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Functional MRI of memory in the hippocampus: Laterality indices may be more meaningful if calculated from whole voxel distributions

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Lateralization of memory by functional MRI (fMRI) may be helpful for surgical planning related to the medial temporal lobe (MTL). Most fMRI memory studies have calculated lateralization indices (LI) in the MTL from suprathreshold voxels only, but the selection of threshold remains highly arbitrary. We hypothesized that LIs could be reliably extracted from the distribution of voxels encompassing all positive *T* statistical values, each weighted by their own statistical significance. We also hypothesized that patient LIs that are two or more standard deviations (SD) away from the control group mean LI may be more clinically relevant than LIs that are not compared to control group. Thirteen healthy subjects had memory fMRI, and five epilepsy patients had both fMRI and the intracarotid amobarbital procedure (IAP). The fMRI task consisted of encoding patterns, scenes, and words. We found that normal subjects' LIs extracted from whole weighted statistical distributions tended to lateralize to the left for words, to the right for patterns, and intermediately for scenes, consistent with previous research. Weighted LIs were less variable than those calculated from suprathreshold voxels only. Using this approach, all patients had fMRI memory lateralizations consistent with IAP results. The weighted LIs provided a more clear-cut distinction of patients from the normal group (in terms of SDs from the group mean) than the suprathreshold voxel count approach. Our results suggest that using weighted distributions can be a useful strategy for assessing memory lateralization by fMRI in the MTL.

Keywords: Memory; MTL; fMRI; Epilepsy; Neurosurgery

Introduction

The medial temporal lobes (MTLs) are essential for encoding and retrieval processes of declarative memory (Scoville and Milner, 1957; Squire, 1992; Eichenbaum, 2000). Because the MTL is a frequent seizure focus in medically refractory epilepsy, well-selected patients may find relief from seizures through surgical resection of the diseased MTL. However, understanding the relative contributions of the two MTLs, particularly the competency of the contralateral MTL, in supporting memory is essential before undertaking such resective surgery in order to avoid post-operative memory deficits. Therefore, pre-operative memory testing is routinely performed at most epilepsy centers in order to identify the dominant MTL of each patient. Measures of memory lateralization can help physicians to assess the functional reserve on both sides and thus decide whether to proceed with surgery and perhaps how far to extend the resection (Akanuma et al., 2003).

Traditionally, the intracarotid amobarbital procedure (IAP or Wada test) has been employed for memory lateralization (Wada and Rasmussen, 1960; Milner et al., 1962). The IAP consists of the injection of sodium amobarbital, an anesthetic, into the internal carotid artery, causing a temporary deactivation of the ipsilateral hemisphere. During hemispheric inactivity, neuropsychological testing is performed to determine cognitive functions supported by the contralateral side. The IAP was originally developed to determine language lateralization but is commonly used for memory lateralization as well. As a test of memory lateralization, however, the IAP is flawed in several ways: it has poor spatial and temporal resolution; it is not clear whether it directly deactivates or simply deafferentiates the MTL structures (particularly the posterior MTL regions perfused by the posterior circulation; Jack et al., 1989); it is not readily repeatable (Simkins-Bullock, 2000); and it is invasive (carrying risk related to the catheterization; Dion et al., 1987). Nevertheless, because the IAP simulates the effects of

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actual surgical ablation and has a long track record, it is considered the gold standard pre-operative technique for assessment of memory lateralization (Akanuma et al., 2003).

