time needed to obtain significant results, or make it possible to scan in multiple paradigms in the same amount of time.

Another advantage of increased field strength is the potential for increased spatial resolution (smaller voxel size) with greater SNR given the same acquisition time than at lower fields. Increasing spatial resolution can enhance the sensitivity of the mapping technique, particularly where small differences in localization of function are crucial to the clinical decision or outcome. Large voxel size limits fMRI sensitivity because functional changes at cortical capillaries, which are orders of magnitude smaller than voxel size and represent only a small fraction of total voxel size, are drowned out at the level of the voxel. This partial-volume effect is reduced with smaller voxel sizes. Ultimately, if voxel sizes are too large, a lack of difference between subjects or groups may not actually mean there is no difference. Rather, this may represent a sensitivity limitation of the technique.

However, higher field strengths also pose problems that, in some brain regions or in some clinical conditions, may prove insurmountable. The most difficult complication arising from increased field strength is the associated increase in susceptibility artifact, especially near air–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 fMR images. This is of particular importance for language mapping, in which investigators expect to find several temporal lobe language areas.[18] Lack of signal in these regions does not indicate lack of activity, but may be due to lack of sensitivity to identify appropriate signals. Devlin and colleagues have proposed alternate strategies when imaging these regions of high susceptibility, but they also acknowledge that these artifacts can only be partially overcome and that alternative data acquisition paradigms are necessary to address this issue.[19] 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 imaging (EPI) sequence. Echo planar imaging is the fast scanning technique that acquires all slice locations with a single response time (TR), and which has made fMRI practical.[20] The gradient echo sequence is optimized to maximize susceptibility due to blood oxygenation level-dependent (BOLD) contrast. An unfortunate but necessary side effect is that it also maximizes unwanted susceptibility artifacts at tissue interfaces, especially at high field. In certain brain regions—particularly the amygdala, basal temporal region, and orbitofrontal cortex—the susceptibility artifacts may make imaging these regions impossible.

Clinical fMRI within patients who have had prior brain surgery may be complicated by the presence of implanted devices, such as plates and screws. Whereas 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 that include massive signal loss and spatial distortion. It also should 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.

There are a variety of simple approaches to reducing susceptibility artifacts at air–tissue interfaces and around objects during functional imaging. Reducing voxel size is one. In the amygdala, for instance, Merboldt and colleagues[21] calculated that voxel sizes of 4 to 8 microliters or less are necessary to recover sufficient signal. Fransson and colleague[22] used a high-resolution acquisition method to receive signal in the hippocampus using coronal acquisitions and in-plane resolution of two square millimeters and slice thickness of one millimeter. For most centers, this approach is impractical, both to a lack of non-standard sequences on clinically oriented machines and because for many systems the associated reduction on field of view (FOV) is not acceptable. However, for patients with a focal lesion in which a small FOV is all that is necessary, small voxel studies may be appropriate. The loss of CNR within small voxels also may prohibit the practical use of this approach.

To some extent, use of alternative pulse sequences can improve, but not wholly overcome these artifacts. Port and colleagues[23] performed a series of imaging studies on titanium screws embedded in gel to determine parameters that would decrease susceptibility artifacts in echo planar (EPI) images. They reported three factors that can reduce artifacts: reducing the echo time (TE), increasing the frequency matrix, and reducing slice thickness. The latter two approaches are identical to those reported by Merboldt and colleagues[21] for imaging at air–tissue boundaries. However, the effect of reducing TE on susceptibility is controversial. Susceptibility artifacts due to signal loss at air–tissue interfaces are greater with longer TEs. One approach to reducing susceptibility artifact is to reduce the TE. Gorno-Tempini and colleagues[24] used a double echo EPI sequence to compare susceptibility artifacts and BOLD signal changes at tissue interfaces, comparing TEs of 27 and 40 milliseconds. They used a face-processing task, which is known to activate the fusiform gyrus in the base of the temporal lobe, an area likely to suffer from susceptibility-induced signal loss. Whereas the lower TE did not reduce their ability to detect BOLD signal in those regions unaffected by susceptibility artifacts, the lower TE was not sufficient to recover the BOLD signal.

