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METHODOLOGIC PERSPECTIVES

The Evolution of Clinical Functional Imaging during the Past 2 Decades and Its Current Impact on Neurosurgical Planning

J.J. Pillai

SUMMARY: BOLD fMRI has, during the past decade, made a major transition from a purely research imaging technique to a viable clinical technique used primarily for presurgical planning in patients with brain tumors and other resectable brain lesions. This review article briefly examines the history and evolution of clinical functional imaging, with particular emphasis on how the use of BOLD fMRI for neurosurgical planning has changed during the past 2 decades. Even more important, this article describes the many published studies during that same period that have examined the overall clinical impact that BOLD and DTI have made on surgical planning.

ABBREVIATIONS: AF = arcuate fasciculus; ASFNR = American Society of Functional Neuroradiology; BOLD = blood oxygen level–dependent; CPT = current procedural terminology; CPU = central processing unit; CSM = intraoperative cortical stimulation mapping; DTI = diffusion tensor imaging; DTT = diffusion tensor tractography; EPI = echo-planar imaging; FA = fractional anisotropy; FDA = US Food and Drug Administration; fMRI = functional MR imaging; GLM = general linear model; MEG = magnetoencephalography; PACS = picture archiving and communication system; QC = quality control; RAM = random access memory; SPM = Statistical Parametric Mapping; TL = temporal lobe; TLE = temporal lobe epilepsy; Wada = intracarotid sodium amobarbital test

fMRI is a physiologic imaging technique that has rapidly evolved since the early 1990s when Ogawa et al[1-3] first described the BOLD principle, which was based on animal imaging studies and was considered novel. Human imaging applications arose only in 1991, when Belliveau et al[4] described mapping of the human visual cortex by using fMRI. Since those early days, fMRI has burgeoned into one of the most useful research techniques in modern cognitive neuroscience, with use by a wide variety of researchers in fields as diverse as psychology, neurology, psychiatry, and linguistics. However, clinical use of fMRI is a relatively recent phenomenon, with only slightly more than a decade of collective experience. This review article examines the history and evolution of clinical functional imaging, with special emphasis on BOLD and, to a lesser extent, DTI applications in clinical brain tumor imaging, which have served as early models for the clinical translation and maturation of these imaging modalities. In addition, this article describes the clinical impact that BOLD and DTI have made on surgical planning.

The ASFNR was established in 2004 to address the unique concerns relating to clinical use of functional imaging, comprising not only BOLD imaging but also DTI, perfusion imaging, MEG/magnetic source imaging, and molecular and metabolic imaging, including MR spectroscopy. As all of these physiologic imaging modalities enter mainstream clinical neuroradiology, a growing need to establish national standards for their clinical use and standardized quality control metrics has emerged. The ASFNR, by planned launch of a multicenter study that will assess the effectiveness of BOLD and DTI in surgical planning, is well-poised for this role. The steadily increasing membership of the ASFNR and successful annual meetings, such as the one conducted in late February 2009 in San Antonio, Texas, are a testament not only to the increasing popularity of these techniques but also to the growing need for incorporation of these modalities into mainstream clinical neuroradiology practice. While a description of all the research and clinical applications of these diverse physiologic and metabolic imaging modalities that are embraced by the ASFNR is clearly beyond the scope of this article, we can examine the technique that has historically served as the springboard for the birth of the ASFNR—BOLD imaging—and, to a lesser extent, the complementary role of DTI in presurgical mapping, which are the main currently accepted clinical applications of these techniques. There are broadly 3 main categories of patients who commonly undergo preoperative fMRI: 1) patients with structural brain lesions in close proximity to eloquent cortex who need preoperative functional risk assessment, 2) patients who need determination of preoperative language hemispheric lateralization (and possibly, in the future, memory lateralization), and 3) patients with epilepsy needing preoperative seizure-focus localization with electroencephalographic-correlated fMRI.[5] We will focus on the first 2 categories in this article.

The Early Era of Clinical BOLD Imaging

In the early days of BOLD imaging (the 1990s), all such imaging was conducted at most centers under institutional review board–approved research protocols because no accepted clinical application existed, and much investigation into the basic principles of BOLD contrast was necessary. Because EPI was relatively new and most MR imaging scanners were operating at field strengths of 1.5T or below, with limited gradient strengths and low slew rates, BOLD imaging was relatively difficult to perform. While FDA-approved EPI sequences were

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developed by scanner manufacturers, the software for BOLD image analysis was not FDA-approved but was rather designed strictly for research applications.