More recently, functional neuroimaging techniques such as [^{18}F]fluorodeoxy-glucose positron emission tomography and functional MRI (fMRI) have been evaluated as potential substitutes for the IAP (Akanuma et al., 2003). Functional MRI is particularly promising as a technique to assess memory function because it is non-invasive, has very good spatial resolution, is easily repeatable, and permits the study of multiple brain functions. Its capacity to identify activations in the MTLs during memory encoding has been demonstrated in normal subjects (Stern et al., 1996; Gabrieli et al., 1997; Kelley et al., 1998; Dolan and Fletcher, 1999; Martin, 1999; Schacter and Wagner, 1999; Golby et al., 2001), as well as in epilepsy patients (Bellgowan et al., 1998; Detre et al., 1998; Killgore et al., 1999; Dupont et al., 2000; Jokeit et al., 2001; Deblaere et al., 2002; Golby et al., 2002; Richardson et al., 2003). Despite these strengths, there are a number of unresolved issues with the use of fMRI to determine memory lateralization. One issue is how to set the threshold for generation of activation maps. Most studies that have used fMRI for clinical mapping of memory followed the standard approach of arbitrarily selecting a *P* value, which varied from 0.00003 to 0.01 (Bellgowan et al., 1998; Detre et al., 1998; Killgore et al., 1999; Dupont et al., 2000; Jokeit et al., 2001; Deblaere et al., 2002; Golby et al., 2002; Richardson et al., 2003). Because fMRI research relies largely on activation maps, no study on memory has used weakly activated voxels, which may still be useful, considering that the thresholds are chosen arbitrarily. This might be particularly important for the MTL region, which generally shows weak activation with memory tasks because of local susceptibility artifacts (Glover and Law, 2001) and because the MTL region is believed to be continuously active (Buckner et al., 2001), leading to small relative changes in the level of neural activity between task and control conditions, as well as other possible reasons.

Weak activation results in statistical parametric *T* maps (SPTM) that contain voxels with low *T* values. Because laterality indices (LI) are traditionally calculated from above-threshold voxels only, MTL LIs cannot be estimated at high thresholds in many cases because there may be very few or even no voxels above the threshold. In addition, thresholds that yield approximately equivalent numbers of activated voxels vary from subject to subject. A given subject may lateralize to either side depending upon the threshold selected, further complicating the problem of arbitrarily selecting thresholds and comparing LIs calculated for different subjects at the same threshold. Some fMRI studies have tried to apply lower thresholds in order to include less significant voxels into the LI calculation, and thus get activations for a greater number of subjects, but few have explored the use of threshold-independent methodologies (Nagata et al., 2001). This is partly a consequence of the fact that LI calculations have been primarily performed to evaluate lateralization of language functions (Desmond et al., 1995; Binder et al., 1996; Springer et al., 1999; Deblaere et al., 2002; Rutten et al., 2002; Adcock et al., 2003; Sabbah et al., 2003), which tend to involve widespread regions of activation and typically result in higher signal-to-noise characteristics. Also, because there is a relatively large number of highly activated voxels in these regions, a simple voxel count (VxCt) procedure is usually sufficient to identify the dominant side. MTL regions, however, are small and memory lateralization actually varies depending upon several variables such as the verbalizability of the encoded stimuli (Golby et al., 2001) and the nature of the memory task. We thus hypothesize that MTL lateralizations extracted from the entire distribution of voxels at all *T* statistical values, each weighted by their statistical significance, may be more consistent than those calculated by simply comparing the activated voxels above an arbitrary threshold.

Another relevant issue that has been rarely discussed in the literature is the quantitative comparison of LIs from clinical populations to those from healthy subjects. Although it is possible to calculate LIs from the IAP, most centers report IAP results in a qualitative way (left, right, or bilateral) because IAP memory scores are based on a limited number of trials and stimuli. Functional MRI, however, allows the calculation of a much wider range of numerical LI values that can be compared against a mean from a population. A left dominant IAP result, for example, may ascertain hemispheric dominance, but it says little about how that particular patient compares to the degree of left dominance in a healthy population. We hypothesize that a patient's memory fMRI lateralization that is two or more standard deviations (SD) away from the mean of a control group may carry more clinical significance for pre-surgical evaluation.