Various pulse sequences have differential effects on susceptibility artifacts. One alternative to the commonly used gradient echo EPI scan is the asymmetric spin echo. Both spin echo and gradient echo sequences base their signal on magnetic susceptibility contrast as described above, as well as in the previous chapters. 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 also will result in CNR

loss due to reduced BOLD contrast. At 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 and colleagues[25] have demonstrated that varying these parameters can optimize for a particular perturbation size (i.e., a small or large blood vessel). Several fMRI studies have used a spin echo sequence effectively in high susceptibility areas such as hippocampus and amygdala.[26–28] Figure 5.2 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, although not complete.

Other modifications to the EPI sequence may reduce susceptibility artifacts. Cordes and colleagues[29] advocated using a second refocusing gradient in the slice-selection orientation to reduce susceptibility

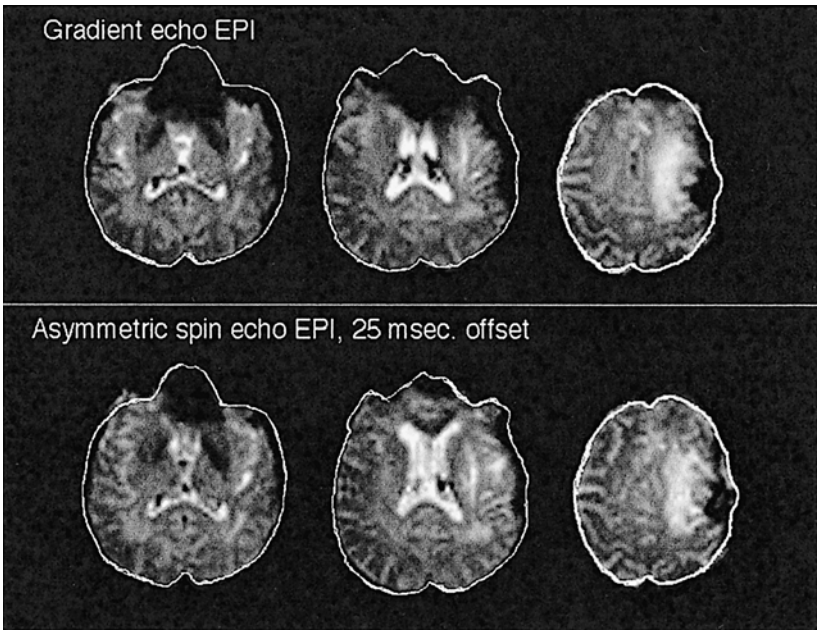

Figure 5.2. Gradient echo versus asymmetric spin echo (ASE) EPI. Gradient echo (TR = 2.5, TE = 45, 64 × 64 matrix, FOV = 20, 1 NEX) and asymmetric spin echo (TR = 2.5, TE = 45, offset = 25 msec, 64 × 64 matrix, FOV = 20, 1 NEX) EPI scans in two areas of high susceptibility (left) at air–tissue interfaces 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.

artifacts. A more complicated approach offered by Stenger and colleagues[30] used three-dimensional (3D) tailored radiofrequency (RF) pulses to refocus regions where the susceptibility is greatest, using a modified spiral *k*-space trajectory.

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[31] reported that a spiral-in trajectory or combinations of in–out trajectories can both increase SNR while reducing susceptibility. Yang and colleagues[32] developed a reverse spiral scanning technique simultaneous with perfusion imaging with arterial spin labeling. 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-encoded (SENSE) sequencing[33] that shortens the readout duration, thus minimizing signal loss. However, the effects of BOLD signal recovery were less dramatic.

