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Clinical utility of functional magnetic resonance imaging for brain mapping in epilepsy surgery

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Summary Functional magnetic resonance imaging (fMRI) is commonly used to localize brain function, but its utility in the clinical setting remains unclear. Subdural electrode implantation provides opportunities to correlate the spatial relationship of the blood oxygen level-dependent (BOLD) response to areas defined by extraoperative electrical stimulation mapping (ESM) in patients undergoing staged epilepsy surgery. 4 subjects underwent pre-operative fMRI using the analogous paradigms to those used for ESM to delineate language and motor function. Coregistration of the pre-operative MRI to a post-operative CT and MRI scan was performed in order to assess the spatial relationship between the BOLD response and the location of electrode contacts used for ESM while accounting for brain shift. fMRI was accurate in predicting the location of motor cortex with sensitivity and negative predictive value (NPV) of 1.0. Specificity was .96 with a positive predictive (PPV) value of .8. In all 4 subjects, a laterality index of the fMRI for language was accurate in predicting lateralization measured by Wada testing. While *T*-scores over regions where ESM-induced language deficits occurred were significantly higher ($p < .05$, Student's *t*-test) than those over regions where there was no ESM-induced deficit, sensitivity, specificity and predictive values were poor over a range of threshold criteria. Sensitivity and specificity were improved by excluding sites within 1 cm of the base of the frontal and temporal bone and sites where ESM showed motor function of face. Despite this, sensitivity and specificity were .47 and .76, respectively (*T* score 2.5, $p < .01$ corrected FDR) with PPV and NPV of .40 and .77, respectively. Sensitivity for predicting areas within 1 cm of ESM-defined language sites was higher at .82 with an NPV of .94. The results indicate that fMRI is clinically useful for lateralizing language and the localizing motor cortex. fMRI localizes language less accurately, but it may be useful in estimating the region of ESM-induced deficit in areas away from the base of the frontal and temporal bone.

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Table 1

Gender	Age	Handedness	fMRI laterality index	Wada language	Ictal onset	Resective procedure
M	22	Right	28	Left	Left mesial temporal	Left temporal lobectomy
F	21	Right	44	Left	Right parietal	Right parietal resection
F	20	Left	77	Left	Bitemporal	None
F	23	Right	28	Left	Bifrontal	None

Introduction

fMRI, which measures the blood oxygen level-dependent (BOLD) response (Ogawa et al., 1990) is a noninvasive methodology that is commonly used to localize functional brain areas. In the clinical setting, fMRI is increasingly being used to lateralize language function and to localize motor and language function (Hirsch et al., 2000; Ruge et al., 1999; Binder et al., 1996, 1997; Carpentier et al., 2001; Desmond et al., 1995; Gaillard et al., 2004; Rosenberger et al., 2009). However, the utility of fMRI in guiding surgical decision-making remains unclear. The ability to validate fMRI signal analysis with a more direct invasive method may help resolve this issue. Staged epilepsy surgery, where invasive electrodes are implanted in order to define the ictal onset and functional zones, provides an opportunity to correlate the noninvasive BOLD signal to more invasively obtained methods such as electrical stimulation mapping (ESM) in the extraoperative setting (Carpentier et al., 2001).

A good correlation has been demonstrated between language lateralization assessed using fMRI and the intracarotid amytal (Wada) test (Gaillard et al., 2004; Thesen et al., 2007). Localization of the motor cortex using BOLD signal has been accurate in some studies (Ruge et al., 1999). However, factors such as brain shift may limit their utility in patients undergoing electrode implantation for staged epilepsy surgery (Hill et al., 2000). Prior studies have shown poor sensitivity, specificity and predictive values of the location of the BOLD signal to areas defined by language using intraoperative ESM (Roux et al., 2003). The present study aims to assess the clinical utility of fMRI in the circumstance of extraoperative ESM with additional image processing is performed to account for the brain shift caused by the electrodes. Use of extraoperative ESM allows for more accurate integration and coregistration of intracranial electrodes while accounting for brain shift. In addition, time is permitted to perform reliability testing and to integrate ESM and fMRI data prior to the operative intervention that involves the possibility of resection.

