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Functional MRI measurement of language lateralization in Wada-tested patients

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Summary

In this study the use of functional MRI (fMRI) for measuring language lateralization non-invasively was examined. The subjects were seven patients with histories of temporal lobe epilepsy who had undergone Wada testing for pre-surgical evaluation. Four patients were left-hemisphere-dominant and three were right-hemisphere-dominant for language. They received fMRI scans while they made semantic or perceptual judgments about visually presented words. Regions of the inferior frontal gyrus (pars triangularis and pars orbitalis) and neighbouring orbital cortex, corresponding to portions of Brodmann areas 45, 46 and 47, exhibited significant increases in activation during semantic relative to perceptual judgments. Lateralization of the increases in activation were consistent with the Wada test assessments of hemispheric language dominance in each of the seven patients. These results suggest that, in addition to providing a tool for investigating human cognitive processes, fMRI has significant clinical potential as a non-invasive measure of language lateralization.

Key words: language lateralization; functional MRI; Wada test; epilepsy; hemispheric dominance

Abbreviations: fMRI = functional MRI; LI = lateralization index

Introduction

The intra-arterial administration of sodium amobarbital is a procedure first described by Wada (1949) and Wada and Rasmussen (1960) for anaesthetizing cerebral hemispheres for the purpose of lateralizing language functions. The vast majority of epilepsy surgery programmes now routinely use the intra-arterial amobarbital procedure, or Wada test, in patients who are candidates for surgical resections of their epileptic foci. Hemispheric dominance for language can be inferred by observing the degree of disruption of language production and comprehension after anaesthetizing each hemisphere. This information is important for surgical planning and can determine whether additional functional mapping (i.e. cortical stimulation) is necessary to avoid resecting eloquent cortex.

Despite its usefulness, Wada testing has several major drawbacks: (i) the intracarotid catheterization carries a morbidity risk as high as 5% (Rausch *et al.*, 1993); (ii) many patients find the paralysis and speech arrest induced by the procedure to be distressing; (iii) it is expensive; (iv) it provides information about language lateralization but cannot localize speech or other primary language functions. The recent development of fMRI techniques for measuring brain activation can be seen as a significant step toward replacing the Wada test with a procedure that is noninvasive, considerably less risky and unpleasant for the patient, at least an order of magnitude less expensive, and more informative with respect to localization. These fMRI techniques are based on changes in regional blood flow that occur in response to neuronal activity. Local increases in neuronal activity lead to greater blood flow to the cortical tissue parenchyma (Belliveau *et al.*, 1991). The blood arriving in the activated region contains a higher proportion of diamagnetic oxyhaemoglobin and a lower proportion of paramagnetic deoxyhaemoglobin compared with non-activated regions. The subtle blood-oxygen-level-dependent differences in magnetic state results in a larger T_2* signal from the activated region (Ogawa *et al.*, 1990).

In order to infer whether fMRI-derived activation is related to a particular mental function it is necessary to compare the activation during two experimental conditions that are as similar as possible except for the mental function or process of interest. This strategy has been employed with considerable success in PET studies of cognition (e.g. Fox *et al.*, 1988; Posner *et al.*, 1988; Frith *et al.*, 1991; Sergent *et al.*, 1992). For the present study, we selected a task that is based on the finding that words are better remembered if studied for meaning (semantic or 'deep' encoding) rather than for appearance (perceptual or 'shallow' encoding) (Craik and Lockhart, 1972). Studies with PET have consistently shown greater activation in left frontal lobe during conditions that result in superior memory for words (Petersen *et al.*, 1988; Shallice *et al.*, 1994; Tulving *et al.*, 1994) including a study that directly compared semantic and perceptual encoding of words (Kapur *et al.*, 1994). In the latter study, increased activation was observed in left inferior frontal regions during semantic processing of words, but an absence of activation was observed in posterior regions (Kapur *et al.*, 1994). These results influenced our decision to focus on the frontal cortex for the purpose of lateralizing hemispheric dominance for language. Consistent with PET studies, we have obtained patterns of left frontal activation using fMRI in normal healthy subjects who were required to judge words as abstract or concrete during a semantic condition, and as appearing in upper-case or lower-case letters during a perceptual condition (Gabrieli *et al.*, 1995). We hypothesize that the increase in left frontal lobe activity observed in these studies is related to the side of language dominance. In the present study we tested this hypothesis in volunteers who have undergone Wada testing and whose side of language dominance is known, thus providing an opportunity both to validate the fMRI method and examine its clinical applicability.