Mapping the Oxy/Deoxyhemoglobin Signal

The choice of mapping signal has become an interesting debate. Although the debate has not yet entered the clinical arena, it deserves brief mention here. Following functional activation, cerebral blood flow (CBF) increases in excess of the cerebral metabolic rate of oxygen ($CMRO_2$), thereby causing a decrease in deoxyhemoglobin (due to an overperfusion of oxyhemoglobin).[34] This functional change in the relative abundance of the different hemoglobin moieties is responsible for the increased BOLD MR signal observed with functional activation. This theory is consistent with several studies that have documented that functional CBF increases exceed that of $CMRO_2$ using multiple modalities, including: positron emission tomography (PET);[35] optical imaging of intrinsic signals (OIS);[5,36] and optical imaging of fluorescent dyes.[37] Recently, an initial decrease in BOLD signal, or initial dip, has been reported that precedes the increased BOLD signal described above. The initial dip is thought to represent an initial burst in oxidative matabolism, which increases local deoxyhemoglobin concentrations before any perfusion changes occur.[37,38] It has been proposed that if this initial negative signal does in fact represent an initial burst in oxidative metabolism, it may be more highly spatially correlated with electrophysiological activity than the later positive BOLD signal.[39] Accordingly, Kim and colleagues[40] was able to use the initial dip signal in cats to map ocular dominance columns in cats using BOLD techniques.

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; however, 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, three issues of particular importance in clinical fMRI will be discussed: choice of control conditions, the effect of practice on observed fMRI activations, and the appropriate level of difficulty 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 simple subtracting rest or control condition images from those acquired during a task.[41,42] 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 repeatedly use the same strategy to perform a task, nor can all the cognitive processes that are required to complete a given task function be deduced easily. This challenge is 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. Tasks that are suitable for brain mapping in the general healthy population may not be appropriate in an impaired population. Finally, this approach assumes that 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).[43] 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 question subtraction methodology and the assumption that tasks can accurately decompose.

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.[44] 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, whereas the last five were considered to be various controls. Not surprsingly, 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 ROI intimately depended on the control condition used. This study highlights two important points. First, rest does not mean that the brain is quiescent; the brain is cognitively active even during rest. Second, 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 baseline to evoke a functional hemodynamic response. This highlights the need for careful selection of baseline tasks and even more careful interpretation of observed activation patterns.

Gusnard and Raichle[45] reviewed the concept of a physiological baseline, suggesting that in fact 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. Importantly, they provided a thorough discussion of task-related decreases in activation and argued that while some of these decreases 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.[45]

Practice Effects

Paradigm design is not only important with respect to selection of tasks, but also with respect to 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.[46–49] Raichle and associates were the first to report that functional activation patterns can be altered by relatively brief periods of practice.[46] 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 minutes 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 an automatization of the task that was reversible. Van Mier and colleagues[48] and Petersen and colleagues[47] reported similar findings of shifts in activation patterns, or changes in functional neuroanatomy, from one part of the brain to another with practice. This is thought to represent an activity-

dependent shift in effortful task performance to skilled, automatic task performance.

Similarly, Madden and colleagues[49] 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). 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 both groups initially 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 and, whereas 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. This 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.[50] 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 are consistent with the fact that the task used continues to tax the VSWM system and could not be automated completely, regardless of 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 relatively rapidity of onset are important technical considerations 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 one hour to complete, during which time brain-activation patterns may be modified secondary to practice. Therefore, it is 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, practice-related effects are under investigation.)

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 areas 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 is 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 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.[3,10] The observed decrease in primary motor activation cannot be unambiguously attributed do decreased number of functional neurons in the motor strip compression due to mass effect (although the observation was independent of 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.[3] 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 level of difficulty of the given motor task. Could a more significant signal be elicited from the primary motor strip if the motor task was made more complex and drove the remaining primary motor neurons harder? What if the motor task was made simpler? Could a simpler task induce greater activation by giving the remaining primary motor neurons a task they are fully capable of executing? These may be important points of consideration in interpreting clinical data.

In the same study, the investigators reported larger secondary motor activations within patients with paresis than without paresis. This is most likely attributable to the difficulty of the task for the paretic patients.[3] Similar to the case of elderly patients recruiting a broader network of neurons than younger controls in order to execute a memory task,[49] 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 concluded, 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.[3]

In tasks of higher cognitive functioning, the problem of task difficulty may be even more complex. For example, 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.[51] This increase in activation correlated with functional decline after two years. However, among subjects who have mild AD, the same memory paradigms produced the opposite effect; there was a significant decrease in magnitude, spatial extent, and

total number of regions showing activation in those subjects who had great difficulty performing the task.

