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Functional Magnetic Resonance Imaging of Language in Epilepsy

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Abstract Functional magnetic resonance imaging (fMRI) has revolutionized our understanding of functional networks and cerebral organization in both normal and pathological brains. In the present review, we describe the use of fMRI for mapping language in epilepsy patients prior to surgical intervention including a discussion of methodological issues and task design, comparisons between fMRI and the intracarotid sodium amobarbital test, fMRI studies of language reorganization, and the use of fMRI laterality indexes to predict outcome after anterior temporal lobectomy.

Keywords fMRI · Language · Epilepsy ·
Intracarotid sodium amobarbital test · Reorganization ·
Cognitive outcome

Introduction

Clinical neuropsychology historically has studied brain behavior relationships through the examination of the behavioral correlates of focal lesions or neurological diseases. With the advent of functional magnetic resonance imaging (fMRI) in the early 1990s, neuropsychologists and neuroscientists have examined cognitive processing in intact brains, in individuals with neurological disease, and prior to and following neurosurgical intervention. These studies have challenged older notions of cerebral organization and expanded our knowledge of the complexity of functional localization. For example, investigations that aim to activate cerebral language zones in healthy adults have yielded data that partially conflicts with classical models of anterior expressive (Broca's area) and posterior receptive (Wernicke's area) language organization (Binder et al. 1997). These data reveal a more extensive language network than previous focal lesion studies have suggested. Thus, fMRI has advanced our knowledge of localization of cognitive operations relevant to both healthy and patient populations.

One of the most studied clinical applications of fMRI has been the pre-operative evaluation of epilepsy patients. Clinical applications for epilepsy surgery candidates include determination of hemispheric lateralization of memory functions, (Detre et al. 1998; Golby et al. 2002; Koylu et al. 2006; Powell et al. 2004) and localization of language networks or component language functions, which will be described below. In addition, fMRI has been used for predicting side of seizure focus (Bellgowan et al. 1998; Jokeit et al. 2001b) and to predict outcome after temporal lobectomy with regard to seizures (Killgore et al. 1999), language (Sabsevitz et al. 2003), and memory (Rabin et al. 2004; Richardson et al. 2004). The present review will include: (1) a discussion of methodological issues relevant to language assessment during fMRI; (2) a review of studies comparing fMRI and the intracarotid amobarbital test (IAT); (3) comparisons between fMRI and IAT in patients with atypical (bilateral or right hemisphere) language dominance on IAT; (4) fMRI studies of reorganization and plasticity; and (5) the use of fMRI language activation for predicting cognitive outcome after temporal lobectomy.

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Methodological Considerations

Functional magnetic resonance imaging is a noninvasive and widely available technique for detecting regional changes in blood oxygenation resulting from neural activity (Kwong et al. 1992; Moonen and Bandettini 1999; Ogawa et al. 1992). To use fMRI effectively and responsibly as a clinical tool requires a full understanding of methodological issues affecting reliability and validity. The usefulness of fMRI language maps depends on how well the activation protocols, including both probe and control or contrast tasks, are designed to identify specific cognitive domains as well as the sensitivity and specificity of the cerebral activation patterns with regard to the clinical predictions being made. Activation maps and their reproducibility change with alterations in a number of imaging parameters, including the statistical threshold, voxel size, cluster size, degree of spatial smoothing, number of images acquired, and magnetic field strength (Binder 2003; Jansen et al. 2006). Intrasubject factors that affect the signal to noise ratio include head motion, age, body habitus (head size, neck length), motivational state, task strategy, and task performance (Hammeke et al. 2000; Weber et al. 2006). Improved control and detection of task-correlated movement artifacts and the availability of new higher performance gradient systems operating at 3 Tesla are leading to better signal-to-noise ratios. The effects of antiepileptic medications on imaging results should also be considered. While few studies have examined the effects of AEDs on blood oxygen level dependent (BOLD) response, bilateral medial temporal lobe activation was negatively correlated with serum carbamazepine levels in one study (Jokeit et al. 2001a).

Behavioral Monitoring The importance of knowing how well subjects perform tasks during fMRI studies is becoming increasingly evident. Behavioral monitoring of performance during language activation tasks helps ensure task compliance and reduce unsolicited cognitive processing. Care should be taken to match the control and probe task for task difficulty and behavioral performance accuracy. Epilepsy patients have varying levels of cognitive abilities and will have different performance levels on the activation tasks. For example, there are likely large differences across patients in the number of words generated during covert fluency tasks. Little is known about the relationship between number of words generated and activation volumes or activation laterality indexes (LIs). A recent study examined fMRI language maps in patients with vastly different performance levels on a semantic decision task (Weber et al. 2006). Activation volumes and lateralization were examined relative to performance levels in 195 epilepsy patients. The task was to determine if visually presented words were semantically related and the control task was to determine whether visually presented consonants strings were the same or different. There was no significant difference in the LIs for the group with the best performance compared to patients with the worst performance; however, task performance was related to the intrahemispheric activation profile. A larger area of activated volume in temporoparietal areas and a smaller area in the inferior frontal region was found in those with better task performance. The authors concluded that since the fMRI language LIs seem to be independent of task performance, at least for this task contrast, language LIs can be used in patients with variable levels of performance accuracy.