Because paradigms for motor, language, and visual mapping were just beginning to emerge and limited literature was available regarding optimal paradigm design and stimulus-presentation techniques, much of the work being conducted in the realm of paradigm design and implementation was home grown at a number of academic institutions. Many different software packages were available for BOLD processing, but no consensus existed as to which was most appropriate for clinical use and multiple approaches to data processing existed.[6] Some of these packages relied on the GLM for statistical analysis (eg, SPM, University College London, London, UK),[7] while others relied on cross-correlation approaches, *t* test analyses, independent component analysis, or multiple different options for data analysis (eg, Analysis of Functional NeuroImages; Medical College of Wisconsin, Milwaukee, Wisconsin).[8] Even within each of these general approaches, much debate existed as to the optimal statistical thresholding for research and clinical applications. Different iterations of the software were developed during the years (eg, SPM evolved from the early SPM96 to the current SPM8), and new, more conservative statistical approaches evolved (eg, various corrections for multiple comparisons, the false discovery rate).[9]

During the early era of clinical BOLD imaging, the same basic interdisciplinary approach that served as the hallmark of BOLD research applied equally to clinical examinations. Often an MR imaging physicist or 2, research assistants, image-processing personnel, a statistician, and, at some centers, a psychologist or neurologist were participants in a multidisciplinary fMRI research team along with a neuroradiologist either with or without a dedicated MR imaging technologist. The fMRI systems used had to be essentially assembled by the research team, with stimulus-presentation software and hardware, patient-monitoring equipment, and paradigm design and implementation all independently developed or purchased from different vendors. No integrated commercially available fMRI system existed, and the home grown systems were not designed to be MR imaging technologist–driven.

Although unprecedented high-resolution structural brain imaging had been realized with the advent of structural MR imaging in the early 1980s, study of in vivo higher level cognitive function was not possible before the advent of BOLD fMRI. BOLD imaging allowed assessment not only of sensorimotor and visual function but also of complex language, memory, emotion, and even higher level reasoning functions, such as abstract mathematic reasoning.[10] BOLD imaging complemented established but relatively spatial-resolution-limited electrophysiologic methods such as electroencephalography and transcranial magnetic stimulation for the study of brain function, and it preceded the emergence of MEG as a readily available alternative technique. This has led to an explosion of BOLD-related literature in the cognitive neurosciences during the past 2 decades. Even unlikely applications such as in the medicolegal arena with evaluation of truth-telling have recently been noted.[11,12]

BOLD fMRI Validation Studies during the Early Era

BOLD Motor Mapping

During the early era of functional imaging, many individual institution-based clinical validation studies emerged that strove to compare BOLD results with those of the intracarotid sodium amobarbital (Wada) test for language lateralization and intraoperative cortical stimulation mapping for language and motor cortex localization. For example, many studies have compared CSM with preoperative motor fMRI; these studies have found high correlations between the 2 modalities.[13-20]

BOLD Language Mapping Compared with Wada Testing

Language mapping has been less standardized than motor mapping across medical centers and has thus been more difficult to validate than simple sensorimotor mapping. Nevertheless, many studies have compared preoperative BOLD imaging with the Wada test for language lateralization. For example, Binder et al[21] studied 22 patients with epilepsy with both Wada testing and fMRI by using a semantic decision task and found high correlation between the lateralization on fMRI and Wada testing ($r = 0.96$). Bahn et al[22] also found similar results (100% concordance) in a comparison of language fMRI to Wada lateralization in their study of 7 patients with epilepsy. Similarly, Hertz-Pannier et al[23] reported perfect language lateralization concordance between Wada and preoperative fMRI results by using a word-generation task in a group of 6 children with partial epilepsy. Sabbah et al[24] reported language lateralization concordance in 19 of 20 patients with epilepsy between preoperative Wada testing and fMRI by using a silent word-generation task. Meneses et al[25] also studied 5 patients with epilepsy with a verbal-fluency fMRI language task and have similarly reported 100% lateralization concordance with Wada testing. On the basis of these and other studies, many epileptologists now think that fMRI is adequate for language lateralization, though the failure thus far to establish widely accepted memory activation paradigms still makes fMRI fall short of a definite substitute for the Wada test for overall hemispheric lateralization. Nevertheless, many believe that fMRI is well on its way to serving as a reliable noninvasive substitute for the Wada test.[26]