Some studies have examined the effect of varying the threshold for activation for language localization in efforts to reduce Type 1 and Type 2 error, but no standard criteria exist (Loring et al., 2002). This type of analysis is critical for determining the clinical utility of fMRI and may be explored by examining the relationship between ESM and fMRI across a range of statistical values. A further analysis beyond the traditional post hoc analysis would be focused upon determining which ESM-positive sites do not show fMRI activation in order to determine whether certain areas should always be tested via ESM, regardless of fMRI activation. The present study investigates these issues in order to determine the clinical utility of fMRI language mapping in predicting the effects of extraoperative ESM.

Methods

Subjects

Four patients were used as subjects for this study. Demographics are shown in Table 1. All patients, after undergoing video electroencephalographic testing, MRI and neuropsychological assessment, were deemed candidates for epilepsy surgery based upon medication-resistant partial complex epilepsy. All subjects had normal MRI with no lesions, dysplasia or masses, and therefore, electrodes were implanted primarily in order to assess seizure localization. When electrodes were near regions of function based upon either fMRI signal or clinical judgment, functional mapping was performed. Two subjects had electrodes over the presumed hand motor area, and fMRI and ESM performed to localize the hand area of motor cortex in these subjects. All subjects underwent language fMRI and an intracarotid amobarbital (IAP) procedure to lateralize language dominance. Three subjects had implantation of electrodes over areas suspicious for language function and were used to assess the relationship of the results of fMRI and ESM. Of the two subjects that underwent resection, one had mesial temporal gliosis and the other had a Type 2a cortical dysplasia. Informed consent was obtained in keeping with guidelines specified by the institutional review board of the North Shore-LIJ Health System (Protocol #07-125).

Surgery

Patients underwent electrode implantation surgery via frameless stereotactic craniotomy and using fluoroscopic guidance for placement of strip electrodes. The number and location of electrode contacts to be implanted were made upon clinical grounds. The craniotomy was photographed to define the relationship between the electrode contacts and anatomic and vascular landmarks. Two patients were implanted with a 64 channel grid electrode in addition to strip electrodes and two patients underwent implantation of strip electrodes, only. Subdural electrodes were placed by performing a craniotomy and replacing the bone flap.

Imaging

All MRI and fMRI data were acquired on a GE 3T whole body scanner with an eight channel head coil. Images were acquired using a gradient echo, echoplanar (EPI) sequence (TR = 2000 ms, TE = 27.6 ms, FOV = 220 mm, Flip angle 70°, matrix size 64×64, slice thickness 4 mm, 34 transverse slices per scan, 124 volumes, voxel resolution = $1 \times 1 \times 1$). High-resolution anatomical T1-weighted images were acquired using a 3D sequence with the parameters (TR = 7.8 ms, TE = 3 ms, FOV = 256 mm, Flip angle 8°, resolution 256×256, slice thickness 1.2 mm, no skip, 170 sagittal slices).

fMRI

Stimuli were presented using E-Prime software (Psychology Tools, Pittsburgh, PA) run on an IFIS-SA system (In-vivo Corporation, Orlando, FL). The task used was a covert picture naming task. For the fMRI, the patient viewed 30 s epochs displaying line drawings of common objects presented every 2 s. The patient was asked to covertly name the displayed object. In the analogous control task, scrambled lines were presented while the patients fixated. In a separate set of 30 s epochs designed to elicit a motor cortex response, patients either tapped their fingers while fixating (active condition) or just fixated upon a point (control).

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Motion correction was done using MCFLIRT (Jenkinson et al., 2002). The BET (brain extraction tool) method was utilized to separate brain tissue from non-brain tissue (Smith, 2002), and spatial smoothing was performed using a Gaussian kernel of FWHM 4.0 mm. Highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s) was done, and time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001). Z (Gaussianised T/F) statistic images were thresholded using GRF-theory-based maximum height thresholding with a (corrected) significance threshold of $p = .0005$ (Worsley, 2005). Comparison of the amplitude of the BOLD response from the active versus control conditions (as defined above) was performed for each voxel. This yielded whole brain *T*-score maps. Registration of the functional data to the patient's high resolution structural image was carried out using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002).