Task Design The field is far from developing standardized tasks for mapping language. Similar to the IAT, investigators tend to retain task paradigms known to them. Currently, a wide variety of language activation protocols are being used. With regard to the variety of language tasks, the most common methodological limitation of previous language functional imaging studies has been the failure to incorporate a control or contrast task in the activation protocol that serves to minimize the effects of unwanted mental activity. Rigorously designed probe and control tasks that include measures of behavioral performance are critical. Most task designs use a subtraction or contrast technique. The contrast between the component functions subsumed by the tasks is theoretically selected to isolate the substrate of interest. For example, a semantic decision task used by Binder et al. (1995, 1997), based on a task introduced by Demonet et al. (1992), requires subjects to press a button in response to an animal name if the animal is both found in the United States and used by humans. This is contrasted with a tone monitoring task in which a series of brief tones of varying pitch are presented. Subjects are instructed to press a button in response to tone trains containing two high tones. The semantic and tone tasks were matched for stimulus intensity, stimulus duration, trial duration, and frequency of positive targets. The contrast task is nonlinguistic and controls for auditory, motor, executive, and working memory functions that are not specific to language (See Table 1, part A). Comparing a language with a perceptual control task allowed areas equally activated by both tasks, i.e., not specific to language, to be subtracted from the language activation maps.

Rest, which can be characterized as unconstrained conceptual processing, does not provide an optimal baseline condition for language or memory studies (Stark and Squire 2001). Since most tasks will not activate only the specific cognitive function of interest, rest, fixation on a crosshair, or fixation on a dark screen are inadequate contrasts for studying cognitive operations. Rest is known to be an active state during which self-initiated linguistic and semantic processes occur (Binder et al. 1999; McKiernan

Table 1 Functional components of two language activation tasks

Functional components	A. Semantic monitoring task		B. Covert fluency task	
	Tone discrimination	*Semantic decision*	*Symbol discrimination*	*Covert fluency*
Semantic processing		+		+
Phonetic processing		+		+
Attention, working memory	+	+	+	+
Auditory processing	+	+		+
Visual Processing			+	
Motor response	+	+	+	

et al. 2003, 2006). In fact, contrasts between a language task, tone monitoring task, and a resting state demonstrated that there is more activation in many regions during a conscious resting state than during a tone monitoring task (see Fig. 1). Thus *fewer* areas of activation were seen in the contrast [semantic decision—rest] compared to the contrast [semantic decision—tone monitoring]. Specifically, as shown in Fig. 1, activation observed in the left angular gyrus, posterior cingulate gyrus, left medial frontal lobe, and left medial temporal lobe during semantic decision contrasted with tone monitoring disappeared when semantic decision was contrasted with rest. Since semantic retrieval and information manipulation occur during resting states, language activation protocols employing rest as a contrast may lack sensitivity. More specifically, this potentially could lead to a poor cognitive outcome from surgery since, when language maps derived from task contrasts employing rest are used, a portion of the language zones will be inadvertently removed from the activation maps.

While rest is not an appropriate control condition for activation paradigms designed to image higher cognitive functions, results will be equally obfuscated when the control task is not theoretically designed to subtract specific unwanted cognitive components. For example, some investigators have used a verb generation task where participants covertly generate a verb in response to an auditorily presented noun (Rutten et al. 2002). The control task involved viewing symbols (/ or *) and pressing a button in response to an asterisk. Table 1 shows the hypothetical cognitive components engaged during the semantic decision task and this covert fluency task as well as their respective control tasks components. Specifically, the control task for semantic decision subtracts attention, auditory processing, and motor response components, isolating semantic and phonetic processing. The control task for covert fluency subtracts a motor response (though none was made during the probe task), visual processing (though there is no visual processing in the probe task) but

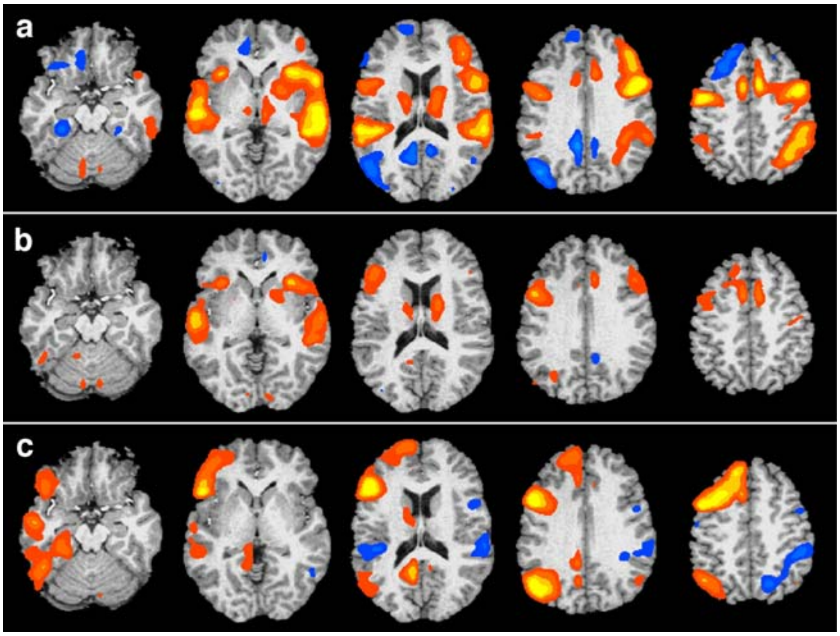

Fig. 1 Activation patterns obtained for contrasts between **a** Tone discrimination versus rest, **b** Semantic decision versus rest, and **c** Semantic decision versus tone monitoring. Three fMRI activation maps were obtained from the same 30 healthy adult participants. The maps show group activations thresholded at whole-brain corrected $p<0.05$. The left side of the brain is on the reader's left. **a** Tone monitoring contrasted with "rest." Note regions in blue that are more active during the resting state ("default network") than during this non-linguistic task, including angular gyrus, posterior cingulate gyrus, medial and ventral frontal lobe, and ventral temporal lobe. **b** Semantic decision contrasted with "rest." Note that the default network regions in (**a**) show relatively little activation, indicating equivalent BOLD signals during the semantic decision task and the resting state. **c** Semantic decision contrasted with tone monitoring. Strong left-lateralized activation is observed throughout the default network, inferior frontal lobe, and temporal lobe. *BOLD* = blood oxygen level dependent; *fMRI* = functional magnetic resonance imaging

does not subtract auditory processing involved with the presentation of the nouns. With this covert fluency paradigm, one has not isolated language components and has subtracted functions not activated in the probe task. Thus, more activation might be seen in the control than the probe task.