BOLD Language Mapping Compared with Intraoperative Mapping

Other studies were performed comparing preoperative language fMRI results with those of awake intraoperative CSM results. For example, Yetkin et al[13] in their study of 28 patients who performed finger, lip, and tongue motor tasks in addition to silent word-generation and counting tasks, found 100% concordance between the fMRI activation sites and intraoperative stimulation sites within 20 mm and 87% concordance within 10 mm. Furthermore, Benson et al[27] reported correct language lateralization by using a verb-generation task in 22 of 23 patients who also underwent either Wada testing ($n = 12$) or CSM ($n = 11$) as a reference standard. Hirsch et al,[16] in their study of 125 patients and 63 controls using multiple fMRI tasks, found sensitivities for detection of the Broca area of 93% and 77% and for the Wernicke area of 100% and 91%, respec-

tively, for the control and patient groups; they also noted overall concordance with CSM and Wada results.

Memory Mapping with BOLD fMRI

While memory mapping has been the subject of extensive research during the past decade, it has not yet gained widespread clinical acceptance despite the publication of 3 validation studies, which have compared preoperative memory fMRI lateralization with preoperative Wada test results and/or postoperative memory outcome.[28-30] For example, Janszky et al[28] in their study of 16 patients with right mesial TLE who performed the Roland hometown walking test found a high correlation ($r = 0.71$) between the preoperative fMRI memory lateralization and individual postoperative memory outcome following right anterior TL resection. Similarly, Richardson et al[30] noted high correlations between preoperative fMRI hippocampal encoding asymmetry and postoperative memory outcome in their study of 10 patients with left TLE who underwent a verbal-encoding task.

In the study of Rabin et al[29] of 35 patients with TLE and 30 healthy controls who performed a complex visual-scene-encoding memory task, the authors evaluated medial TL regions of interest that encompassed the hippocampus, parahippocampal gyrus, and fusiform gyrus. The control subjects showed almost symmetric activation within these regions of interest, whereas the patients with TLE showed greater asymmetry. Preoperative fMRI activation asymmetry ratios from the regions of interest correlated significantly with both memory lateralization by preoperative Wada testing and postoperative memory outcome, as determined by a change in scene recognition between presurgical and postsurgical evaluations.[29]

Limitations in the Early Era of Functional Imaging

Many of these studies were fairly unsophisticated because in that era, export of postprocessed functional activation maps into neuronavigation systems was not possible and most radiology departments did not even have PACS, but were rather relying on hard copy films. Neurosurgeons using such data at most centers had access to only relatively primitive neuronavigation systems that only permitted use of 3D structural brain images; for this reason, hard copy images of BOLD results were often posted in the surgical suites for planning purposes. As PACS servers became more common around the turn of the century with the digitization of radiology departments, more impetus for electronic transfer of functional activation maps to PACS servers developed. Along with the development of PACS, we have seen a tremendous increase in computational capacity since the 1990s. In those days, much of the processing of BOLD data was extremely time-consuming due to relatively slow CPU processing capability and relatively low memory (RAM) capacity of high-end computer workstations in that era, and the data-storage needs were colossal, considering that a single clinical study could exceed 1 gigabyte of data. It was not uncommon for a single clinical fMRI study to require up to 8–12 hours of processing by using GLM approaches. A minimum of 1 terabyte of storage capacity was considered optimal in those days, which seems minute compared with the requirements of the current era.

Multimodality image fusion, now the standard, was not widely available due to the inherent limitations of BOLD processing and coregistration with other functional imaging datasets. For example, coregistration with DTI maps, such as FA-weighted color directional maps or DTT, was generally not feasible because different research software packages were used for generation of the DTI maps, which were not necessarily compatible with the software used for the BOLD image analysis. Scanner vendors did not provide commercially available software for DTI processing, and only standard 3-direction diffusion encoding was available for generation of typical diffusion-weighted images and postprocessed apparent diffusion coefficient maps. Similarly, dynamic susceptibility contrast perfusion MR imaging was in its infancy as well, and commercially available software generally allowed only acquisition of time-to-peak maps and basic cerebral blood volume maps, not corrected for contrast-leakage effects or capable of providing permeability information. Even the phenomenon of neurovascular uncoupling had not yet been described, and many of the potential pitfalls of the clinical application of BOLD imaging were just being acknowledged for the first time.