In this study, we focused specifically on the anterior hippocampus (AHC) because medial temporal lobectomy most usually includes the anterior MTL, but not the more posterior MTL regions. Clinical evidence from such resections suggests that the anterior hippocampus is critical for successful memory encoding, but many fMRI studies have shown activations to be more intense in the posterior hippocampus (Stern et al., 1996; Detre et al., 1998; Kelley et al., 1998; Dupont et al., 2000; Kirchhoff et al., 2000; Golby et al., 2001; Powell et al., 2005). Whether this is secondary to weak fMRI signal in the AHC, leading to a predominance of weakly activated voxels, or to smoothing of highly activated areas posterior to the MTL, such as the fusiform and lingual gyri, is still unclear. We thus compared fMRI lateralization during an encoding task in the AHC of normal subjects calculated using the standard VxCt approach with those calculated from weighted whole voxel distributions in an attempt to find a stronger correlation between fMRI and clinical findings. We tested three types of weighting factors: one method using *T* statistics and two methods using *P* statistics. In order to find out which method would be more consistent (less variable), we used the SD in a healthy control population as an indicator of variability. To validate our approach, we selected five patients for whom memory lateralization was previously ascertained by bilateral IAP and evaluated to what extent fMRI LIs in these patients, calculated by these different methods, could be differentiated from the normal subjects' LI mean.

Materials and methods

Subjects

Thirteen healthy right-handed native English-speaking volunteers (7 female, 6 male, mean age 23.6 years) and five MTL epilepsy patients were enrolled in the study. The patients were selected because they had a bilateral IAP, required in order to calculate an IAP LI. The patients were selected from a cohort of eight patients that had both IAP and memory fMRI. Three were excluded because IAP was performed only unilaterally. Clinical data on patients are presented in Table 1. This study was approved

Table 1
Clinical data for patients

Patient	Gender	Age	Handedness	History	Structural MRI	EEG	IAP language	IAP memory lateralization	IAP free recall scores		IAP recognition scores		fMRI memory lateralization	fMRI memory recognition performance		
									R hemisphere injection	L hemisphere injection	R hemisphere injection	L hemisphere injection		Patterns	Scenes	Words
1	F	34	Right	Epilepsy onset at the age of 32	Normal	Epileptogenic activity in right temporal lobe	N/A	L >> RLI_{IAP} = +0.4	3/8	0/8	7/8	3/8	Left	15	2	17
2	M	43	Right	Epilepsy onset at the age of 1 following traumatic brain injury	Lesion of left hippocampus and amygdala	N/A	Left	R >> L LI_{IAP} = −0.2	0/8	1/8	4/8	6/8	Clearly right	30	33	35
3	F	49	Left	Medically intractable MTL epilepsy	Normal	Epileptogenic activity in left temporal lobe	Left	Failed test. Left slightly better LI_{IAP} = +0.33	0/8	1/8	4/8	2/8	Right	26	27	32
4	F	50	Right	Medically intractable MTL epilepsy	Normal	Left greater than right bilateral theta with sharp components	Left	Failed test. Left slightly better LI_{IAP} = +0.14	0/8	0/8	4/8	3/8	Inconclusive	30	23	34
5	M	27	Right	Epilepsy onset at the age of 10 months in the context of febrile illness	Left medial temporal sclerosis	Normal	Left	R >> L LI_{IAP} = −0.2	0/8	1/8	2/8	3/8	Clearly right	N/A		

Note that the IAP memory lateralization is not only determined by IAP scores, but also by other observations during the procedure, such as the details recalled concerning the procedure before and during the phase of injection. For fMRI memory recognition performance, values indicate the number of remembered stimuli (of 44 presented). Note poor performance in patient 1.

by the Partners' Institutional Review Board and informed consent was obtained from all subjects.