Patients with aphasia due to brain lesions showed similar alterations in brain activity. For instance, Sonty and colleagues[52] showed that patients with primary progressive aphasia had activation like normal patients in primary language areas, but also had additional language activation in regions outside language cortices, suggesting the use of compensatory strategies. Kim and collegues[40] found that the pattern of reorganization within patients with focal lesions varied across individuals and appeared related to whether the lesions were cortical or subcortical. Calvert and colleagues[53] found that patterns of fMRI activation during language tasks in a frontal lobe cerebrovascular accident (CVA) patient depended upon the task; increased right-hemisphere Broca's analog was activated during the most difficult task, whereas the left-hemisphere Broca's was active for a matched control subject.

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 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 differential capability to cope with task difficulty. It is suggested that 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 than the comparison group.

Analysis

Adequate study and task design is not sufficient to be able 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 the results of the study. Analysis in the clinical studies differs from other studies most significantly with respect to the type of analysis done: within subject versus group analysis. Attention also must be paid to the technique used to quantify fMRI activations and techniques used to minimize false–positive and false–negative results.

Within Subject Versus 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 add little to the clinical utility of these skills. 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 a single individual based on their fMRI results. First, the broad nature of the question to be answered will be considered.

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, to name a few. The optimal analysis technique will depend upon the question asked. In general, the former category of questions will be answered best by within-subject analysis, and in these cases, there will be a strong emphasis on reliability, reproducibility, and signal magnitude and on accounting for factors that may alter one of these variables. In the latter case, approaches may contrast a particular brain against a databank of brains with and without the disorder in question, calculating the degree of difference for the normative sample and similarity to a diagnostic group probabilistically. While this approach is not currently available, new attempts to find functional landmarks such as the International Consortium for Human Brain Mapping should further such efforts. Here, we will focus on reliability of methods for within-subject analysis in the common current applications.

Given an experimental design that includes at least one activation and *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 pixel intensities, on Komogorov–Smirnov tests that show differences not only in mean, but also in variance, all produce a statistical value that the investigator must threshold and display in some way. Current controversies include how to threshold data and whether to use a statistical value or magnitude measure (percent change) or to count volume of activation—that is, the number of pixels exceeding a statistical threshold as a dependent variable. Each technique has its 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 into two dimensions: spatial extent and magnitude of activation. Calculating activation size by means of pixel counting has become the most common

approach to quantifying fMRI activity, especially in the clinical arena. This approach to activity quantification has several limitations that are discussed below. As an example, the application of pixel counting to studies of language lateralization will be reviewed.

Binder and colleagues[54] compared language lateralization using both fMRI and the intracarotid amobarbital procedure (IAP, the Wada test). For fMRI activations, they studied the contrast between semantic word categorization and a perceptual discrimination task, observing variable amounts of right and left hemisphere activation. The variable activation was quantified using a laterality index (LI), defined as $[V_L - V_R]/[V_L + V_R] \times 100$, where V_L and V_R are activation volumes for the left and right hemispheres, respectively, such that a LI of –100 indicates complete left-sided dominance and a score of +100 would indicate complete right-sided dominance. Volume of activation was defined as the number of pixels exceeding a statistical threshold of correlation with a derived hemodynamic function. A similar index was calculated for errors made during Wada testing using the error rates for each hemisphere injected. Statistical comparisons between the two different measures of laterality, or asymmetry, indicated a strong correlation between the two procedures. This led the authors to suggest a model of relative laterality, which was not completely novel because studies had already indicated by that time that the non-dominant hemisphere had participated in language processing.[54]

These results are striking considering the methodology used. As discussed earlier in this chapter, disruption-based mapping (i.e., Wada testing) and activation-based mapping (i.e., fMRI) may map very different processes. Whereas Wada testing will identify those areas that are essential for language function, fMRI identifies all areas that are involved, essential or not, with language processing. For example, activation paradigms used in fMRI mapping may engage a number of brain systems not specifically related to language, including, including, motor, sensory, and attentional systems that may not be essential and therefore may not cause language disturbance by Wada testing. The high-correlation of the two methods is therefore impressive. The authors proposed that their use of a control paradigm (perceptual discrimination task), in part, controls for these factors, which is probably, in fact, true, but it cannot account for all the methodological differences that seemingly are unimportant in the analysis. They proposed that this be accounted for by the control task.