Advances in the Current Era of Functional Imaging

In the current era of functional imaging, arising at the start of the current millennium, what was originally a novelty from a cognitive neuroscience investigation standpoint has evolved into an essential element in such exploration of human brain function, and this has led to development of new models of language function (eg, the ventral and dorsal stream model) and working memory based on empiric evidence provided by functional neuroimaging.[31]

Furthermore, BOLD imaging has made a major transition from a research to a clinically viable imaging technique. The development of the new CPT codes for fMRI in January 2007 signifies this transition to an essential clinical tool that has elevated the surgical standard of care. From the very beginning, our neurosurgical colleagues have been primarily responsible for advocating the clinical use of this technique, and currently neurosurgeons at a growing number of academic medical centers consider the combination of BOLD and DTI to be an indispensable component of their practices. Such imaging has influenced preoperative risk assessment, intraoperative mapping strategy, and surgical trajectory.

Many major improvements in the current decade of clinical functional imaging have made performance of these examinations much more streamlined and practical. Newer commercially available fully integrated FDA-approved fMRI systems are now available that offer turnkey solutions from a data-acquisition and paradigm-delivery standpoint as well as rapid and often technologist-driven streamlined processing. No institutional review board protocol is needed for use of these FDA-approved clinical systems. A variety of well-documented paradigms are available for motor, language, and visual mapping. Three-dimensional fusion of DTI and BOLD datasets and delivery of postprocessed images to PACS servers and neuronavigation systems are now possible due to software improvements. Image-processing time has been drastically reduced to $\leq$1 hour for BOLD processing, largely due to vastly more powerful computer workstations with faster CPUs and greater RAM. While the need for increased data-storage ca-

CPT Codes for fMRI[35]	
Code No.	Description
70554 fMRI brain by technologist	Includes test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration.
70555 fMRI brain by physician/psychologist	Requires physician or psychologist administration of entire neurofunctional testing.
96020 functional brain mapping (must be used with 70555)	Neurofunctional testing selection and administration during noninvasive imaging functional brain mapping, with test administered entirely by a physician or psychologist, with review of test results and report.

pacity has grown, the cost associated with incremental expansion of data-storage capability has decreased substantially. Perfusion imaging or cerebrovascular reactivity mapping is also performed at many centers along with BOLD fMRI to evaluate the potential for lesion-related neurovascular uncoupling.

Establishment of CPT Codes Reflecting Advances of the Current Era

The establishment of the CPT codes has been based both on the numerous single-center clinical validation studies described above and on several landmark studies that have shown the great value of preoperative functional imaging in surgical planning.[32-34] See the Table for a description of these codes.[35] Specifically, in the study of Petrella et al[32] of 39 patients with brain tumors who underwent preoperative fMRI, the BOLD fMRI altered treatment planning in 19 patients ($P < .05$) and resulted in reduced surgical time (15–60 minutes) in 22 patients. Medina et al[33] evaluated 60 patients with preoperative language ($n = 53$), motor ($n = 33$), or visual ($n = 7$) fMRI. In 38 (63%) patients, fMRI helped to avoid further studies, including the Wada test. In their series, intraoperative mapping was altered in 31 (52%) patients, and overall surgical planning was altered in 25 (42%) patients by the preoperative fMRI results.[33] Roessler et al[34] studied 22 patients with gliomas near the motor cortex who underwent both preoperative fMRI on a 3T MR imaging system and CSM. fMRI detected the primary motor cortex in all patients, but CSM was possible in only 17 of 22 patients (77.3%). The authors reported 100% agreement between CSM localization and fMRI localization of the primary motor cortex within 10 mm.[34]

Complementary Role of DTI in Eloquent White Matter Mapping

DTI for depiction of eloquent white matter has been as useful in clinical practice as BOLD imaging for delineation of eloquent cortex because surgical severing of these white matter tracts can produce similar postoperative neurologic deficits. Many scanner vendors now offer streamlined DTI and DTT packages, and the overall value of DTI for preoperative risk assessment is excellent.[36] See Fig 1 for an example of how the combination of BOLD and DTI is used in the evaluation of a patient with a brain tumor.

Emerging Role of BOLD and DTI in Neuronavigation

One relatively recent advance has been the ability to import digital BOLD and DTI data directly into neuronavigation systems. Some of the neuronavigation companies even offer their own BOLD and DTI processing software, including software for basic tractography. Several recent studies have shown great promise for DTI incorporation into neuronavigation systems for surgical planning,[37-40] and similar studies have shown the added value of BOLD results when incorporated into neuronavigation systems.[41] Each of these studies will be described briefly.