Functional MRI

Behavioral paradigm

The behavioral task was designed to demonstrate encoding effects in the MTL. During each run, subjects performed 88 trials in an event-related paradigm in which 44 stimuli were presented only once (novel) and 2 stimuli were presented 22 times each (repeated). Three different runs were performed by each subject, one for each stimulus modality – patterns, scenes, and words – in an attempt to systematically vary the verbalizability of the material to be encoded (Golby et al., 2001). Stimuli in each run were comprised of half from each of two different categories: words were concrete or abstract; scenes, indoor or outdoor; and patterns, regular or irregular. Subjects were instructed to indicate by button push the category to which the stimuli belonged. Each stimulus was presented through MRI-compatible video goggles (Resonance Technology, Los Angeles, CA) for 2000 ms. Interstimulus interval (ISI) varied randomly and continuously from 1000 to 1500 ms. The order of stimuli type (i.e., novel or repeated) in each run was also randomized, as was the order of the runs. A custom stimulus presentation program based on the Python Experiment Programming Library (Computational Memory Lab, University of Pennsylvania, Philadelphia, PA) for Linux was used for both stimulus presentation and recording of behavioral responses.

After the fMRI scanning, both patients and normal subjects were submitted to a recognition memory test, in which the same 44 novel stimuli were randomly presented along with 44 other distractor images. Subjects indicated whether each image had been previously presented during the fMRI session. We recorded the number of successfully remembered stimuli for each material type.

Image acquisition

MR images were acquired with a GE Signa 3T Excite VH3 HR1 system (Milwaukee, WI). A standard birdcage head coil was used and foam padding was placed around the head to minimize movement. Whole-brain functional imaging was performed using a single-interleave gradient-echo spiral pulse sequence (Glover and Lai, 1998), imaging 29 contiguous axial slices (5 mm thickness) at 2 s per image volume. In-plane spatial resolution was 3.75 mm; TR = 2000 ms (no gaps in between volumes); TE = 40 ms; 68° flip angle; 24 cm field of view; 64 × 64 matrix acquisition. T2-weighted spin-echo images were acquired for all slices that received functional scans (matrix = 512 × 512). A volumetric T1-weighted magnetization prepared rapid gradient echo (MPRAGE) acquisition was also acquired to provide a high resolution anatomic reference frame (matrix = 256 × 256) for subsequent overlay of functional activations.

Data analysis

Following image reconstruction, motion correction was performed using the SPM2 (Statistical Parametric Mapping) software package (Wellcome Department of Imaging Neuroscience, London, UK). Normalization to the Montreal Neurological Institute (MNI) space was performed in all subjects, including patients, in order to allow region of interest (ROI) analysis. Because lesions were subtle and restricted to the MTL, we believe patient data were not corrupted by normalization. Smoothing was applied using an 8-mm Gaussian kernel. Stimulus onset vectors for novel and repeated stimuli were automatically generated by the presentation program. At the first-level, trial-specific responses in each run were modeled, in an event-related design (Friston et al., 1998), by convolving delta functions for each event onset with the canonical hemodynamic response function (HRF) to create regressors "novel" and "repeated". Time and dispersion derivatives were applied. A covariate was included to handle the first appearance of each repeated image because they actually functioned as novel images. Moreover, for each subject, patterns, scenes, and words were also jointly analyzed using a first-level (within subject) fixed-effects (between materials) approach (FFX). For each of these models (both individual runs and FFX), an image corresponding to the "novel > repeated" contrast was produced. These images were used for second-level random-effects (RFX) analysis.

ROI analysis was focused on the AHC exclusively, and this ROI consisted of the anterior half of the hippocampal ROI supplied by the WFU PickAtlas (Department of Radiologic Sciences, Wake Forrest University, Winston-Salem) (Maldjian et al., 2003, 2004). This ROI contained 497 voxels on the left and 465 on the right. Other MTL regions such as amygdala and parahippocampal regions were not included.

LI calculation

We performed LI calculations in two ways: (i) by the standard VxCt procedure, in which we simply counted activated voxels above a certain threshold; and (ii) by measuring the area under statistically weighted voxel distributions (e.g., by either T or P statistics), where only voxels that had positive T values, and were thus positively correlated with the behavioral task, were included in the calculation.