The sensitivity and specificity of language activation maps depend largely on how well the activation and control tasks are designed. In addition, sensitivity may vary when event-related designs are compared to traditional block designs, with block designs yielding greater sensitivity (Narayan et al. 2005) Event-related single trial designs provide a means for segregating activation trials based on response accuracy or later recall of the stimulus. This has particular relevance in identifying the integrity of functional circuits, e.g., memory encoding circuits. New clustered acquisition techniques allow patients to speak in the scanner, enhancing our ability to image language production systems. In addition, some investigators have advocated use of multiple language tasks or a task panel to improve concordance with the IAT (Gaillard et al. 2004). Sensitivity is also affected by susceptibility artifacts, with brain regions near the sinuses and borders of the brain such as the temporal lobes suffering loss of BOLD signal (Jezzard and Clare 1999).

Reproducibility Despite the fact that fMRI studies are noninvasive and repeatable, limited data exist describing test–retest reliability of language lateralization indexes. In one such investigation, Binder and colleagues found a high correlation between lateralization indexes derived from two separate activation runs of a semantic decision task conducted within the same imaging session ($r=0.89$), demonstrating that such language asymmetry measures can be highly reliable (Binder et al. 2001). Moreover, these authors found that language activation patterns were similar in matched samples of controls—voxel-by-voxel correlation between the activation maps from two subgroups of 15 subjects each was 0.86, with a Spearman–Brown estimated reliability coefficient for the 30 subjects of 0.92 (Binder et al. 1997).

Several studies have examined reliability of activation profiles across imaging sessions. One study examined the test–retest reliability of language LIs as well as language activation maps from epilepsy patients within and across sessions (Fernandez et al. 2003). The reliability of the language LIs derived from different regions of interest (ROIs) was compared using a split-half comparison (comparing the first and second half of a session). In addition, test–retest reliability was examined in a small set of patients who had fMRI across two separate sessions. In this study a synonym judgment task was contrasted with a letter string matching task, both of which were visually presented. Higher reliability was found in frontal regions (range $r=0.837$ to 0.982) than in parieto-temporal regions ($r=0.695$). The percentage of spatial overlap in the activation clusters for first and second sessions ranged from 42 to 49% depending on the threshold used. These authors concluded that the activation maps were sufficiently reproducible in individual patients for these maps to be clinically useful. Similar results were found in small groups of patients tested twice using a variety of language tasks. Laterality indexes were found to be reproducible, with the highest test–retest reliability found in frontal ROIs for verb or word generation tasks (Harrington et al. 2006). Maldjian and colleagues found higher reproducibility but more extraneous activation using a word generation task (Maldjian et al. 2002) compared to a text listening task.

Subject Factors Not all epilepsy surgery candidates will be able to undergo fMRI. Patients with vagal nerve stimulators can be scanned on a 1.5 Tesla but not a 3 Tesla scanner. Just as a few patients will not be able to undergo amobarbital testing because of vascular anomalies, patients with claustrophobia, obesity, slow processing speed, severe inattention, cranial anomalies resulting in macrocephaly, or mental retardation are not suitable for fMRI language mapping with most paradigms in current use.

Comparisons between fMRI and the Intracarotid Amobarbital Test

Numerous studies have compared fMRI and IAT, as this provided one of the first opportunities to examine the validity of fMRI language maps for determining hemispheric language dominance. These studies are listed in Table 2 with a description of the task employed, region of interest, subject sample size, number of participants with atypical language, concordance or correlation, and activation patterns (Baciu et al. 2001; Bahn et al. 1997; Benke et al. 2006; Benson et al. 1999; Binder et al. 1996; Carpentier et al. 2001; Deblaere et al. 2004; Desmond et al. 1995; Gaillard et al. 2002, 2004; Hertz-Pannier et al. 1997; Lehericy et al. 2000; Liegeois et al. 2002; Rutten et al. 2002; Sabbah et al. 2003; Spreer et al. 2002; Woermann et al. 2003; Worthington et al. 1997; Yetkin et al. 1998). The IAT (Wada 1949) is used routinely and considered the "gold standard" for language lateralization prior to epilepsy surgery, though the procedure provides no information about localization within a hemisphere.

Comparisons can be made between fMRI and IAT by examining the concordance between the methods in a qualitative fashion (left, right or bilateral) or by examining correlations between quantitative laterality indexes. Lateralization indexes often are computed for fMRI using the

Table 2 Concordance rates and correlations between IAT and fMRI

Tasks					IAT						
Study	Year	*n*	Probe	Control	*L*	R	B	ROI	Regions activated	Concordance	*r*
Desmond	1995	7	Semantic	Perceptual control	4	3	0	Frontal	IFG, Brodman's areas 45, 46, 47	100%	
Binder	1996	22	Semantic	Perceptual control	18	1	3	Whole brain	Lateral frontal, temporo-parieto-occipital	100%	0.96
Worthington	1997	12	Covert fluency	Rest					Not reported	55%	
Bahn	1997	7	Covert fluency	Rest	5	2		Frontal opercular	Frontal and temporal	100%	
			Covert rhyming					Posterior temporal			
Hertz-Pannier	1997	6	Covert fluency	Rest	5		1	Frontal	Inferior, middle and superior frontal gyrus	100%	
Yetkin	1998	13	Covert fluency	Rest	12	1		Frontal	IFG, precentral gyrus, SMA, anterior cingulate	92%	0.93
Benson^{a}	1999	23	Covert, verb generation	Visual Fixation	20	2	1	Whole brain		96%	
Lehericy	2000	10	Covert fluency	Rest				Various frontal, temporal and parietal ROIs			−0.62 to 0.88^{b}
			Covert sentence repetition	Rest							
			Story listening	Backward speech							
Baciu	2001	8	Rhyme detection	Perceptual control	7		1	Frontal, temporal parietal	IFG, superior temporal gyrus, supramarginal gyrus, angular gyrus, middle frontal gyrus, cingulate gyrus, insula, middle occipital gyrus, superior parietal lobule	94%	
Carpentier	2001	10	Semantic and syntactic decision (visual and auditory)	Perceptual control (visual and auditory)	8	2		Whole brain and BA45 and BA22	Temporal, fusiform, and frontal	80%	
Gaillard	2002	18	Reading/naming	Perceptual control	13	2	2	Whole brain	Inferior and middle frontal gyrus, Wernicke's area	83%	
Rutten	2002	18	Verb fluency	Visual control	11	3	4	Frontal, temporal, parietal	Frontal, temporal, parietal	67–91%	
			Covert naming	Visual control							
			Phonemic fluency	Rest/fixation							
			Reading	Perceptual							