Coregistration

3D MRI images were obtained during the functional imaging section and post-operative anatomical MRI images and CT images were acquired for each patient. Scans fully covered the patient's head and extended down to the cervical level of the spine to allow for maximally accurate rigid body cross-modal registration. Implanted electrodes were interactively identified in the CT images using Bioimagesuite (http://www.bioimagesuite.org/). Registration of the post-operative CT to the post-operative MR images allowed projection of the electrodes onto the aligned post-operative MR. The effect of brain shift was reduced by stripping the skull from both the post- and pre-operative MR images. A nonlinear intensity based registration was performed to align the pre-operative high resolution 3D MR images to the post-operative MR images. This type of registration accounts for both brain displacement and allows for accurate placement of the electrodes on a brain surface with clear anatomic structures and landmarks. The pre-operative functional MRI scan was then aligned to the high resolution 3D MR allowing for overlay of the electrodes on the functional data as well. The post-operative MRI scan and the intraoperative photograph were used to confirm the actual location of the electrodes with respect to the derived location using the coregistration method.

Finally, the whole brain *t*-maps derived from the FSL analysis were aligned to the same high resolution image so that the electrode location file could be overlaid on the statistical maps. After overlaying the file on the whole brain *t*-maps, the average *t*-value of the voxels directly underneath each electrode was extracted using the Bioimagesuite software (http://www.bioimagesuite.org).

Electrocortical stimulation

Electrical stimulation of the cerebral cortex was conducted using a Grass S-12 Isolated Biphasic Stimulator, which delivers a constant current output. The stimulus parameters were set to a pulse width of 200 μs, pulse frequency of 50 Hz, and maximum pulse train duration of 2—10 s. The stimulus current was manually controlled during the stimulation and ranged from 4 mA to 12 mA. Stimulation was applied to adjoining electrode pairs. If a response was obtained at this pair of electrodes, a remote reference electrode located in a functionally silent location was used to deliver stimulation at the two contacts separately.

All electrode contacts over the dorsolateral posterior frontal lobe, inferior frontal lobe and dominant temporal lobe were tested for ESM-related effects. For language, speech arrest and naming were tested separately, with naming assessed over those sites in the inferior frontal and language-dominant temporal lobe where speech arrest did not occur. First, patients were asked to recite a common well-rehearsed saying (Pledge of Allegiance), while areas of ESM-induced speech arrest were identified. For the remainder of sites, an analogous task to the fMRI naming task was performed. The patient was presented with flash cards with line drawings (the same ones used for the fMRI) while simultaneous electrical stimulation was delivered to the area of interest. Stimulation was applied prior to display of the line drawing, and continued until the patient named the drawing or until 5 s elapsed. Areas where ESM interfered with naming were identified. Typically 3—5 pictures were presented per site of interest. Areas where stimulation caused clonus of the hand, fingers or wrist and movement of the face (jaw opening or closing, tongue movement or facial twitching) were noted.

Data analysis

Laterality index was calculated from the fMRI for each subject using the formula: $(L - R)/(L + R) \times 100$. $LI > 20$ was classified as left dominant; $LI < -20$ was classified as right dominant.

For each electrode tested by stimulation mapping, a t score was obtained under the area that coregistered to the pre-operative fMRI. Sensitivity, specificity and positive and negative predictive values were calculated for all sites in all subjects for motor and language function using different *T* score criteria. The distance of the electrodes from the base of the frontal and temporal bones was measured from post-operative CT scans and used to exclude certain areas from analysis.

Results

Motor cortex

67 sites were tested with ESM for motor function of the hand in 2 subjects. ESM at 8 sites elicited motor response of the contralateral hand. For these sites, using a threshold of a *T* score of 2.5 ($p < .01$ corrected FDR), sensitivity for hand motor cortex was 1.0 and specificity was .96 for the two subjects where electrode contacts lay over the hand area of motor cortex (Fig. 1). PPV and NPV were 0.8 and 1.0, respectively. In the two remaining subjects an additional 10 sites were found on ESM corresponding to face motor cortex. However, no fMRI data for face motor function were obtained from any of patients.

Language lateralization

Laterality index are shown together with patient demographic data in Table 1. In each case a laterality index of >20 correlated with the side of language dominance as assessed by selective intracarotid amytal injection during clinical testing.