Voxel count at $P \leq 0.1$ (VxCt10)

For lateralization based on simple VxCt, we set a threshold at a $P = 0.1$, which corresponds with a T of approximately 1.3 for 141 degrees of freedom (*df*—the number of *df* was calculated specifically for our design matrix by SPM2). We chose this relatively lenient threshold because of the low signal obtained from the MTL region. To calculate VxCt LI, we used the standard formula

$$\mathrm{LI} = (\mathrm{Lvx} - \mathrm{Rvx})/(\mathrm{Lvx} + \mathrm{RVx}), \quad (1)$$

where LI is the laterality index, Lvx is the number of suprathreshold voxels in the ROI on the left side, and Rvx is the number of suprathreshold voxels on the right.

Activation patterns were examined by graphing the voxel distribution (Fig. 1a).

Weighted LIs

The VxCt10 method described above is equivalent to comparing the areas under those segments of the left and right voxel distribution curves that contain voxels with P values lower than 0.1 (or $1 - P$ values greater than 0.9, or T values greater than 1.3). Those segments are represented to the right of the vertical bar in Fig. 1a, which contains sample data for the purpose of illustrating the technique. By visual inspection of the figure, it is possible to note that VxCt10 lateralization is to the left (greater area under left curve); on the other hand, a threshold arbitrarily set to $T = 2.2$ would yield a lateralization to the right. This is not an uncommon situation that illustrates how subjective and potentially misleading an arbitrary choice of threshold setting can be for LI analysis.