Table 2 (continued)

Tasks					IAT						
Study	Year	*n*	Probe	Control	*L*	R	B	ROI	Regions activated	Concordance	*r*
Liegeois[c]	2002	8	Covert fluency	Rest	5	2	1	Inferior frontal gyrus	Inferior frontal gyrus	100%	
Spreer	2002	22	Semantic decision	Color discrimination	18	3	1	Whole brain, Frontal and temporoparietal		Frontal: 100% Temporal:91%	
Adcock	2003	19	Covert fluency	Rest	15	1	3	Whole brain	Different regions activated for Left and right TLE patients	89%	
Woermann[d]	2003	94	Covert fluency	Rest	71			Whole brain	Frontolateral, Temporo-posterior, parietal	91%	
Sabbah	2003	20	Covert fluency	Rest	12	8		Whole brain	Inferior frontal gyrus, middle and superior frontal gyri, pre and post central gyri, supplementary area, inferior middle and superior temporal gyri	95%	
Gaillard	2004	25	Covert fluency Reading responsive naming Reading Compr. Auditory Compr Auditory responsive naming	Rest Perceptual control Perceptual Reverse speech Rest	22	2	1	Whole brain	IFG, MFG, middle and superior Temporal	88%	
Deblaere	2004	17	Covert word chain	Covert counting	15		2	Frontal, Temporal parietal		88–100%	
Benke[e]	2006	68	Semantic decision	Perceptual control	54			Frontal and temporal		Frontal: 89% Temporal: 79%	

The *n* includes only those with valid fMRI and IAT

IAT Intracarotid sodium amobarbital test, *IFG* Inferior frontal gyrus, *MFG* medial inferior frontal gyrus, *ROI* regions of interest, *SMA* supplementary motor area, *TLE* temporal lobe epilepsy.

[a] Language dominance was assessed using IAT in 12 patients and electrocortical stimulation in 11 patients.

[b] Correlations between IAT and fMRI varied by ROI and task (18 correlations were reported).

[c] Language dominance was assessed using IAT in four patients and electrocortical stimulation in four patients

[d] Twenty-nine patients had atypical language, but it was not specified if dominance was right or bilateral. Also, all 100 had IAT, but six had an artifactual fMRI.

[e] Fourteen patients had atypical language, but it was not specified if dominance was right or bilateral.

formula $[V_L - V_R]/[V_L + V_R] \times 100$, where V_L and V_R are activation volumes for the left and right hemispheres. Functional magnetic resonance imaging studies using quantitative indexes of activated language voxels in neurologically normal individuals and epilepsy patients have demonstrated a continuum of language distribution with a higher incidence of atypical (bilateral or right) hemisphere language representation in both adult (Berl et al. 2005; Springer et al. 1999) and pediatric (Yuan et al. 2006) epilepsy patients relative to neurologically normal controls. Springer and colleagues' study of 50 right-handed epilepsy patients and 100 neurologically normal individuals found that 78% of the epilepsy patients were left hemisphere dominant, 16% had bilateral language and 6% were right hemisphere dominant for language. When the epilepsy group was separated into those with onset of epilepsy or brain injury prior to age five versus those whose epilepsy or brain injury occurred after age five, the language dominance patterns from fMRI were fairly similar to those reported in previous studies examining dominance patterns based on IAT (Rasmussen and Milner 1977), though bilateral language is reported at a higher rate with fMRI (See Table 3). Studies have shown that atypical language dominance is associated with left-handedness or weaker right hand dominance, having first degree biological relatives who are left-handed, left extra-temporal epilepsy, left lesion or left-sided seizure focus, and earlier age at onset of seizures or brain injury (Berl et al. 2005; Springer et al. 1999; Szaflarski et al. 2002; Weber et al. 2006; Woermann et al. 2003).

The first published study comparing fMRI and IAT was conducted using a frontal lobe ROI in seven patients, six of whom had undergone anterior temporal lobectomy (Desmond et al. 1995). Epilepsy patients performed a semantic judgment task contrasted with a perceptual judgment task using visually presented abstract and concrete nouns presented in either lower or upper case. The task was to press a button for abstract or concrete nouns in one condition and to press for upper or lower case in the control condition. The stimulus characteristics of the tasks are perfectly matched, and the task includes behavioral monitoring. The control task may inadvertently result in some language activation since the patients likely automatically read the text while making the perceptual judgment, though more semantic activity would be expected in the semantic judgment task. Activation was seen in the inferior frontal gyrus and orbital cortex corresponding to Brodmann's areas 45, 46, and 47. The sum of the functional activation values was used to compute a lateralization index for each patient. Four patients had left and three had right hemisphere dominance based on IAT, and 100% concordance was found between IAT and fMRI. In a study of pre-surgical epilepsy patients who underwent whole brain imaging, a high correlation ($r=0.96$) and 100% concordance was found between fMRI LIs and IAT LIs (Binder et al. 1996). Most studies have not computed laterality indexes for IAT, and some have only conducted visual analyses of the activation on fMRI. However, in this study the IAT LIs were computed from scores on measures of language comprehension, naming, repetition, reading and a rating of paraphasic errors during each injection. The IAT LI was the difference $[P_L - P_R]$ where P_L and P_R are the percentage scores based on correct responses during the IAT language tasks. Activation on fMRI was observed primarily in lateral frontal lobe, temporal lobe, and temporal–parietal–occipital junction. More specifically, activation was observed in inferior and middle frontal gyri, superior precentral sulcus, superior frontal gyrus and sulcus, angular gyrus, posterior inferior temporal gyrus, fusiform gyrus, posterior superior temporal sulcus, and middle temporal gyrus. Frontal areas of activation are similar to those reported by Desmond et al. (1995).