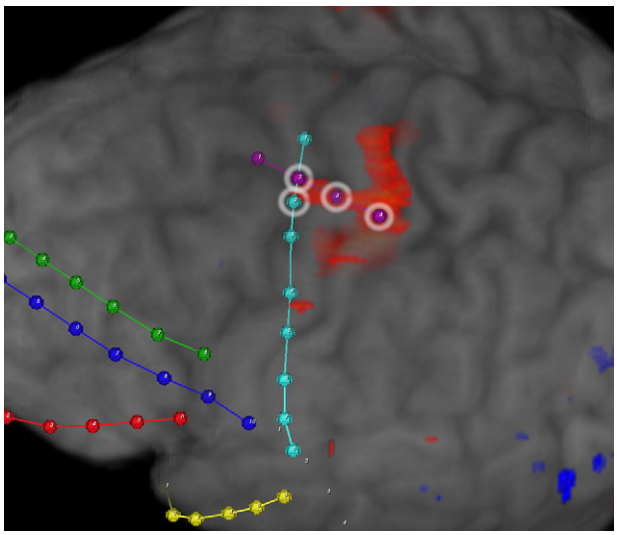

Figure 1 Correlation of fMRI and ESM for hand motor function. Subdural strips are shown overlaid with the area of BOLD signal related to contralateral finger tapping in one patient. Contacts where clonus of the hand occurs are circled in white.

Language localization

107 sites were tested by ESM for language in the temporal lobe and the inferior frontal lobe of the Wada-defined dominant hemisphere of three subjects. Of these, electrical stimulation either interfered with picture naming or resulted in speech arrest in 26 sites. A typical case is demonstrated in Fig. 2. ESM at 8 sites demonstrated face motor responses and other motor function was demonstrated at another 8 sites. The fMRI *T* score under areas critical for picture naming as assessed by ESM was 1.79, and the *T* score under areas not critical by ESM was 0.72 and significantly lower ($p < .05$, one-tailed Student's *t*-test). Using *T* score of 2.5 ($p < .01$, corrected FDR) the sensitivity was .32 and specificity was .81. Positive and negative predictive values

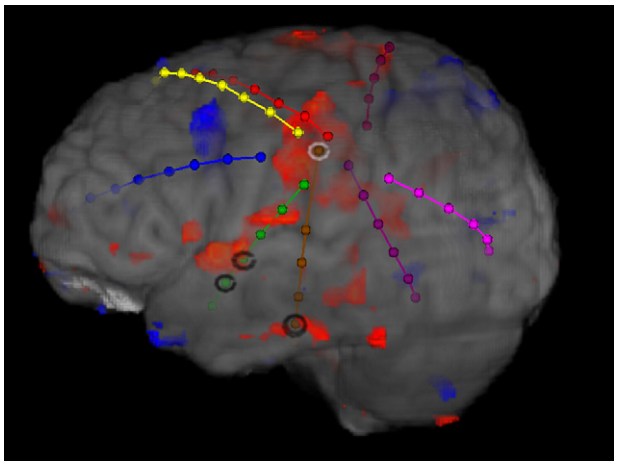

Figure 2 Correlation of fMRI and ESM for picture naming. Subdural strips are shown overlaid with the BOLD signals related to the covert picture naming task. Contacts where ESM produces a naming deficit are circled in black. A site producing mouth movement, corresponding to face motor cortex is shaded white.