Methods

Subjects

Three male and four female patients with medically intractable localization related epilepsy of temporal lobe origin gave their informed consent to participate in this study, which was approved by the Institutional Review Board at Stanford University. All but one of the patients (SL2) had undergone surgical resection of the epileptic focus 14–32 months prior to fMRI testing. Patient characteristics are summarized in Table 1.

Wada tests

Intracarotid sodium amobarbital testing was performed as part of each patient's pre-surgical evaluation. Sodium amytal (125 mg in 5 cm^3 saline solution) was injected at a rate of ~1 cm^3/s into the internal carotid artery via a transfemoral approach. All patients had both left and right carotid injections that were no less than 1 h apart, with the side ipsilateral to the presumed seizure focus injected first. Stimuli were presented to the patient once unilateral hemisphere slowing of the EEG was observed. Hemispheric language dominance was assessed by the presence or absence of paraphasia, speech arrest, and errors in naming, repetition, reading and comprehension of aural commands. Four patients were left-hemisphere dominant for language (Patients SL1–SL4 in Table 1) and three patients were right-hemisphere dominant for language (Patients SR1–SR3).

Neuropsychological assessment

All patients received a comprehensive neuropsychological examination in conjunction with their pre-surgical evaluations. In addition, some of the subjects in the present study have completed post-surgical evaluations. Table 1 presents selected IQ and memory test scores drawn from these larger clinical batteries. For each patient, data are included from the testing session that was closest in time to the fMRI scan.

Each patient's self-reported handedness is presented in Table 1. We also administered the Crovitz Handedness Questionnaire (Crovtiz and Zener, 1962), a continuous measure of hand preference. In each case, the patient's Crovitz score was consistent with the self-reported hand preference.

Task design

Materials

Stimuli consisted of 320 words, each three to eight letters in length, that were visually presented to the patients. Half of these words were abstract and half were concrete, and they were divided randomly into blocks of 20 words such that 10 words in a block were abstract and 10 were concrete. Half of the abstract and half of the concrete words within each block appeared in upper-case letters, and the other half appeared in lower-case. Thus, each block had five abstract/upper-case words (e.g. 'TRUST'), five abstract/lower-case words (e.g. 'love'), five concrete/upper-case words (e.g. 'CHAIR') and five concrete/lower-case words (e.g. 'book'). The words in each block were arranged in a pseudorandom order with the constraint that no more than four abstract, concrete, upper-case or lower-case words appeared consecutively.

Procedure

Each patient completed two repetitions of an encoding experiment, with each repetition occurring at a separate coronal slice described below. The encoding experiment consisted of four task cycles, and each cycle consisted of two blocks of 20 words as described above. On one block of each cycle, the patient's task was to press a squeeze ball (always using the right hand) according to the abstract or concrete nature of the word. This is referred to as the semantic

Table 1 *Characteristics of epileptic patients*

Patient	Age (years)	Sex	Handedness	Surgery	WAIS-R FSIQ	WMS-R General	Medication
SL1	32	M	Right	LTE	128 *	89*	Tegretol
SL2	20	F	Right	PRE	119	131	Dilantin
SL3	35	F	Right	LTE	94	–	Dilantin
SL4	53	M	Right	RTE	106	95	Tegretol
SR1	31	F	Right	LTE	78 *	79*	Dilantin
SR2	39	F	Right	LTE	89 *	82*	Tegretol
SR3	28	M	Left	LTE	91	84	Dilantin

WAIS-R = Wechsler Adult Intelligence Scale—Revised; FSIQ = Full Scale IQ; WMS-R = Wechsler Memory Scale—Revised; General = General Memory index; LTE = left temporal lobe excision; RTE = right temporal lobe excision; PRE = pre-surgical at the time of fMRI testing. Wada tests indicated that Patients SL1–SL4 were left-hemisphere dominant for language and that Patients SR1–SR3 were right-hemisphere dominant for language. *The test score was obtained after surgery; otherwise the score was obtained prior to surgery.

encoding condition. On the other block of the cycle, the patient's task was to press the squeeze ball depending on whether the word appeared in upper-case or lower-case letters (the perceptual encoding condition). The number of target stimuli to which the patients responded was equal for the semantic and perceptual conditions and, thus, the motor component of the task was balanced for the two conditions. Each block was preceded by an instruction card that informed the patient of the task that should be performed. The semantic and perceptual encoding conditions always alternated in a consistent manner for each patient, but across patients the semantic/perceptual order of occurrence was counterbalanced. The type of stimulus to which the patient responded with the squeeze ball (i.e. abstract or concrete for semantic encoding, and upper-case or lower-case for perceptual encoding) was also counterbalanced.