Table 3 Rates of language dominance in right-handed subjects based on fMRI and IAT

References		Left	Bilateral	Right
Springer et al. 1999	fMRI			
	Normals ($n=100$)	96	6	0
	Epilepsy ($n=50$)	78	16	6
	Early brain injury ($n=25$)	64	28	8
	No early brain injury ($n=25$)	92	4	4
Rasmussen and Milner 1977	IAT			
	Epilepsy			
	Early brain Injury ($n=42$)	81	7	12
	No early brain injury ($n=140$)	96	0	4

fMRI Functional magnetic resonance imaging, *IAT* intracarotid sodium amobarbital test

Reprinted from (Springer et al. 1999)

The largest study to date comparing IAT and fMRI, conducted by Woermann et al. (2003), included 100 epilepsy patients (71 left language dominant, 29 atypical dominance) who performed a covert fluency task alternating with rest in a block design. Images were visually inspected for asymmetries; no voxel counts or lateralization indexes were calculated. The concordance between IAT and fMRI was 91%. Five patients found to have left hemisphere dominance on IAT had bilateral language on fMRI, and three patients with bilateral or right hemisphere language on IAT had left language dominance on fMRI. In addition, 25% of the patients with left-sided extratemporal epilepsy were falsely categorized with fMRI.

A number of studies have compared IAT and fMRI using covert fluency tasks alternating with rest (Hertz-Pannier et al.

1997; Woermann et al. 2003; Worthington et al. 1997; Yetkin et al. 1998) with generally good concordance or correlation (Yetkin et al. 1998). Concordance was low in one study (55%), and the authors acknowledged that this may have been related to their language paradigm (Worthington et al. 1997). Yet other studies reported good concordance with a similar task (Hertz-Pannier et al. 1997). In general the fluency or word generation tasks have shown reasonable concordance with IAT but activation is predominantly frontal. In an effort to obtain more temporal lobe activation, Gaillard et al. (2002) designed a reading responsive naming task (name an object described by a written phrase) that alternated with a visual perceptual control task. They found left lateralized activation in the inferior and middle frontal gyri and in the posterior temporal lobe, with a concordance rate between fMRI and IAT of 83% and somewhat greater discordance in those with atypical language on IAT or fMRI.

Concordance Rates Differ by ROI Concordance rates between fMRI and IAT may differ depending on the task used as well as the region of interest. Several studies have reported higher concordance rates using frontal rather than temporoparietal ROIs (Benke et al. 2006; Deblaere et al. 2004; Spreer et al. 2002). Deblaere et al. (2004) examined the concordance between IAT and fMRI LIs from various ROIs including whole hemisphere, frontal and temporal–parietal using a 1.0 Tesla magnet. They used a covert word chain task where subjects were instructed to generate a list of words starting with the last letter of the previous word. This language task alternated with covert counting. Concordance was 100% for fMRI and IAT using a frontal ROI. This included 15 patients found to have left hemisphere dominance for language on IAT and two who were bilateral on IAT. The concordance was lower using a whole hemisphere or temporal–parietal ROI, with patients who were bilateral on IAT more likely to be classified as right dominant with fMRI. Using a semantic decision task alternating with a color discrimination task, higher concordance between IAT and fMRI was found in frontal (100%) compared to temporoparietal regions (91%) (Spreer et al. 2002). The discordant cases were both patients with atypical language on IAT (one right and one bilateral) who appeared to have left language based on the temporoparietal ROI. Another study found that fMRI and IAT scores were more highly correlated in frontal than temporal ROIs using both covert semantic fluency and story listening tasks (Lehericy et al. 2000). Carpentier et al. (2001) found modality specific activation patterns when comparing visual and auditory semantic decision tasks. The visual semantic decision task resulted in more lateralized frontal activation compared to the auditory task.

As noted above, a number of studies report better concordance between IAT and fMRI in frontal regions of interest but this may be function of the language task selected. Most language tasks do not produce robust anterior temporal lobe activation, the region typically resected in epilepsy surgery. A series of studies by Hamberger and colleagues demonstrated that auditory responsive naming sites are located anterior to visual picture naming sites in the temporal lobe using electrocortical stimulation mapping (see Hamberger article from this issue) (Hamberger et al. 2001, 2007). Furthermore, these authors noted that sparing of visual naming sites did not prevent post-operative naming decline while resection or sparing of auditory naming sites was associated with post-operative naming outcome (Hamberger et al. 2005). In an effort to obtain better anterior temporal lobe activation and based on the findings of topographically distinct modality specific naming sites, an fMRI responsive naming task was developed at our center (Hammeke et al. 2003). A clustered acquisition scanning protocol was used that allows patients to orally name nouns in response to brief auditory definitions (e.g., “What a king wears on his head”). This task is contrasted with an auditory discrimination task that also requires a verbal response. Preliminary findings indicate that the language LIs derived from this responsive naming task are highly correlated with LIs derived from a semantic decision task. Further the responsive naming task produced more extensive activation of the anterior temporal lobes than the semantic decision task.