Beyond differences in methodology between the two techniques, the use of pixel counting to compare relative activity between the two hemispheres may not be valid under all circumstances. Pixel counting has been shown to be remarkably susceptible to noise, and therefore may not be an accurate or precise way of quantifying relative fMRI activation.[55,56] Moreover, this methodology does not account for differences in the magnitude of activation at activated pixels. What if the LI were 0 (indicating equal number of active pixels in both hemispheres), but the average magnitude of activation were three times greater in the left hemisphere? Should one conclude that there is no hemispheric asymmetry? The reliability of language lateralization studies is limited by

the preponderance of left-hemisphere–dominant subjects included in the studies and the concomitant lack of right-hemisphere–dominant individual individuals. Therefore, it is not possible to conclude, with confidence, that fMRI using pixels counting is, in fact, a reliable method of identifying hemispheric dominance.

The limitations of using fMRI for language lateralization is demonstrated by Springer and colleagues, who studied 100 normal subjects and 50 epilepsy patients to compare laterality in the two populations.[57] Methods were similar to that of Binder and colleagues[54] except that Wada testing was not used to confirm results. Despite reports in the literature that approximately four percent of the general population is right-hemisphere dominant,[57] the authors did not identify any right-dominant individual in their normal population of 100 (expected number should have been four). Amongst their epilepsy population, four percent demonstrated right-hemisphere dominance, allowing the authors to conclude that laterality is differentially affected in early onset epilepsy patients than in normal populations. The low base rate of right-hemisphere speech makes it very difficult to compare populations accurately. Moreover, without a gold standard against which to validate results, there is no objective means to conclude that the data are valid.

A study by Lehericy and associates, in which they studied 10 patients for temporal surgery, compared fMRI activity with WADA testing, looking at LI in direct lobes using different language tasks: semantic verbal fluency, covert sentence repetition, and story listening.[59] This group also used LI as a measure of fMRI activity, counting pixels that exceeded a statistical threshold. 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. Functional MRI asymmetry in the temporal lobes (regardless of language task) did not correlate with Wada asymmetries. Moreover, story listening did not correlate with any Wada asymmetry indices in any lobe. It would be interesting to reanalyze this data to determine if better correlation could be identified across tasks and lobes if signal magnitude where considered instead of only the number of pixels exceeding the statistical threshold. This study highlights that fMRI is not completely reliable for assessing asymmetries and that measures of asymmetry may be task and lobe dependent.

Conjunction Analysis

Considering the intrinsic noise associated with fMRI data acquisition (both physiological and equipment related), alternative strategies have been devised in order to extract significant mapping signals that are consistent across tasks (see Figure 5.3).[60,61] Conjunction analysis identifies all voxels in the brain that exceed statistical threshold for two or more independent, yet related, tasks. By Bayes theorem, the probability of observing significant pixels by chance on multiple scans is equal to the product of the prior probability of chance activation on each. For example, if two separate tasks are used, using a Pearson's correlation