Patients performed the four cycles of semantic/perceptual encoding while fMRIs were recorded. Stimuli were generated from a computer and were back-projected onto a screen located above the patient's neck via a magnet-compatible projector (Resonance Technology, Inc., Van Nuys, Calif., USA). Visual images were viewed from a mirror mounted above the patient's head. Each word was presented for a 1.0 s duration, and the words appeared at a rate of one every 2.0 s. Thus, the total duration for the four cycles was 336 s. In three cases (Patients SL3, SR1 and SR2), the rate of presentation was slowed to one every 2.8 s because the patient had difficulty responding at the faster pace. In these cases three cycles were completed over a 360 s interval.

Data acquisition

Imaging was performed with a 1.5 Tesla whole body MRI scanner (General Electric Medical Systems Signa, Rev. 5.3). For functional imaging, two 5-inch diameter local receive coils were positioned bilaterally over the frontal lobes to obtain cortical signal. Head movement was minimized for normal subjects and patients using a 'bite-bar' that was formed with the person's dental impression. A T_2* sensitive gradient echo spiral sequence (Meyer *et al.*, 1992) was used for functional imaging with parameters of TR = 75 ms, TE = 40 ms, and flip angle = 23°. Twenty interleaves were obtained for each image, so total acquisition time per image was 1.5 s. Two 7 mm thick slices (in-plane resolution of 2.4×2.4 mm) were acquired separately in the coronal plane of Talairach and Tourneaux (1988) at 32 and 39 mm rostral to the anterior commissure, and 224 images were acquired continuously every 1.5 s over a 336 s session (for three patients that were responding at the slower pace, 240 images were collected over 360 s). T_1-weighted, flow compensated spin-warp anatomy images (TR = 500 ms, minimum TE) were acquired for all slices that received functional scans, and pixels that were found to be significantly activated during the functional scan were overlaid on these structural images.

Data analysis

Image reconstruction was performed off-line by transferring the raw data to a Sun SparcStation. The data were resampled into a Cartesian matrix and then processed with a 2D Fast Fourier transform. Time series of each pixel were then formed from the reconstructed individual images. These time series were cross-correlated with a sinusoidal reference function at the frequency of the expected activation (based upon the timing of stimulus presentation). Cross-correlating a pixel's time series with a reference waveform can effectively remove artifactual signals such as CSF or brain pulsatility that are randomly timed with respect to the activation paradigm (Bandettini, 1993; Lee *et al.*, 1995). Sinusoids serve as reasonable reference functions because of the temporal low-pass filtering that occurs due to the haemodynamic response. For the present study, one task cycle consisted of a block of semantic and a block of perceptual encoding. Since four of these cycles were presented over a 336 s scan, the target frequency was ~0.012 Hz.

Cross-correlation computations were performed by first removing linear slopes from each time series. Such slopes are caused by signal drift that occurs across the entire scan, and are not related to any particular experimental or control condition. The presence of these linear components in the data can degrade the correlation with the reference waveform, as discussed by Bandettini *et al.* (1993), and are therefore routinely removed. A correlation with a sine (r_s) and with a cosine (r_c) function was computed, which allows the temporal phase of the correlated time series to be computed by the expression,

$$\phi = \tan^{-1}\left(\frac{r_s}{r_c}\right)$$

and the correlation magnitude by the expression

$$r_m = \sqrt{r_s^2 + r_c^2}$$

To construct functional activation maps, pixels were selected so that r_m exceeded a correlation threshold, $r_{thresh} = 0.152$ (representing significance at $P < 0.01$, one-tailed); and exhibited a phase lag of 0°–90° with respect to a sine wave. The phase lag window chosen reflected pixel values that increased during semantic and decreased during perceptual encoding. (Note that the phase window of 0°–90° is appropriate for identifying pixels that increase during semantic and decrease during perceptual encoding only when the semantic encoding condition occurs first. Because order of task presentation was counterbalanced, a phase window that was shifted by 180°, i.e. 180°–270°, was used when the semantic encoding task followed perceptual encoding.) The resulting map was then processed with a median filter with spatial width = 3 to emphasize spatially coherent patterns of activation, and each slice was normalized by scaling according to the maximum correlation observed at that slice; thus each significant pixel's correlation magnitude was transformed into a proportion by the equation

$$r' = \frac{(r_m - r_{thresh})}{(r_{max} - r_{thresh})}$$

where r_{max} is the maximum correlation observed for that slice. This normalization was useful for identifying peaks of activation for each slice independent of the absolute magnitudes of the correlations, which could vary from slice to slice and from patient to patient. The resulting map was overlaid on a T_1-weighted structural image.