Gaillard et al. (2004) noted that previous studies have found discordance between IAT and fMRI in approximately 10% of epilepsy patients. Several authors have suggested that the discordance rate between IAT and fMRI can be reduced by using a panel of language tasks (Gaillard et al. 2004; Rutten et al. 2002). Agreement between IAT and fMRI using a visual clinical rating of the activation images was improved using a panel of language tasks designed to activate different language functions. Some studies employing multiple language tasks with rest or non-perceptually matched control tasks or a limited number of runs may be more likely to note improved concordance when the results of multiple tasks are combined as this increases their statistical power.

One issue with determining the concordance between IAT and fMRI is that most investigators typically assume that fMRI is inaccurate when discordance occurs. There is room for error in the IAT, for example in association with abnormal vasculature (Hietala et al. 1990), obtundation or reduced level of arousal (Malmgren et al. 1992), perseveration, dysarthria, abulia, and other behavioral disturbances that can interfere with language assessment and result in false positive language errors. Conversely, early motor return or short drug effect may result in over-interpreting the presence of language. Thus, the discordance or error rate between the two methods can be related to measurement error with either method. This issue can be addressed by examining the degree to which IAT or fMRI is better able to predict language outcome, as discussed below.

Hemispheric language representation as determined by fMRI has been compared to the results of extra- and intra-operative cortical stimulation mapping (Carpentier et al. 2001) with concordance reported in seven of seven cases. However, this comparison is limited because the region of electrode coverage is typically limited to only a portion of one hemisphere.

Concordance and Atypical Language Another issue affecting concordance rates between IAT and fMRI involves dichotomizing (left versus atypical language) or trichotomizing (left, right, bilateral language) a continuous variable. Bilateral language is on a continuum that is not easy to demarcate. Further, some patients with atypical or bilateral language will have dissociations between the hemispheres in what are traditionally considered anterior and posterior language functions (Kurthen et al. 1992; Risse et al. 1997). The utility of fMRI for mapping language in individuals with atypical language or right hemisphere dominance has been questioned (Bookheimer 1996). Some authors have suggested that a panel of language tasks results in improved concordance between IAT and fMRI in patients with atypical language representation (Gaillard et al. 2004; Rutten et al. 2002). These authors have noted that while fMRI and IAT may be highly correlated, fMRI as a predictor of language dominance in individual patients has not been demonstrated. One could argue that this has been demonstrated based on the studies of concordance rates between fMRI and IAT as well as by the fact that fMRI language LIs have been shown to predict language outcome (Sabsevitz et al. 2003).

Nevertheless, because most studies have included only a limited number of patients with atypical language dominance, investigators have questioned the accuracy of fMRI in patients with right or bilateral language. Using a multi-task language protocol in patients with temporal lobe epilepsy, Rutten et al. (2002) found concordance rates of 91, 75 and 67% respectively in patients who had left (n=11), bilateral (n=4), or right (n=3) language dominance. Concordance rates thus appear to be lower in those with atypical language, though sample sizes were very small in this study. When the patients with atypical language in the Gaillard study are examined, 13 were left on IAT and fMRI, 2 were bilateral on IAT and left on fMRI, and one was left on IAT and bilateral on fMRI (Gaillard et al. 2002). Therefore all of the patients with atypical language on IAT had results that were discordant with fMRI. Adcock et al. (2003) found that two of 19 patients were discordant between IAT and fMRI. Of these two, one had bilateral language on IAT but was left dominant on fMRI, and one was left dominant by IAT but bilateral on fMRI. The concordance rates were 89% for the whole group, 93% for patients who are left dominant on IAT, and 75% for the three patients with atypical language. Some findings of discordance could be spurious depending on the LI cutting score used. For example, if a cutting score of +30 to −30 is used for bilateral language and a patient has a score of 30 on fMRI and 33 on IAT, they technically could be discordant.

Those with atypical language in other studies had the same concordance rates as those with left language dominance (Binder et al. 1996; Desmond et al. 1995; Hertz-Pannier et al. 1997; Liegeois et al. 2002). Further, in the largest IAT fMRI comparison to date, the discordance rates were 10% for the patients with atypical language and 7% for the patients with left dominance (Woermann et al. 2003) suggesting that fMRI has utility for assessing language localization in patients with bilateral or right hemisphere language dominance.

Several areas that need further investigation include (1) scrutiny of cases where IAT and fMRI are discordant; (2) comparisons between maps obtained from fMRI and cortical stimulation (either intra-operatively or with extra-operative grid mapping) as has been conducted with tumor patients (Lurito et al. 2000); (3) examination of the concordance and correlation differences between different ROIs relative to task selection; and (4) examination of the concordance rates or correlations between fMRI and IAT in a large series of patients who show atypical language dominance on *either* IAT or fMRI. Despite the instances of discordance, fMRI is a reasonable alternative for determining lateralization of language in individual patients prior to epilepsy surgery.

Language Plasticity and Reorganization

Language plasticity may be studied by examining organization of language following lesions of different types and locations, and lesions occurring at different ages (Ewing-Cobbs et al. 2003). Functional magnetic resonance imaging language maps in patients with seizure onset or injury to the left hemisphere at different ages provides information about plasticity and the manner of reorganization of function. Second, conducting serial fMRI scanning prior to and following a known lesion (e.g., temporal lobectomy) provides the opportunity to watch recovery and potentially learn about neural plasticity. For example, patients with post-stroke aphasia have been followed with serial fMRI during their recovery, with imaging revealing dynamic changes in brain activation over time that was not present in control subjects (Fernandez et al. 2004).