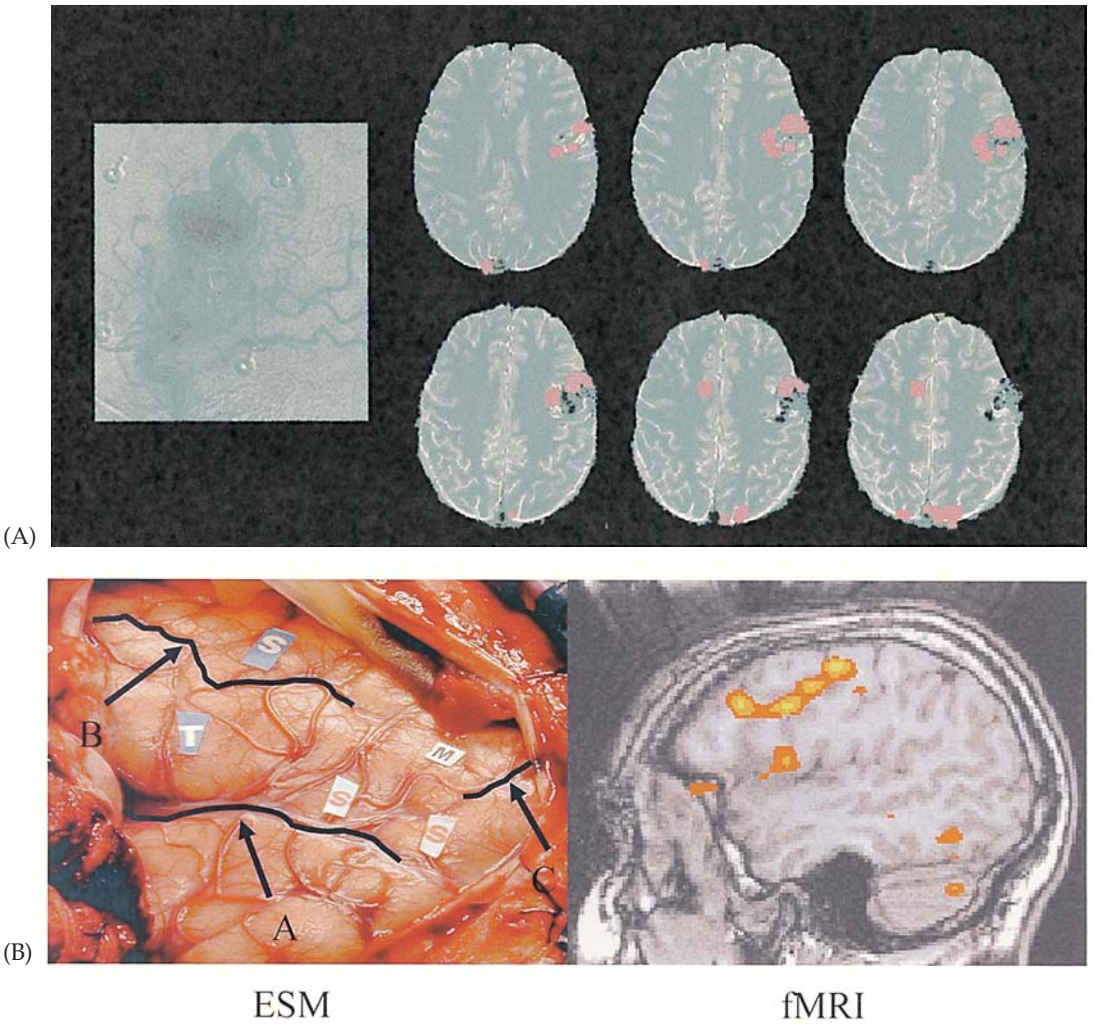

Figure 5.3. (A,B) Functional MRI activations adjacent to AVM. Significant fMRI activations are commonly identified adjacent to a left frontal lobe AVM. In this image, fMRI activations of language expression (created by conjunction analysis) are seen adjacent to a frontal AVM, identifying Broca's Area. 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 (B). Adapted with permission from Pouratian N, Bookheimer SY, Rex DE, Martin NA, Toga AW. Utility of pre-operative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. *J Neurosurg*. 2002(a);97:21–32.

coefficient threshold of 0.2, the probability of correlation by chance for each individual task is 0.063, and the joint probability is less than 0.004. By using a low statistical threshold for each individual scan, conjunction analysis minimizes the probability of eliminating functionally significant voxels due to noise, which effectively reduces false–negative results. However, by requiring that the same voxel must be active across multiple tasks, this analysis minimizes false–positive results by ensuring that only functionally significant voxels are considered in the final analysis.

The power of this technique was recently demonstrated by Pouratian and colleagues in a study comparing language-related fMRI activations with intraoperative electrocortical stimulation map (ESM).[61] The authors created conjunction fMRI maps of expressive language (conjunction of two of three expressive language tasks: visual object naming, word generation, and auditory response naming) and receptive language (conjunction of visual responsive naming and sentence comprehension) and compared these fMRI activations with intraoperative ESM (Figure 5.3A, B). For the population studied, the authors reported 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.

Based on the differences between ESM and fMRI methodology, false–positives consistent with an imperfect specificity should be expected. Whereas ESM is a disruption-based technique that will identify only those areas that are essential to language processing, fMRI is an activation-based technique that will identify all regions of the brain that demonstrate activity-related changes, whether those areas are essential or supplementary. Consequently, areas that are negative for language by ESM may still demonstrate fMRI activations, producing false–positives. The use of the conjunction analysis, however, minimizes this false–positive rate by only identifying those areas that are consistently activated across language tasks. Nonetheless, there clearly are still supplementary and non-essential language areas that are not identified by ESM, but that are consistently active across fMRI activations.