To define a region of interest and quantify asymmetry in frontal lobe activation, standardized composite maps were created. These composites were made by transforming the normalized fMRI activation maps obtained at the $y = 32$ mm section and at the $y = 39$ mm section into the two-dimensional region of a standardized coronal section obtained from the stereotaxic atlas of Talairach and Tournoux (1988) (the coronal slice at $y = 35$ mm was used) and then averaging the functional activation over the two sections. The transformation was achieved by measuring the maximum x and y dimensions of the brain tissue for each section. These measurements were used to scale the maps to the dimensions of the standardized section. The centroid of each functional map was computed (using the set of pixel coordinates that overlapped brain tissue) and the map was translated to the centroid of the standardized section. Minor tilts of the head about the y axis were corrected by rotation. To obtain precise anatomical matching with the atlas, the scaled, centred and rotated functional maps were then warped to fit the perimeter of the atlas-derived coronal section. This procedure involved the following steps. (i) A set of points was defined around the perimeter of the functional map as well as the perimeter of the standardized section. These points were found by casting rays in all directions from the centroid of the image in 0.5° increments of a circle. For each ray, the intersection of the ray with the outer boundary of the image (which was defined by lines that were manually traced) could be found, resulting in an equal number of boundary points for the functional map and the standardized section. (ii) From these boundary points a grid of points was formed across the functional map, and a corresponding grid was formed for the standardized section such that a one-to-one mapping existed for the grid points in each set. (iii) By mapping values from the grid points of the functional image to the grid points of the standardized section, the functional image could be transformed into the confines of the standardized section. This procedure was implemented using routines available in the Interactive Data Language (IDL, Research Systems, Inc., Boulder, Co., USA).

Quantifying fMRI lateralization

Defining regions of interest

Two important questions that must be addressed in order to characterize hemispheric lateralization of brain activation are: (i) What is the relevant region of interest from which activation should be measured? (ii) How can this region be identified objectively in individual patients? We used standardized composite maps, as described above, to address these questions. To define our region of interest, we collected data from four healthy right-handed control subjects (presumed to be left hemisphere dominant for language) and formed an average of the brain activation from these subjects. In order to compute this average, each subject's functional activation had to be transformed into a common coordinate system. Thus, a standardized composite map was created for each subject and these maps were then averaged. From the resulting map, a region of relatively strong functional activation was apparent in the left inferior frontal gyrus. This region, which extends from the inferior frontal sulcus to the posterior orbital gyrus, was outlined, and a mirror-image of the region of interest was formed for the right side. The result of this procedure is illustrated in Fig. 1A. The original data obtained from the healthy control subjects and the averaged composite map computed from these data appear elsewhere (Gabrieli *et al.*, 1995).

To address the second question regarding the objective measurement of lateralization from the region of interest, each patient's functional data were transformed into a standardized

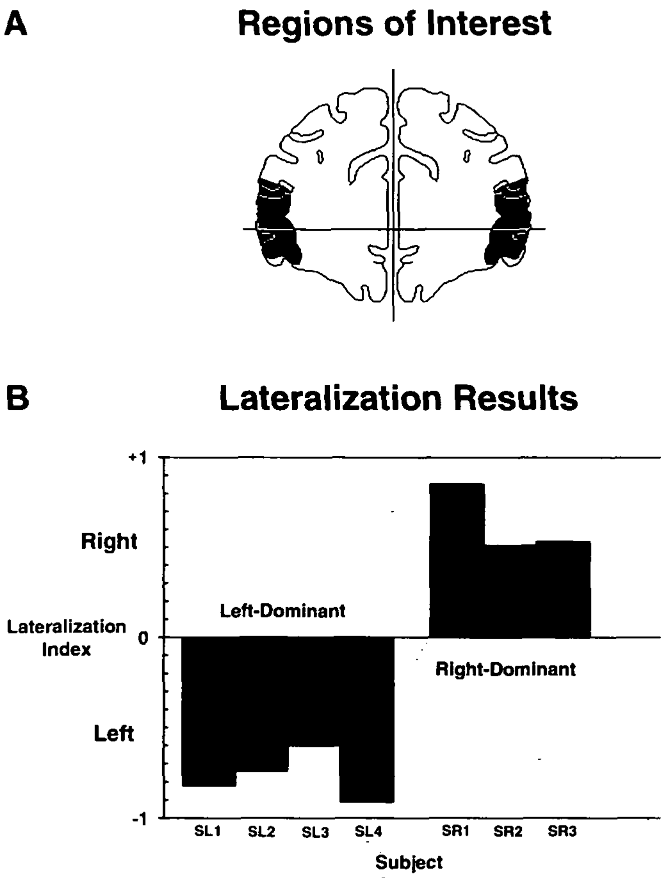

Fig. 1 (**A**) Coronal section at 35 mm rostral to the anterior commissure, based on the atlas of Talairach and Tournoux (1988). This section illustrates the regions of interest in the left and right inferior frontal areas from which the fMRI-based LI was computed. (**B**) Lateralization index scores for Wada-tested patients. The x-axis shows the four left-dominant patients and the three right-dominant patients. The y-axis indicates hemispheric dominance LI scores, with a negative score indicating greater left than right hemispheric activation and a positive score indicating greater right than left hemispheric activation.