Patients with early onset epilepsy may experience intra- or interhemispheric reorganization of language, particularly when the epilepsy or initial precipitating event encompassed a large region in the language dominant hemisphere. As previously noted, earlier age of insult is associated with more bilateral or rightward shift of language, supporting the notion of an early critical window period for reorganization. Swanson and colleagues (Swanson et al. 2002), using a semantic decision fMRI paradigm, showed that age at onset of seizures was correlated with the degree of language lateralization only in patients with left hemisphere seizures. Early onset seizures in the left hemisphere were associated with more atypical or right hemisphere representation of language. Examination of the group fMRI maps revealed that language reorganized to contralateral homologous regions in the frontal and posterior temporal parietal heteromodal regions in those with early left hemisphere seizures. Functional magnetic resonance imaging studies using other language activation paradigms, such as covert verbal fluency (Adcock et al. 2003; Brazdil et al. 2005; Janszky et al. 2006; Sabbah et al. 2003) or object naming in response to a sentence description of the object (Berl et al. 2005), have also shown higher rates of atypical or rightward lateralization of language in patients with left temporal epilepsy.

FMRI has also been shown to be useful in examining *intra* hemispheric language reorganization. Liegeois et al. (2004) reported on a small group of children with intractable epilepsy who sustained early left hemisphere lesions either adjacent to or remote from classic language regions. They found that language functions, as identified by a verb generation fMRI task, did not always shift to the contralateral hemisphere. In this study, four of five patients with lesions in or near Broca's area showed peri-lesional activation within the damaged left hemisphere rather than interhemispheric shift. One advantage of fMRI over IAT is the ability to provide data on intrahemispheric reorganization patterns.

FMRI can also be used to examine mechanisms of neuroplasticity in post-surgical epilepsy patients. Hertz-Pannier et al. (2002) scanned a child with intractable seizures secondary to Rasmussen's syndrome both before and 1.5 years after left hemispherectomy at age nine. The child acquired normal language prior to his surgery, and preoperative fMRI using a covert semantic fluency task relative to rest revealed strong left lateralization of language functions. The child developed a profound aphasia and alexia following the surgery but regained a substantial degree of language (comprehension more so than speech production) over time. Postoperative fMRI using covert semantic fluency, sentence generation, and passive sentence listening relative to rest showed a shift of language functions to the right hemisphere in regions not previously detected on his preoperative scan. Activation was found in homologous right hemisphere regions, including inferior frontal, temporal, and parietal cortex.

Predicting Outcome

The ability to use fMRI data to predict language and memory morbidity is a powerful new pre-surgical use for fMRI. Several studies have shown that the degree of preoperative activation asymmetry in the hippocampus or in medial temporal lobe predicted decline in scene recognition (Rabin et al. 2004) and verbal memory (Richardson et al. 2004) following surgery. Only one study to date has examined the validity of fMRI language LIs for predicting language morbidity after epilepsy surgery (Sabsevitz et al. 2003).

Dysnomia, or impaired naming, is a common cognitive complication of dominant temporal lobectomy (Bell et al. 2000; Davies et al. 1998; Hermann et al. 1999; Langfitt and Rausch 1996; Ruff et al. 2007; Stafiniak et al. 1990). The ability to identify epilepsy patients at greatest risk for post-operative naming decline has important clinical implications to not only the patient but also to the treatment team during the pre-surgical planning stage. Historically, clinical variables, such as age at onset of epilepsy or age at first neurologic insult, have been used to predict naming outcome following dominant temporal resection (Hermann et al. 1999; Ruff et al. 2007; Saykin et al. 1995; Stafiniak et al. 1990). Left temporal lobe epilepsy patients with earlier age at onset have been shown to be at lower risk for language decline following surgery than patients with later age at onset, presumably because they have a greater opportunity to "shift" language to the non-surgical hemisphere. Better pre-surgical naming performance has also been shown to predict poorer language outcome following dominant temporal resection (Hermann et al. 1994). One possible explanation for this relationship is that preoperative naming performance serves as an indirect measure of the functional integrity of the to-be-resected temporal lobe, with better pre-operative performance indicating the presence of more functional or intact tissue. The presence of more viable language tissue pre-operatively increases the likelihood that it will be removed during surgery, resulting in greater post-operative language decline. In addition to these clinical variables, clinicians often rely on IAT language testing to identify those patients at risk for developing postoperative language complications. Intracarotid amobarbital language testing is based on the assumption that lateralization of language toward the surgical hemisphere places a patient at greater risk for language decline following dominant temporal resection than if language is lateralized to the non-surgical hemisphere. While there are anecdotal reports that patients with

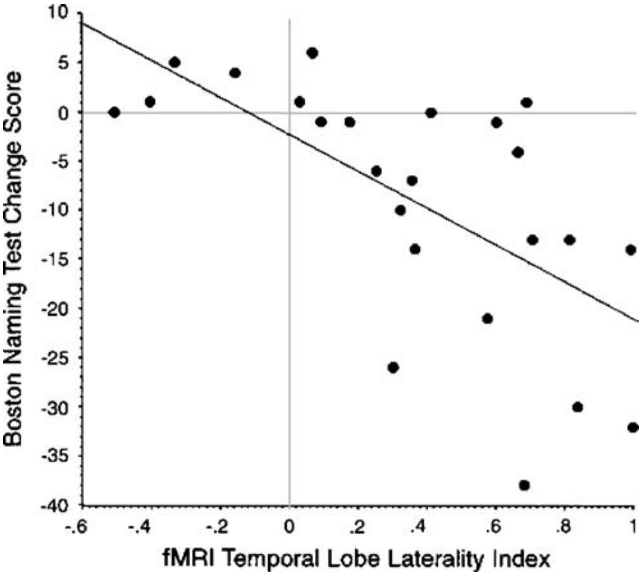

Fig. 2 The relationship between an fMRI temporal lobe laterality index and Boston Naming Test outcome. Reprinted from (Sabsevitz et al. 2003). *fMRI* = functional magnetic resonance imaging

right hemisphere language dominance do not decline following left temporal lobectomy, there has been only one study to date that has formally examined the predictive power of IAT laterality scores and language outcome in this patient group (Sabsevitz et al. 2003). This study found that IAT language laterality scores were in fact predictive of naming outcome following left temporal lobectomy ($r = -0.43$, $p < 0.05$).