Reproducibility

Reproducibility of fMRI activations, either within subjects or across studies, is rarely addressed. Nonetheless, it is an important consideration, especially now that functional brain mapping is being used increasingly for quantification of brain activity and clinical decision making.[54,61]

Cohen and DuBois reported the most extensive and quantitative study to date of fMRI signal reproducibility, with surprising results with respect to signal stability.[55] Studying both visual and motor cortex, they reported that counting pixels exceeding statistical significance is remarkably unstable, with values varying by 750% across trials. This large degree of variability is attributed to differences in noise levels across trials although the actual activation magnitude is likely the same across trials. (Noise may be composed of a variety of artifacts and physiological factors.) The noise variance propagates through to statistical calculations and produces a widely varying number of pixels that exceed statistical threshold. 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 contrast-to-noise ratio (CNR) conditions, the percent

signal change can be determined with relatively good accuracy and precision.[55]

Huetell and McCarthy[56] arrived at a similar conclusion regarding the value of activation size: Group or condition differences may result from differences in voxelwise noise exacerbated by averaging small numbers of trials. By progressively averaging an increasing number of trials to determine activation size, they found that activation size increases exponentially, reaching a plateau at approximately 150 trials averaged a number that is far less than most conventional fMRI studies. This uncertainty in activation size is attributed to noise, highlighting how intrinsic fMRI noise sources can significantly alter activation sizes.

These studies argue strongly for the lack of reliability of activation size as a measure of response magnitude. Instead, measuring the percent signal change or the slope of the regression line is a much more reliable measure of response magnitude. The latter method of measuring percent signal change is also preferable because it can detect changes in response magnitude across tasks in voxels that are already activated in the original task. Investigators should not only be interested in areas of additional activity, but also in changes in response magnitude of already activated regions.[62] Even if pixel counting were a reliable method, it would not be able to account for such differences. Due to the limited reliability of merely counting pixels, we recommend comparing percent signal change within a statistically defined ROI across trials or tasks in order to compare reliable measures.

Applying fMRI to Clinical Planning

Significance of Signal Localization

Earlier, the concept that the fMRI activation is intimately related to and depends upon the characteristics of neurovascular coupling was introduced. The uncertainty and imprecision of neurovascular coupling introduces one of the biggest challenges and one of the most significant sources of error in interpreting clinical fMRI studies. It is well accepted that the time courses of electrophysiological and hemodynamic responses are different by orders of magnitude. Most investigators also assume tight spatial coupling between electrophysiologically active cortex and the observed hemodynamic response. This, in fact, is probably not as robust a relationship as most assume, limited by neurovascular mechanisms and fMRI physics.

Depending on the scan sequence used, the BOLD fMRI signals often center in adjacent sulci[39,63,64] and can be up to one centimeter away from electrophysiologically active cortex.[39] The sulcal localization suggests that the positive BOLD fMRI signal may not be a very specific mapping signal. Offering relatively poor spatial colocalization with electrophysiological maps and emphasizing changes occurring in vasculature rather than within the cortex.[34,63–65] Alternative mapping signals have been suggested, like the initial dip that may offer a more precise colocalization with electrophysiologically active cortex.[37,38]

Despite the imprecision of spatial localization, fMRI mapping signals are still useful and have been shown to spatially correlate with electrophysiologically active.[66] However, in most cases, in order to achieve spatial colocalization, a sphere of influence of fMRI activity often is assumed to be approximately 0.5–1.0 centimeters in order to achieve high correlation rates.[61,66–69] Because of the spatial imprecision of fMRI, especially when doing whole head imaging, it is important not to over interpret 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 has been called into question both with respect to susceptibility artifact induced by intracerebral pathologies and surgical interventions (e.g., atertiovenous malformations, cavernous angiomas, surgical clips), and with respect to the mass effect and possible physiological disturbance induced by the presence of pathology.