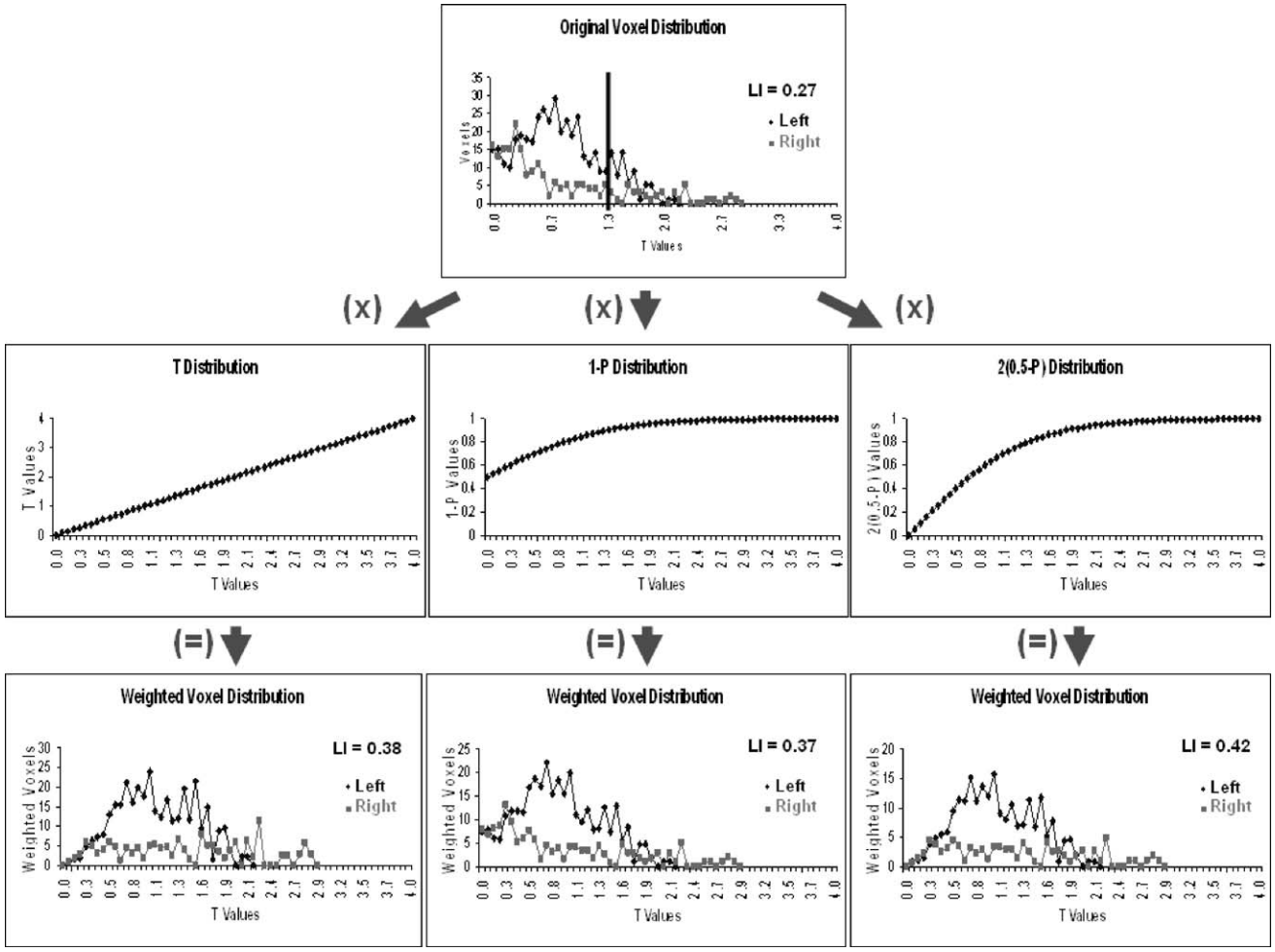

Fig. 1. Calculation of weighted LIs. Row a contains a histogram of voxels activated in the anterior hippocampus region of interest (ROI). The bar indicates $P = 0.1$ ($T \sim 1.3$). VxCt10 laterality indices (LIs) can be extracted from the areas under the curves to the right of this bar (LI = 0.27). Second row graphs contain statistical distributions. The first graph contains T values ranging from 0 to +4; the second, $1 - P$ values ranging from 0.5 to 1, and the third, $2(0.5 - P)$ values ranging from 0 to 1. Third row is the result of the component-wise multiplication of the first by the second row graphs. The LIs are calculated directly from the total areas under the right and left curves of the third row graphs, resulting in left-lateralized LIs equal to 0.38, 0.37, and 0.42, respectively, for the first, second, and third graphs. Data presented in this figure were originated from random-effects analysis for words.

To avoid arbitrarily selecting individual thresholds, we instead made use of the entire range of distribution curves that contained voxels with positive T values (voxels that were positively correlated with contrast "novel > repeated"). However, because the likelihood of falsely activated voxels is inversely proportional to their statistical significance, we weighted the curves by their significance at each point. This was done by simply multiplying the voxel distribution curves by a statistical distribution.

Three statistical distributions were used: T, $1 - P$, and $2(0.5 - P)$ (Fig. 1, second row). T values are a measure of statistical significance and indicate how well correlated the fMRI signal in each voxel is with the stimulus paradigm. When considering probabilities of being true, $1 - P$ values have the significance of indicating the likelihood that a particular voxel represents a true positive activation. However, the $1 - P$ distribution does not suppress the noisier, lower portion of the voxel distribution (Fig. 1, third row). So a variation, the $2(0.5 - P)$ distribution, was used in an attempt to correct this problem. Therefore, we calculated three weighted LIs: Tw (weighted by the T distribution), Pw (weighted by the $1 - P$ distribution), and Pw2 (weighted by the $2(0.5 - P)$ distribution). In our study, we used voxels whose T values ranged from 0 to 6 because no activated voxels with T values greater than 6 was found in the anterior hippocampal ROI in our sample (equivalent $1 - P$ values ranged from 0.5 to 1 and equivalent $2(0.5 - P)$ values ranged from 0 to 1). For RFX analysis, T values ranged from 0 to 8 due to stronger activations (equivalent $1 - P$ and $2(0.5 - P)$ ranges remained the same). A total of 120 sample points were measured for each SPTM at T increments of 0.05. LIs were then calculated from the areas under both the right and the left activation curves (Fig. 1, third row) by the formula:

$$\mathrm{LI} = (\mathrm{LA} - \mathrm{RA})/(\mathrm{LA} + \mathrm{RA}), \quad (2)$$

where LA is the area under the weighted curve for the left ROI and RA is the area under the weighted curve for the right ROI. This formula renders positive values for left lateralizations and negative values for right ones.