composite map, thereby ensuring that activation from symmetrical and equal areas of the inferior frontal cortex would be considered in the computation of lateralization. This procedure was validated by having a scorer outline a left and right region of interest in the inferior frontal cortex on each brain section for each of the seven patients and four control subjects. The scorer did not know whether a given section belonged to a right- or left-hemisphere dominant person. The result of the validation experiment was that the lateralization index (LI) (described below) derived from the scorer's measurements was highly correlated (Pearson r = 0.99) with the lateralization measured via the standardized composite maps. To ensure that the scorer's measurements were unbiased, the difference in the number of pixels in the left and right regions of interest was computed for each scored section; a t test revealed that the mean difference was not significantly different from zero.

Lateralization index

A measure of lateralization was obtained for each patient after the standardized composite map for that patient's activation was computed. For each of the pixels located in the left and right regions of interest, functional activation values were summed and the following ratio computed:

$$\mathrm{LI} = \frac{\Sigma R_i - \Sigma L_i}{\Sigma R_i + \Sigma L_i}$$

where ΣR_i denotes the sum of the functional activation magnitudes found in each of the pixels contained in the right-side region of interest, and ΣL_i denotes a similar sum for the left side. The magnitude of the LI can range from −1.0, which would indicate only left-lateralized functional activation, to +1.0, indicating only right-sided functional activation.

Results

Behavioural data obtained during fMRI scanning confirmed that the patients performed the tasks accurately. Accuracy was scored from the total number of correct responses to target stimuli and correct non-responses to non-target stimuli. The mean performance accuracy for the seven patients was 91.5% (SD = 6.1%).

Figure 1B illustrates the computed values of the LI for the seven patients. Each patient for whom the Wada test indicated left hemisphere dominance for language exhibited negative LI values, with scores ranging from −0.60 to −0.91, (mean value of −0.77). These scores are comparable to those obtained from four healthy right-handed subjects (not depicted in Fig. 1B), presumed to be left-hemisphere dominant for language, who had LI scores ranging from −0.45 to −0.99 (mean value of −0.81). Each patient for whom Wada testing indicated right-hemisphere dominance for language had a positive LI value, with scores ranging from +0.51 to +0.85 (mean value of +0.63). Thus, in all seven cases, the polarity of the LI score was in agreement with the Wada test assessment. Assuming, as a null hypothesis, that the polarity of the LI is random and thus equally likely to be positive or negative, then the probability that the LI would agree with the Wada test result by chance in all seven cases is $(1/2)^7$ or 0.0078.

Functional activation maps for each patient are illustrated in Fig. 2 (activation measured from one slice is depicted for every patient). For the four patients who were found to be left-dominant for language from the Wada test (Patients SL1–SL4, left side of Fig. 2), fMRI activation was predominantly found in the left inferior frontal gyrus (pars triangularis and pars orbitalis) as well as in neighbouring portions of the lateral orbital gyrus and posterior orbital gyrus. These regions correspond to Brodmann areas 45, 46 and 47. Significant activation was also observed in some pixels in the middle and superior frontal regions and in portions of the cingulate gyrus, but the distribution did not appear to be consistent