One advantage that fMRI has over IAT in predicting language outcome is that fMRI can provide information on the intrahemispheric localization of language. The ability to localize language within a given hemisphere or more ideally within the to-be-resected temporal lobe can provide valuable information to the neurosurgeon when planning the surgical boundaries. Sabsevitz et al. (2003) examined the clinical utility of preoperative fMRI in predicting postoperative naming outcome following left anterior temporal lobectomy. In this study, 24 patients with left temporal lobe epilepsy underwent preoperative fMRI language mapping and both pre- and six-month-postoperative neuropsychological testing were examined. Preoperative fMRI language mapping used a semantic decision paradigm alternating with a tone decision task as depicted in Table 1 and described above. The degree of fMRI language lateralization in the temporal lobe significantly predicted naming outcome. That is, stronger lateralization toward the surgical temporal lobe was associated with greater postoperative decline on the Boston Naming Test ($r = -0.64$, $p < 0.001$; see Figs. 2, and 3). Preoperative fMRI accounted for 41% of the variance in predicting naming outcome. Language lateralization in frontal and parietal ROIs was also predictive of naming outcome, but the temporal lobe ROI was more predictive. Using the temporal lobe ROI, fMRI showed 100% sensitivity and 73% specificity in predicting significant naming decline (i.e., >2 SD decline as compared to a right temporal lobectomy control group). IAT also predicted naming outcome in these patients (92% sensitivity and 45% specificity) but not as well as fMRI. Using multiple regression analysis, both fMRI and IAT were found to be more predictive of naming outcome than age at seizure onset and preoperative naming status. The findings from this study suggest that fMRI can be used to stratify patients in terms of risk, potentially allowing patients and physicians to more accurately weigh the risks and benefits of surgery.

Future Directions

The ultimate test of fMRI is the usefulness of the activation maps for guiding the surgical boundaries. While language lateralization toward the surgical temporal lobe has been found to be predictive of naming outcome (Sabsevitz et al.

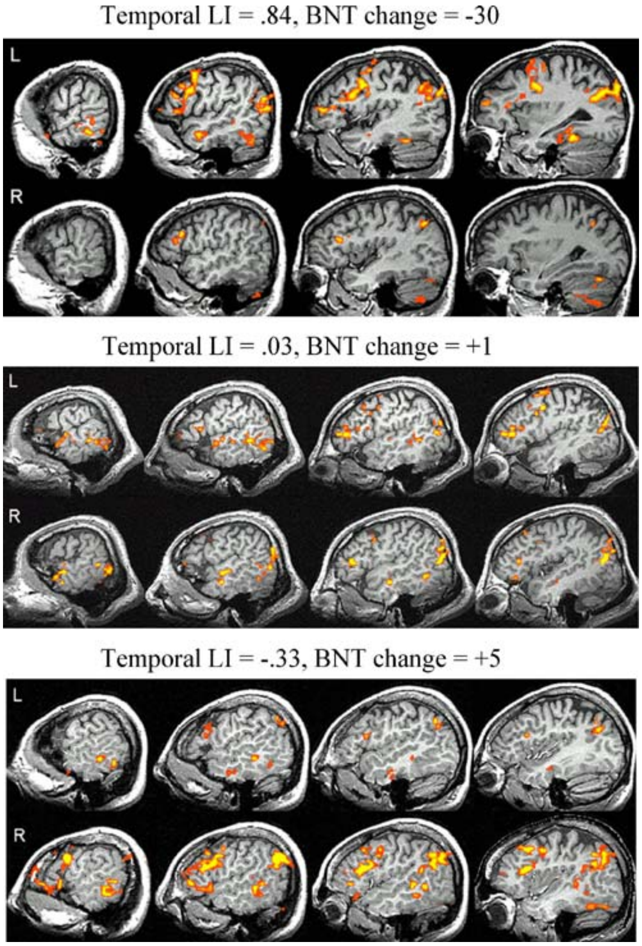

Fig. 3 Activation maps and corresponding naming decline in raw score points for three different patients who underwent left anterior temporal lobectomy. *BNT* = Boston Naming test, *LI* = lateral index

2003), no studies to date have specifically examined whether surgical removal of activated voxels in and/or near the surgical cavity predicts outcome. Several scenarios are possible with regard to resection of brain tissue in the context of fMRI. First, if resection of activated voxels correlates with cognitive decline, then it can be assumed that these voxels are critical for the cognitive function in question and should be avoided, if possible, during surgical planning. If resection of activated voxels does not correlate with cognitive outcome, then it can be assumed that these voxels are either involved but not critical for a given cognitive function or perhaps represent false positive activation due to inadequate control of non-essential cognitive functions. The other question is whether tissue that shows no activation can be safely removed. Distinction between activated voxels that are critical versus expendable can be determined by examining language and memory decline relative to the number of activated voxels resected and by comparing cognitive morbidity across randomly assigned groups for whom the neurosurgeon operates with or without the guidance of fMRI language maps. The use of fMRI language maps to tailor resections still requires experimental validation.

Integration systems that co-register three-dimensional fMRI images and extra-operative stimulation maps are being developed to aid in surgical planning (O'Shea et al. 2006). New research combining data from different imaging methods, such as fMRI and event-related potential data (Calhoun et al. 2006) or fMRI and diffusion weighted imaging tractography (Aron et al. 2007), or, in the future, perhaps fMRI and magnetic source imaging may provide more powerful combinations of mapping data. Such combinations integrating the best features of each imaging method may be useful for further delineating functional networks.

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