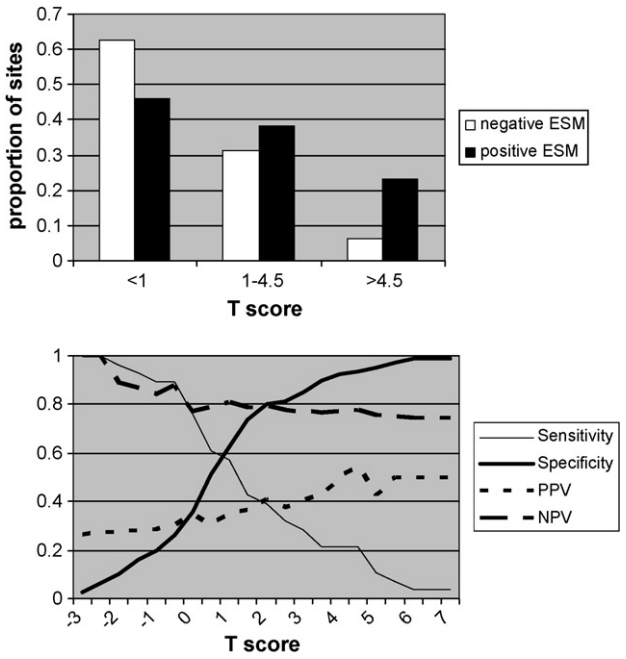

Figure 3 *T* score distribution for language. Top. The proportion of sites falling within one of three ranges of *T* scores is shown. Sites where ESM-induced language deficit occurs are shaded dark and areas where ESM fails to induce a language deficit are shaded white. The white bars with low *T* score indicate true negatives, and the dark bars with the higher *T* scores indicate true positives. Conversely, the dark bars with the low *T* scores indicate false negatives and the white bars with the high *T* score indicate false positives. Even at low *T* scores, the false negative rate is too high (>40% of sites with ESM-induced language deficit) to be useful to clear areas for language function. Bottom. The *T* score threshold criteria are varied over a large range from negative activation to 7. At a large range of *T* score thresholds, sensitivity, specificity and predictive values are too low to be useful for language localization. Therefore, simply altering the threshold for activation will not improve sensitivity in a clinically useful fashion.

were .37 and .77, respectively. A number of sites showed negative *T* scores reflecting a decrease in the BOLD signal in the active condition. To account for the possibility that a high negative *T* score might be significant, a two-tailed analysis was performed on the same data set, but failed to produce a satisfactory sensitivity and specificity, which were.32 and .75, respectively, with NPV .31 and PPV .76 ($p < .01$, corrected FDR, two-tailed). Since these parameters are dependent upon threshold criteria, a number of different *T* score thresholds were used to compute sensitivity and specificity (Fig. 3). Very low criteria are required to have a sensitivity that exceeds 80% and have poor predictive value. These data indicate that a priori assumptions made by standard MRI and post hoc thresholding were insufficient to predict which sites would show language function using ESM.

To improve sensitivity, specificity and predictive value, sites with false negatives and false positives were reexamined for any trends. It was noted that the face motor cortex often produced a BOLD signal during the covert naming

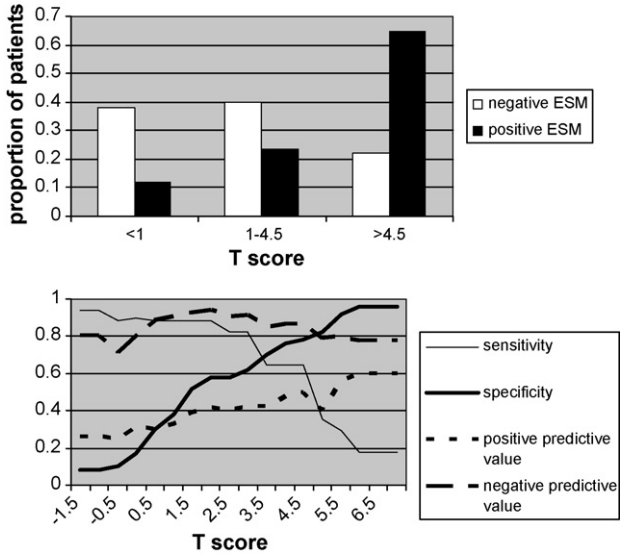

Figure 4 *T* score distribution for language after additional post hoc analysis. Top. Analogous to Fig. 3, after removing sites corresponding to face motor and the base of the frontal and temporal bones and after including any area within 1 cm of BOLD activation, *T* score ranges are computed. Compared to Fig. 3, the false negative rate is much lower (12%) albeit at the expense of an increased false positive rate, improving sensitivity at the expense of specificity. Bottom. Varying the *T* score threshold criteria shows improved sensitivity and NPV profile over the range of a *T* score between 1.5 and 2.5. The NPV is greater than .85 with a sensitivity of greater than .8.

tasks, increasing the false positive rate and thereby, reducing specificity. When the 8 ESM sites corresponding to the face motor cortex were removed from the analysis, specificity improved to .81 and positive predictive value improved to .38 (*T* score 2.5, $p < .01$ corrected FDR).

Areas near the base of the frontal or temporal bone gave poor fMRI activation, possibly due to the artifacts produced by the density of the bone. When 32 of the ESM sites tested that were within 1 cm of the base of the frontal or temporal bones are excluded from this analysis the sensitivity improves to .44 and NPV to .4.

It was also noted that in many cases the BOLD signal was adjacent to, but not immediately underlying the electrode contacts. In order to account for this, sensitivity was recalculated to account for any area within 1 cm from an ESM site. In this scenario, sensitivity is .82, specificity is .52, and PPV and NPV are .4 and .91. The effect of changing the thresholding and *T* score criteria are shown in Fig. 4. This shows a high degree of sensitivity (>.8) and NPV (>.9) over a range of *T* scores (1.5—3), though specificity and positive predictive value remain low.