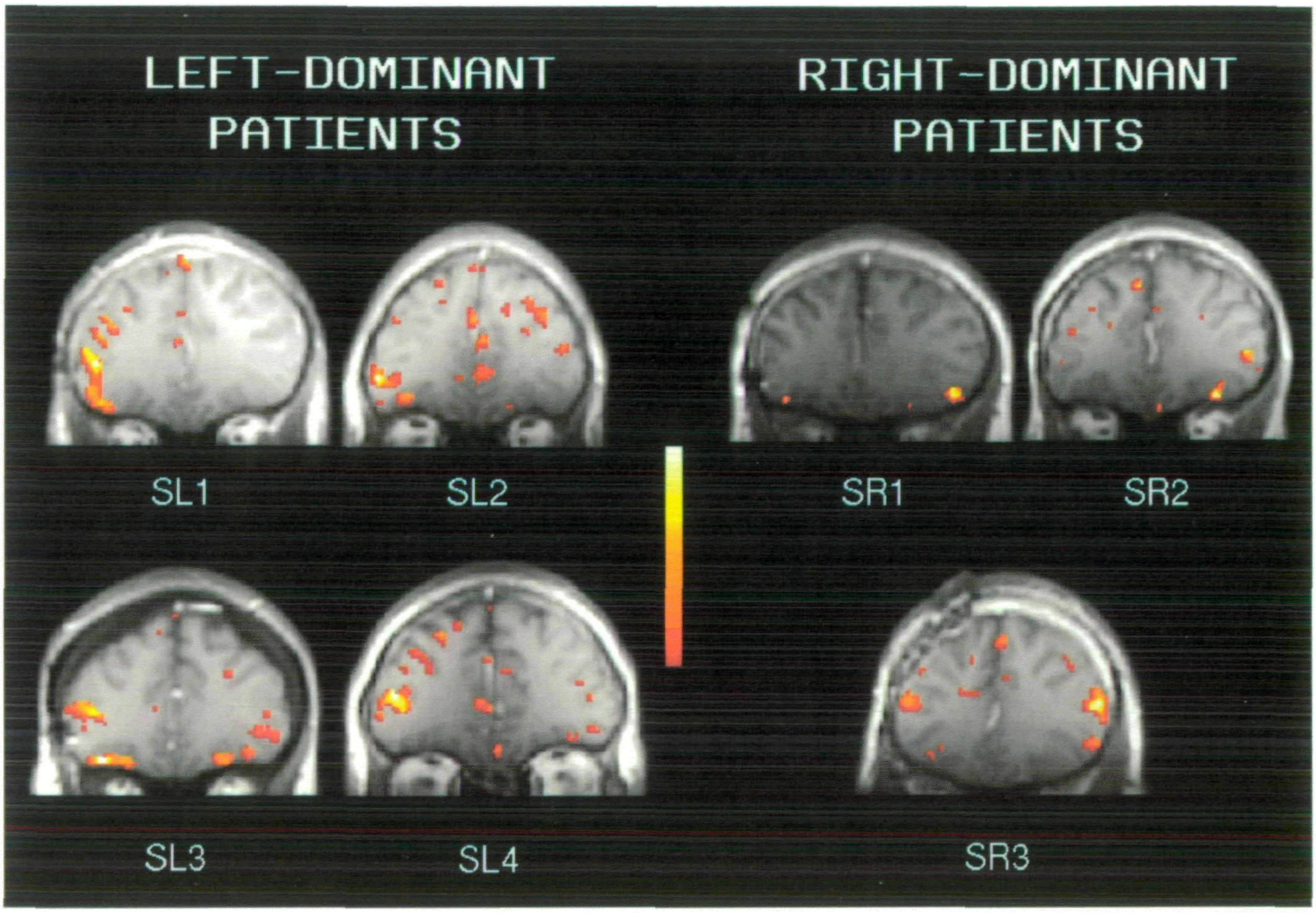

Fig. 2 Functional activation maps for each individual patient. Functional maps are normalized, and the colour scale represents correlation magnitudes that range from 0.152 (the threshold for statistical significance and appearing in dark red) to the maximum value for the slice (which, across the seven slices depicted in the figure, had a mean value of 0.43, SD = 0.12, and appears as bright yellow/white). The left side of the brain is depicted on the left side of the figure and the right side of the brain on the right of the figure.

across patients. Patient SL3 exhibited considerable activation in the right inferior frontal gyrus as well as on the left, but the magnitude of the activation was stronger on the left. For the three patients who were found to be right-hemisphere dominant for language (Patients SR1–SR3, right side of Fig. 2), a similar distribution of inferior frontal and orbital activation was observed, but the activity was concentrated on the right side. Patient SR3 exhibited bilateral activation in the inferior frontal gyrus, with greater magnitudes of activation on the right side. Interestingly, this patient did not exhibit a clear speech arrest when sodium amytal was administered to either hemisphere, although the presence of dysarthria and receptive aphasia after right-hemisphere administration resulted in his right-dominant classification. Compared with other patients, Patients SR1 and SR2 exhibited fewer significant pixels in their fMRI activation maps; however, consistent with their Wada test results, the pixels that were significant were largely distributed in the right inferior frontal regions.