In the study of Bello et al[37] of 52 patients with low-grade gliomas and 12 patients with high-grade gliomas, the authors found a high correlation between DTI fiber tracking results and those of intraoperative subcortical mapping; the overall sensitivity was 95% for detection of the corticospinal tract and 97% for detection of language tracts, by using intraoperative mapping as the criterion standard. The combination of both methods decreased surgery duration, patient fatigue, and the incidence of intraoperative seizures.[37]

Wu et al[38] studied 238 patients with brain tumors involving the pyramidal tract to determine the impact of the use of preoperative DTI in neuronavigation on postsurgical outcome and long-term survival; 118 underwent DTI, while 120 underwent only standard 3D structural imaging for neuronavigation. Postoperative motor deterioration occurred in 32.8% of the control cases, compared with only 15.3% in the DTI group ($P < .001$). In addition, significantly higher 6-month Karnofsky Performance Scale scores were noted in the DTI group.[38] In 81 patients with high-grade gliomas, the median survival of patients undergoing preoperative DTI was 21.2 months compared with only 14.0 months for the control patients ($P = .048$).[38]

Coenen et al[39] compared the location of the preoperative DTI-based pyramidal tract outlined in neuronavigation with the tract outlined in surgery through subcortical intraoperative mapping in 13 patients with tumors adjacent to the pyramidal tracts or in perirolandic regions. They found that in 11 of the 13 patients (92%), the motor pathways were correctly predicted by preoperative DTT, by using subcortical intraoperative mapping as the criterion standard.[39]

Berman et al[40] performed DTT of the corticospinal tract with DTT overlay on T1- and T2-weighted anatomic images for import into a neuronavigation system for surgical planning in a total of 9 patients with gliomas; in 7 patients, additional magnetic source imaging was performed to identify the functional somatosensory cortex. Intraoperative subcortical stimulation mapping of the corticospinal tract was performed by using a bipolar electrode with a total of 16 subcortical motor stimulations identified in the 9 patients.[40] The mean distance between stimulation sites and DTT-determined tracts was 8.7 ± 3.1 mm, which included the inherent error associated with both the actual DTT technique and the stereotactic navigation/image coregistration.[40]

Krishnan et al[41] investigated the correlation between the lesion-to-fMRI voxel activation distance and the occurrence of new postoperative motor deficits in 54 patients with peri-