Discussion

Sensitivity and specificity

Comparing the results of fMRI and ESM is complicated by the fact that fMRI involves the observation of normal function while ESM involves interference with function. Therefore, it may be hypothesized that fMRI could show participation of brain areas that are involved in, but not critical to, language function and that these areas overlap with critical sites identified by ESM. If this were the case, then the sensitivity would be high and the specificity would be low. Thus, the BOLD response may be used to highlight areas that are more likely to define sites where ESM perturbs function, namely critical motor and language sites. This, in turn, could reduce the time it takes to perform ESM and reduce the likelihood of inducing a seizure by ESM.

If sensitivity and NPV are high, fMRI may be used to exclude sites where ESM need not be performed in detail. However, if sensitivity is inadequate at even lenient statistical criteria, the utility of fMRI would be low for ruling out sites that are not important for performing ESM. By varying the *T* score criterion, fewer or more areas will show ''significant'' BOLD signal. This would effect which areas of activation overlap with ESM-positive sites and thus affect the relationship between the two methods. Clinical utility may be best if a criterion is selected at which the sensitivity is high and the predictive value of a negative test is high.

Extraoperative ESM

Intraoperative ESM carries the advantage of avoiding staged surgery and the mass effect of intracranial electrodes. However, ESM may produce very subtle errors in language that may be difficult to ascertain during a surgical procedure when multiple factors, such as discomfort, anxiety, drowsiness and equipment and drapes near the face and mouth, can confound the assessment. In addition, time constraints make reliability testing and complicated image processing difficult in the operating room.

However, ESM can also be performed extra-operatively, as is often done in the work-up for epilepsy surgery, through implantation of intracranial strip and grid electrode. This allows for significantly more time to be devoted to exploring wider cortical areas and allows assessment of language function when the patient is fully awake and cognitively intact. This is critical as stimulation of a language site can often result in subtle errors in language that may be difficult to ascertain during a surgical procedure when multiple factors can confound the assessment.

While fMRI results can be loaded onto frameless stereotactic software and accurate freehand ESM performed, this method requires that analysis of the functional data be processed prior to the surgery so it can be loaded into the stereotactic device. This usually means that a fixed statistical threshold is chosen for the comparison between the two modalities, impacting the results and precluding more complex post hoc analysis of the data. Additionally even if the fMRI images are aligned to MRI images of the patient's brain prior to the surgery, once a portion of the skull is opened or removed the brain can shift creating a larger margin of error for the precise localization of the functional activation. If one performs ESM extra-operatively utilizing intracranial electrodes the exact location of the grids can be confirmed by CT and MRI imaging post-implantation and aligned to the fMRI images without fear of further anatomic shift, and more complex post-processing and comparisons of the two modalities can be made.

Motor cortex

The findings presented here show excellent correlation in terms of sensitivity and specificity in the case of motor cortex. Previous studies correlating motor fMRI with intraoperative ESM have reported good concordance, but no formal analysis of sensitivity and specificity was performed for individual sites (Ruge et al., 1999). A more formal analysis using extraoperative ESM mapping yielded poor sensitivity, specificity and predictive values and highlighted the need to correct for brain shift produced by the electrode arrays (Hill et al., 2000). To correct for this, we registered all images to the post-operative MRI scan with the electrodes implanted after performing skull stripping. By performing this type of image processing, our results show excellent predictive values for predicting the location of ESM sites for the motor hand area with extraoperative ESM.

Language laterality

Similar to the case of ESM, Wada testing is involves interference with function. Given the invasiveness of the Wada test, a noninvasive methodology to define language function may avoid the risk of complications from angiography. Several groups have shown fMRI laterality indices to correlate with results of the Wada test, and our results for corroborate these findings in 4 out of 4 patients (Thesen et al., 2007; Arora et al., in press). Laterality indices of >20 by calculations described in the methods section have been shown to be predictive of left language dominance (Desmond et al., 1995; Binder et al., 1997; Thesen et al., 2007). Larger case series would be required to determine whether fMRI could potentially replace Wada for lateralization of language in high risk patients or in cases where angiography or Wada testing is not possible.