Discussion

The results of this study suggest that hemispheric asymmetry in inferior frontal lobe activation observed when words are processed at a semantic rather than perceptual level depends on the side of language dominance. The laterality of language dominance, as assessed by fMRI activation, was consistent with that determined by Wada testing in each of the seven patients who participated in the study. The pattern of frontal lobe activation may therefore provide useful clinical information for patients requiring assessment of hemispheric language dominance. The measurements of functional activation were obtained using conventional magnetic resonance equipment available in most hospital settings and, thus, fMRI has the potential for offering a widely available and noninvasive alternative or supplement to Wada testing.

To date, the few studies investigating language lateralization in Wada-tested patients have reported successful language lateralization using a semantic monitoring task of aurally presented nouns (deciding whether animal names satisfied a semantic criterion; Binder *et al.*, 1995; Swanson *et al.*, 1995), and a verb-generation task for visually presented nouns (Pardo and Fox, 1993; Benson *et al.*, 1994). The verb-generation task, which was initially employed in PET investigations of language (Petersen *et al.*, 1988, 1989), requires the subject to produce an appropriate verb in response to a noun; e.g. saying 'EAT' in response to 'CAKE'. Like the semantic monitoring task (Binder *et al.*, 1995; Swanson *et al.*, 1995) and the semantic/perceptual processing task used in the present study, the verb-generation task involves semantic processing of words (Petersen and Fiez, 1993), results in superior recall of words (Tulving *et al.*, 1994), and consistently produces lateralized activation of inferior frontal regions (Petersen *et al.*, 1989; Benson *et al.*, 1994; Raichle *et al.*, 1994). Thus, either task could reasonably be employed in functional studies to elicit language-related activation. Methodologically, however, the semantic/perceptual processing task has the advantage of not requiring vocalized speech from the patient. Overt speech significantly increases the risk of introducing head motion artifacts in the data of fMRI experiments, a phenomenon which we encountered in preliminary studies and which has been noted by other investigators (Hinke *et al.*, 1993). An alternative procedure is to use covert (internal) speech in such tasks. In pilot studies we observed considerable loss of signal in tasks requiring covert speech, as have other investigators using 2.1 T magnets (McCarthy *et al.*, 1993). Larger magnetic field strengths may be advantageous for imaging covert-speech-generated brain activity, as successful functional imaging using internal speech has been reported at 4.0 T (Hinke *et al.*, 1993; Rueckert *et al.*, 1994). Nevertheless, tasks requiring covert speech have another disadvantage in that it is not possible to monitor the task performance of the patient. In contrast, performance during the semantic/perceptual task, as measured by squeeze ball presses (or other motor responses of the hand), can be readily monitored, thereby allowing for both the use of a bite-bar device to restrain head-motion and validation of the subject's performance during scanning.

The activation of the left inferior frontal gyrus observed for the left-language-dominant patients in the present study is consistent with results we obtained from healthy right-handed control subjects (Demb *et al.*, 1995; Gabrieli *et al.*, 1995), as well as with results obtained from PET studies (Kapur *et al.*, 1994). This similarity between patients and controls in the distribution of activity suggests that unilateral resection of temporal lobe structures, regardless of whether the resection is ipsilateral or contralateral to the side of language dominance, does not significantly influence the pattern of frontal lobe activation for this task. Moreover, in the one case in which fMRI testing occurred prior to surgical resection (Patient SL2), the presence of non-resected epileptic tissue in the left temporal lobe did not prevent the manifestation of correctly lateralized frontal lobe activation. However, further investigation of the effects of epileptic foci on fMRI measurements are needed as are prospective studies to assess the presurgical concordance of fMRI-derived lateralization with Wada test results. The present study measured functional activation only from patients with a history of temporal lobe epilepsy and, thus, further studies are needed to determine whether the same task and methods will be applicable if the foci originate in frontal lobes or other non-temporal regions.

By the nature of the experimental design used in the present study, semantic processing of words is implicated as a likely source of the observed increases in inferior frontal lobe activation of the language-dominant hemisphere. The type of stimuli presented to the subjects, the yes/no decision requirement, and the motor response requirement were identical during each semantic and perceptual half-cycle. The only essential difference between the two tasks was the differential requirement to access word meaning. Nevertheless, it could be argued that deciding the abstract/concrete nature of words is generally more difficult than deciding the case of the words, and that frontal lobe activation reflects this difference in task difficulty. Evidence from a previous study, however, suggests that frontal lobe activation does not simply reflect task difficulty (Demb *et al.*, 1995). A task design identical to the one described for the present study was employed except that the difficulty, as assessed by reaction times, of a different perceptual task (deciding whether the first letter of a word preceded or followed the last letter of the word alphabetically) was comparable to that of the semantic task. Again, we observed patterns of increasing frontal activation during semantic compared with perceptual processing that were nearly identical to those observed using the original upper-case/lower-case perceptual task, suggesting that frontal activation is more related to semantic processing rather than to task difficulty.