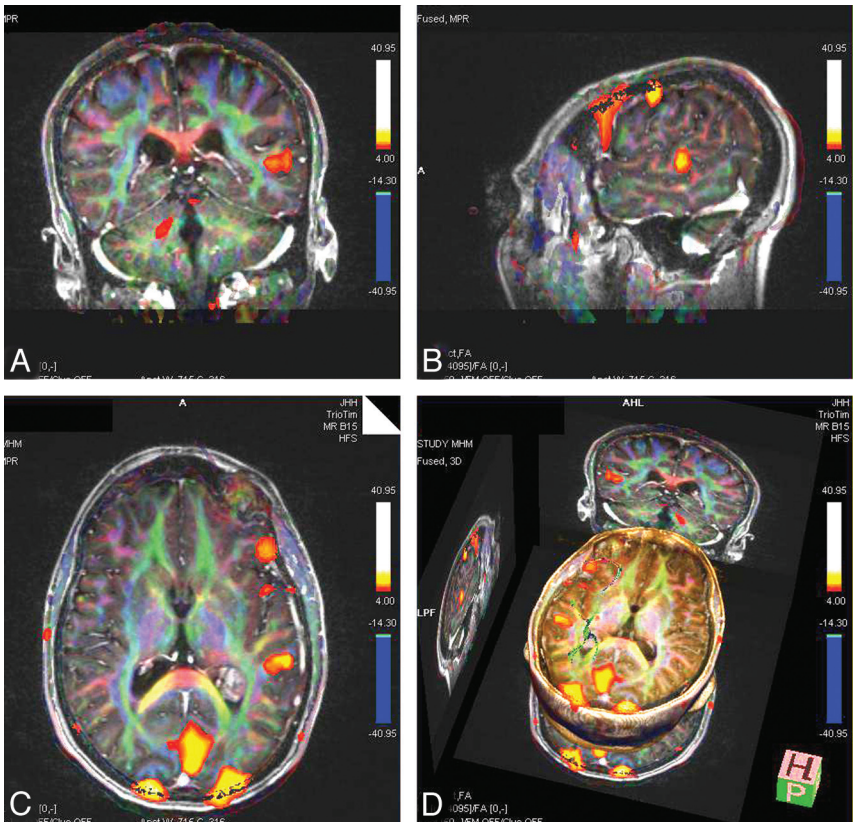

Fig 1. Multiplanar views of language BOLD activation overlaid on FA-weighted color directional diffusion maps superimposed on postgadolinium 3D magnetization-prepared rapid acquisition of gradient echo high-resolution anatomic images in a patient with a left trigonal intraventricular mass. The BOLD paradigm used is a silent word-generation task. Red-green-blue coding convention is used for DTI display, in which red refers to mediolateral; blue, to superoinferior; and green, to anteroposterior preferential diffusion. Note the activation of both Broca and Wernicke areas in the left hemisphere in this left-language-dominant patient.

rolandic lesions who performed hand, foot, and tongue motor fMRI tasks. In 45 patients, gross total resection was accomplished, while 80%–95% of resection was performed in the remaining 9 patients; postoperative neurologic status was noted to be improved relative to baseline in 29.6% of patients, unchanged in 53.7%, and worsened in 16.7%.[41] The authors concluded that a lesion-to-activation distance of <5 mm may be associated with a higher risk of postsurgical neurologic deterioration, whereas within a 10-mm range, CSM should be performed for safe resection, while for distances of >10 mm, a complete resection can be safely accomplished.[41]

See Fig 2*A*, -*B* for examples of language and motor BOLD-activation maps imported into a neuronavigation system.

New Insights and Challenges Provided by Clinical Functional Imaging

During the past 2 decades, fMRI has not only served a vital role in presurgical mapping in patients with resectable brain lesions but has also contributed greatly to the evolution of our knowledge regarding language processing and overall cortical and subcortical language representation in the human brain.[31] The classic model of language processing, invoking the Broca area (left inferior frontal gyrus) and Wernicke area (posterior left superior temporal gyrus) as well as the AF, which connects the expressive language areas to the receptive language cortex, has recently been replaced with a more complex model describing a more expansive language network. In particular, the new concept of "dual-stream model," which has been described in the current decade, has been recently evaluated with fMRI/DTT by Saur et al.[31] These authors observed that sublexical speech repetition is subserved by a dorsal pathway, connecting the superior TL and the premotor cortices in the frontal lobe via the AF and superior longitudinal fasciculus.[31] In addition, higher level language comprehension is mediated by a ventral pathway connecting the middle TL and ventrolateral prefrontal cortex via the extreme capsule.[31] The dorsal pathway involves sensorimotor mapping of sound to articulation, whereas linguistic processing of sound to meaning involves the ventral pathway.[31]

Some technical pitfalls of clinical BOLD imaging have been highlighted as a result of the growing use of this technique. Foremost among these is the phenomenon of neurovascular uncoupling, which refers to the uncoupling of the regional microvascular blood flow changes from adjacent neuronal activity often seen in high-grade brain tumors with tumor angiogenesis or in arteriovenous malformations that alter local cerebral hemodynamics; many biochemical mediators of the neurovascular coupling have been implicated, such as nitrous oxide, certain neurotransmitters, etc.[42-44] Cerebral vascular reactivity mapping by using carbon dioxide challenges or breath-holding, MR perfusion imaging to assess the presence of regional hyperperfusion, and complementary intraoperative mapping evaluation are methods that different centers are