Language localization

Prior studies have shown inconsistent results in the correlation of language fMRI with ESM, which remains the gold standard to identify eloquent cortex in preparation for surgical resection. Using different paradigms for fMRI and ESM may be part of the reason for this. Another issue is that the majority of the published studies have attempted to correlate fMRI with freehand intraoperative ESM rather than utilizing fixed intracranial subdural arrays (Roux et al., 2003; Schulder et al., 1998). Roux et al., showed poor sensitivity, specificity and predictive values for language fMRI and intraoperative ESM. Two other groups have reported high concordance between fMRI and sites causing deficits during extraoperative (Carpentier et al., 2001) and intraoperative (Ruge et al., 1999; Hirsch et al., 2000) ESM. However, in both of these cases, the concordance measure was not performed formally by coregistering the fMRI to the location of the stimulated site and calculating sensitivity and specificity, but by estimating the location of specific language areas (Wernicke's, Broca's or basal temporal) defined by fMRI and ESM. Atypical language representation in patients with epilepsy (Gaillard et al., 2007) may make this type of analysis suboptimal.

We found that the language fMRI T score was significantly higher ($p < .05$, two-tailed Student's t-test) under those electrode sites that were tested where ESM produced a language deficit. However, a significant increase in T score does not necessarily imply utility in the clinical setting, where a high degree of exactitude is required. As opposed to the case for the localization of the hand area, the initial analysis of the correlation of the BOLD signal location with the foci of ESM-induced language deficit was poor. Given the fact that fMRI may be showing areas that participate in but are not critical to language function, it may be reasoned that high specificity may not be possible, but sensitivity may be of value in clearing certain sites. A priori, it may also be reasoned that the threshold for considering what is significant on fMRI should be set low in order to have a high sensitivity. However, our initial analysis failed to show a sensitivity and NPV that would be sufficient for clinical utility. Over a range of thresholds, the false negative rate and false positive rates remained high with resultant low predictive values.

In an effort to improve predictive values, false negatives and false positive sites were reexamined. Many false positives occurred in areas that corresponded to the face motor area, which produced a BOLD response despite the nature of the covert naming task. ESM, while causing a movement of the mouth, did not result in any language deficit per se. Therefore, in an effort to reduce the false positive rate, these sites were removed from the analysis.

Susceptibility artifact produced by adjacent bony structures at the base of the anterior and middle skull base may distort the BOLD signal, especially with a 3T magnet. Our analysis of false negatives showed a number that were close to the skull base in the basal temporal, basal frontal and anterior temporal areas. To reduce the false negatives, sites within 1 cm of the skull base were excluded from analysis, with the reasoning that the fMRI is not accurate in that region. It is possible that the accuracy of fMRI may be improved in this region if lower strength MRI is used.

Finally, at a number of sites where an ESM produced a language deficit, the BOLD response was immediately in approximation to, but not right under the area that was stimulated. After accounting for the poor correlation near the skull base and at the motor area of the mouth, recomputing the sensitivity and specificity for a significant BOLD response ($p < .01$ corrected FDR) being within 1 cm of the area of ESM-induced language deficit approaches clinical utility. Over a range of thresholds, sensitivity is greater than .8 and NPV is greater than .9. It is possible that modifications to the fMRI or ESM behavioral paradigms might produce even better results.

Conclusion

Many noninvasive and invasive methodologies are available to study the structure/function relationship in cortex, each with a different advantages and disadvantages. Ultimately, an approach that involves multiple invasive and noninvasive methodologies may provide a better understanding about the localization of brain function in the human cerebral cortex and its application to the clinical setting. The precise identification of the spatial limits of these processing modules in patients undergoing invasive monitoring for epilepsy

provides an opportunity to improve surgical outcomes and to study directly from the working human brain. Important considerations in surgical planning involve a distortion of expected localization of function when an epileptic zone lies near functional tissue (Rosenberger et al., 2009). In addition, invasive methodologies such as ESM can provide validation for noninvasive methodologies such as fMRI.

Our results show that using the fMRI tasks and ESM protocols described, fMRI may be used to localize motor cortex and lateralize language. Image processing that involves a post-operative MRI and accurate coregistration using skull stripping algorithms is critical for accuracy in localization when extraoperative ESM is performed. fMRI is also useful in estimating the region of language function in areas away from the skull base, but even then, intraoperative or extraoperative ESM is required to improve accuracy beyond 1—2 cm.

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