With respect to susceptibility artifact, it is clearly impossible to obtain a signal from within a pathology with significant susceptibility artifact. The question remains as to whether reliable signals can be obtained from adjacent to the pathologies. In a study of 14 patients, Schlosser and colleagues reported that fMRI signals within patients with frontal-lobe tumors were comparable to signals in normal controls.[13] Similarly, Righini and colleagues found little difference in motor activations between the affected and unaffected hemispheres in 17 patients with frontoparietal masses.[2] Pouratian and colleagues also recently 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).[61] These reports are consistent with our findings at UCLA, in which we regularly and successfully map motor and language cortices within patients scheduled for neurosurgical intervention near eloquent cortices (see Figure 5.4).

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

Relationship to Outcomes

Although many studies have investigated the relationship between fMRI and electrophysiological maps,[67–72] very few studies have quantified the sensitivity and specificity of fMRI activations relative to electrophysiological maps or determined the relationship between fMRI

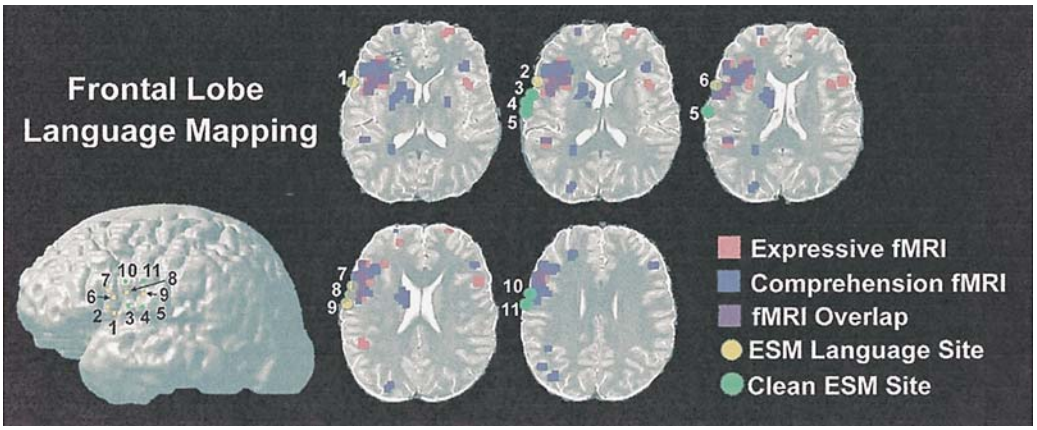

Figure 5.4. Frontal lobe language mapping using fMRI with conjunction analysis. Yellow circles are areas essential for language as determined by ESM. Green circle s are areas that, when stimulated, did not disrupt language function. Red activations are conjunction fMRI maps of language expression. Blue activations are conjunction fMRI maps of language comprehension. Electrocortical stimulation map sites are shown with a five-millimeter 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 with permission from Pouratian N, Bookheimer SY, Sex DE, Martin NA, Toga AW. Utility of pre-operative functional magetic resonance imaging for identifying language cortices in patients with vascular malformations. *J Neurosurg*. 2002(a);97:21–32.

maps and clinical outcomes. These are ultimately the most important factors to be determined with respect to the utility of fMRI as a clinical tool. As fMRI analysis techniques are improved, fMRI will surely play an increasing role in identifying clinically relevant motor and language areas, as well as other eloquent cortices.

As long-term outcomes are ultimately the most important variable in clinical neurosurgery, outcomes studies like that of Haglund and colleagues,[73] which characterized clinical outcomes postoperatively relative to distance of resection from essential language sites as defined by ESM, need to be done across different tasks and cortices to determine the best approach to clinical fMRI mapping.

Conclusions

Functional MRI is a powerful brain-mapping tool whose use has grown exponentially over the last decade. Unfortunately, our understanding of signal etiology, neurovascular coupling, and physiological baselines have not evolved at the same rate. As with most other imaging modalities, fMRI will rapidly enter the clinical arena as a commonly used and accepted modality. Before then, 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 approach, and even equipment can produce different results; valid

application of fMRI to clinical cases will have to demonstrate reliability and validity for each application separately. The field should move rapidly towards developing uniform approaches to clinical fMRI that are valid, reliable, and replicable across centers. We believe that for most applications, clinical decisions should not rest solely on fMRI results. Rather, fMRI may augment existing clinical tools as validation of the techniques continues.

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