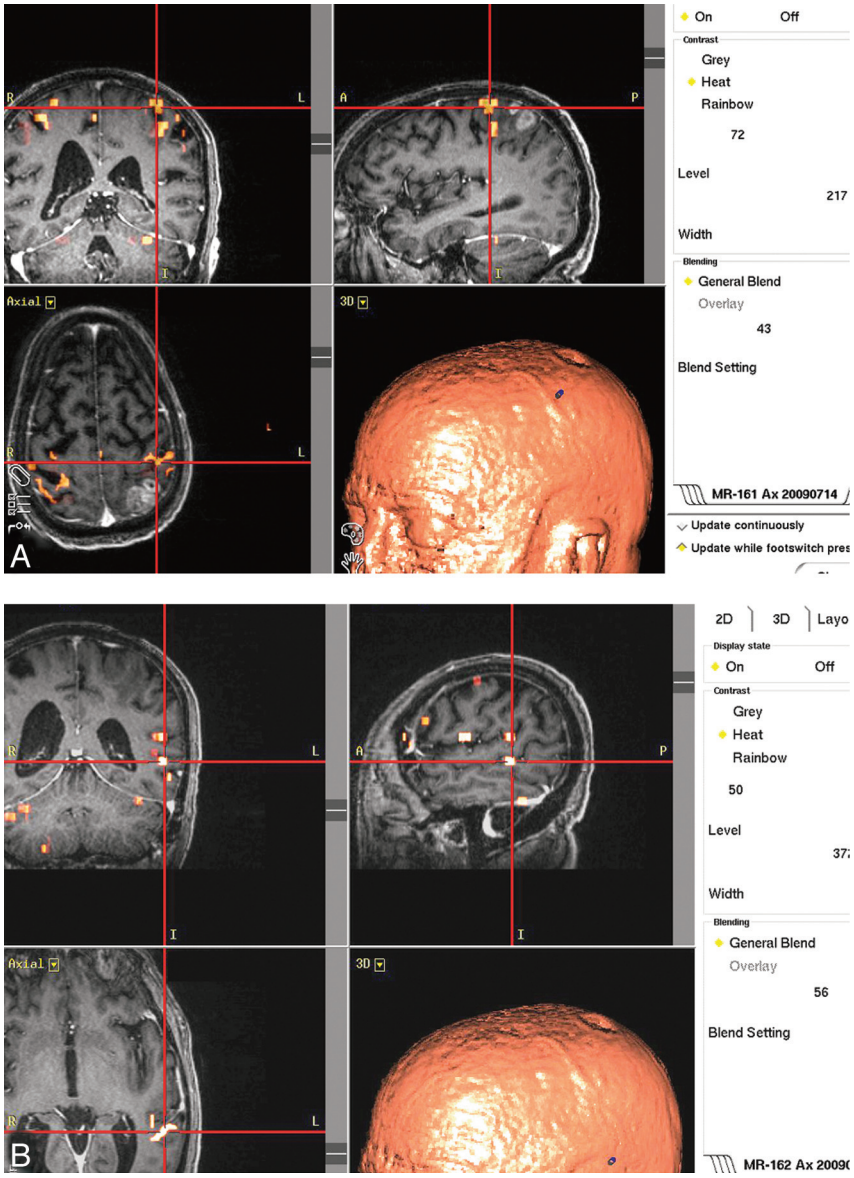

Fig 2. BOLD activation maps imported into a neuronavigation system. *A,* Hand motor activation from an alternating finger-tapping paradigm, with the 3D cursor placed on activation seen anterior to a left parietal lobe tumor. *B,* Language activation (combination of silent word-generation and rhyming tasks), with the 3D cursor on temporal lobe receptive cortical activation, in close proximity to the classic Wernicke area.

using in the current era to assess the validity of BOLD activation in light of this important potential limitation.

Another emerging problem is lack of standardization, which affects DTT as well as BOLD; many different software packages exist for tractography, including traditional DTI-based methods (such as the fiber assignment by continuous tracking algorithm),[45-47]as well as more sophisticated methods that take into account each eigenvector within an individual voxel, such as high angular resolution diffusion imaging[48-50] or diffusion spectrum imaging.[51]

The Future of Functional Neuroimaging

The future of clinical functional imaging holds the opportunity for neuroradiologists to work more closely with neurosurgical colleagues as preoperative functional imaging becomes progressively incorporated into the evolving surgical standard of care. Challenges in a revenue-driven radiology practice model will have to be met with demonstration of the added value of functional imaging in overall patient care, and neurosurgical end-users will continue to provide this necessary impetus for development in this field. Although currently limited to major tertiary care academic centers, clinical functional imaging will likely soon make its way to private practices and smaller academic centers as vendors provide increasingly sophisticated streamlined and integrated packages. In the future, with increasing use of higher field intraoperative MR imaging systems, integration of presurgical and possibly even intraoperative functional imaging data into neuronavigation systems with effective real-time brain-shift correction may become a reality, and this will affect the future role of the functional neuroradiologist. In addition, the need to train neuroradiology fellows in functional imaging is being increasingly

recognized; therefore, fellowship programs will need to provide trainees with more exposure to physiologic/functional imaging in the near future.

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