The role of the frontal lobes in semantic processing suggested by the present study is consistent with evidence obtained from different methodologies. For example, multiple-unit recordings from left inferior frontal regions obtained from a human neurosurgery patient revealed modulation of neuronal firing rates while the patient classified words as abstract or concrete (Abdullaev and Bechtereva, 1993). Such changes in neuronal activity underlie the metabolic increases and subsequent blood flow changes that are imaged with PET and fMRI. Semantic (living/non-living judgements) versus perceptual (detecting presence or absence of the letter 'a') processing has been shown to produce activation of left inferior frontal cortex (Brodmann areas 45, 46, 47 and 10) in PET investigations (Kapur *et al.*, 1994). Other tasks that tap semantic knowledge, e.g. generation of a meaningful verb in response to a noun or monitoring a sequence of words for names of dangerous animals, also produce similar patterns of activation in left inferior frontal gyrus in PET investigations (Petersen *et al.*, 1988), but some bilateral inferior frontal activation has been reported in an fMRI study of verb generation (McCarthy *et al.*, 1993).

A limitation of the present study is that we imaged only frontal regions of the brain. With regard to imaging semantic processing *per se*, this may be a minor limitation because

PET evidence indicates that only this region is more active during semantic than nonsemantic word processing (Kapur *et al.*, 1994). With regard to mapping the lateralization of verbal systems, imaging posterior cortical regions would be desirable because of their known importance for language. Such whole-brain imaging can be performed using echo-planar pulse sequences, but such sequences require gradients that are faster than those available on conventional scanners, and can be used presently in few locations. Spiral techniques are more efficient than Cartesian methods (10 'shots' can provide 128^2 resolution on conventional scanners) and offer reduced sensitivity to brain motion (Glover *et al.*, 1995). This efficiency can allow increased volume coverage, with further improvements extant when echo-planar type hardware is available. Whichever technique turns out to be more practical for clinical applications, comprehensive brain imaging can only be helpful in the noninvasive mapping of neural networks critical for language.

Although the present study has focused on the assessment of hemispheric language dominance, the Wada test is also routinely used to assess hemispheric memory competence. Thus, it is relevant to address whether the task and methods employed in the present study could be used to predict the memory component of the Wada test. Our fMRI studies are consistent with other reports that show that conditions that enhance memory for words produce activation of inferior frontal regions in the language-dominant hemisphere. These conditions include semantic versus non-semantic processing of words (Kapur *et al.*, 1994; Gabrieli *et al.*, 1995), generating words relative to reading words (Petersen *et al.*, 1988; Tulving *et al.*, 1994), and studying words with mild versus severe distraction (Shallice *et al.*, 1994). These findings suggest that inferior frontal cortex may contribute importantly to memory for words, and one would therefore expect that inactivation of this region by sodium amobarbital would consistently compromise memory for words.

The results of the present study, however, were inconsistent with this expectation. The fMRI activation for Patient SL1 was clearly in the left inferior frontal gyrus, in accordance with his Wada test results for language. However, when this patient received sodium amobarbital in the left internal carotid artery, presumably anaesthetizing neural networks in the left inferior frontal regions, his episodic memory performance was quite good, and he was able to recognize three out of three objects, two out of three words and three out of three designs with no false positives, suggesting that episodic memory encoding was intact without the contribution of these left inferior frontal networks. When injected on the right side, his memory performance was considerably worse for words and designs (three out of three objects, zero out of three words, zero out of three designs, with no false positives). Patient SL3 exhibited to a lesser degree a pattern of results similar to that of Patient SL1, with recognition performance of one out of three words with no false positives, three out of three objects with one false positive, and three out of three designs with two false positives after left carotid injection. Performance after right carotid injection was zero out of three words with no false positives, two out of three objects with no false positives, and zero out of three designs with one false positive.

From a clinical perspective, the differential hemispheric lateralization of language and memory for Patients SL1 and SL3 reveals the specificity of the fMRI-derived measure of lateralization. The Wada test in both of these cases indicated left-hemisphere dominance for language and right-hemisphere dominance for memory; the fMRI LI for both patients indicated greater activation of left compared with right inferior frontal regions. These results suggest that the fMRI activation for the task used in the present study is more predictive of the hemispheric language assessment of the Wada test than the assessment of hemispheric memory competence. Because evaluation of memory as well as language functions is needed for surgical planning, tasks and methods that produce functional activation predictive of memory functions will need to be developed before fMRI can completely replace the Wada test.

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