The lateralizations calculated by the four different approaches (one based on VxCt and three weighted) for the three types of materials were analyzed with a 4 (LI method) × 3 (material type) repeated measures ANOVA (using restricted maximum likelihood

(REML) to account for the unbalanced design originated from the null VxCt values), and post hoc comparisons were made with paired *t*-tests.

Intracarotid amytal procedure

In patients undergoing IAP, each hemisphere was separately injected with 112.5 mg sodium amytal. After drug effect was confirmed, hemispheric memory dominance was assessed by presenting the patients with 8 objects. After return of EEG and neurologic examination to baseline, a recognition memory test was performed. The 8 previously presented target items were then randomly presented along with similar distractor objects. An IAP LI (LI_{IAP}) was calculated by the following formula:

$$LI_{IAP} = (ROL - ROR)/(ROL + ROR) \quad (3)$$

where ROL is the number of objects remembered that were presented during testing using the left hemisphere (right injection), and ROR is the number of objects remembered that were presented during testing using the right hemisphere (left injection).

The neuropsychologists who reported IAP results were blind to the fMRI data and the researchers who calculated the fMRI LIs were blind to the IAP results.

Results

Fig. 2 depicts within the anterior hippocampal ROI first-level activations in a healthy subject during scenes encoding and second-level activations for the combined effect of patterns, scenes, and words from the whole normal group.

Healthy subjects

In our data set, 31% of AHC voxel distributions produced lateralization to both sides depending upon the selected threshold. For VxCt10, which used a rather lenient threshold ($P = 0.1$), 8.3% of normal subjects did not have activated voxels in the AHC ROI for scene encoding, 25% for patterns, and 30.7% for words.

Fig. 3 presents LIs for 13 normal subjects obtained from single-subject, single-run, first-level analysis using the four techniques (VxCt10, Tw, Pw, and Pw2). Fig. 4 depicts the average LIs for each technique and stimulus modality. LIs differed across the different materials [$F(2,114) = 9.41$, $P < 0.0005$] and techniques [$F(3,111) = 4.74$, $P < 0.005$]. For all techniques, the average LIs for patterns, words, and scenes were concordant with previous reports (Martin, 1999; Golby et al., 2001); that is, patterns tended to lateralize to the right (−0.45, −0.13, −0.07, −0.11, respectively, for VxCt10, Tw, Pw, and Pw2), words to the left (−0.07, 0.21, 0.17, 0.20, respectively, for VxCt10, Tw, Pw, and Pw2), and scenes intermediately (−0.25, 0.05, 0.09, 0.04, respectively, for VxCt10, Tw, Pw, and Pw2). Despite a slight lateralization of words to the right using VxCt10, lateralization within each of the four analysis approaches still followed this same overall pattern, with lateralization of scenes in between patterns (which were most right lateralized) and words (which were most left lateralized). Words differed significantly from patterns [$t(92) = 3.37$, $P < 0.005$], and there was a trend for the difference between patterns and scenes ($P = 0.064$) and for scenes and words ($P = 0.077$). At the level of individual subject LIs, the VxCt10 method produced stronger lateralizations, although they were also the most variable among subjects, encompassing the entire range from −1 to +1. The weighted distributions, because they included greater numbers of less significant voxels, produced smaller lateralizations, but variability within the group decreased noticeably compared to VxCt10 (SDs ranged from 0.60 to 0.71 for VxCt10, from 0.26 to 0.38 for Tw, from 0.23 to 0.33 for Pw, and from 0.25 to 0.37 for Pw2). All weighted LIs differed significantly from VxCt10 – Pw vs. VxCt10: [$t(65) = 2.62$, $P < 0.05$]; Tw vs. VxCt10: [$t(65) = 2.34$, $P < 0.05$]; Pw2 vs. VxCt10: [$t(65) = 2.37$, $P < 0.05$] – but were not significantly different from one another.

FFX analysis (Fig. 4) allowed for the estimation of laterality indices that included the three material types combined. The LI

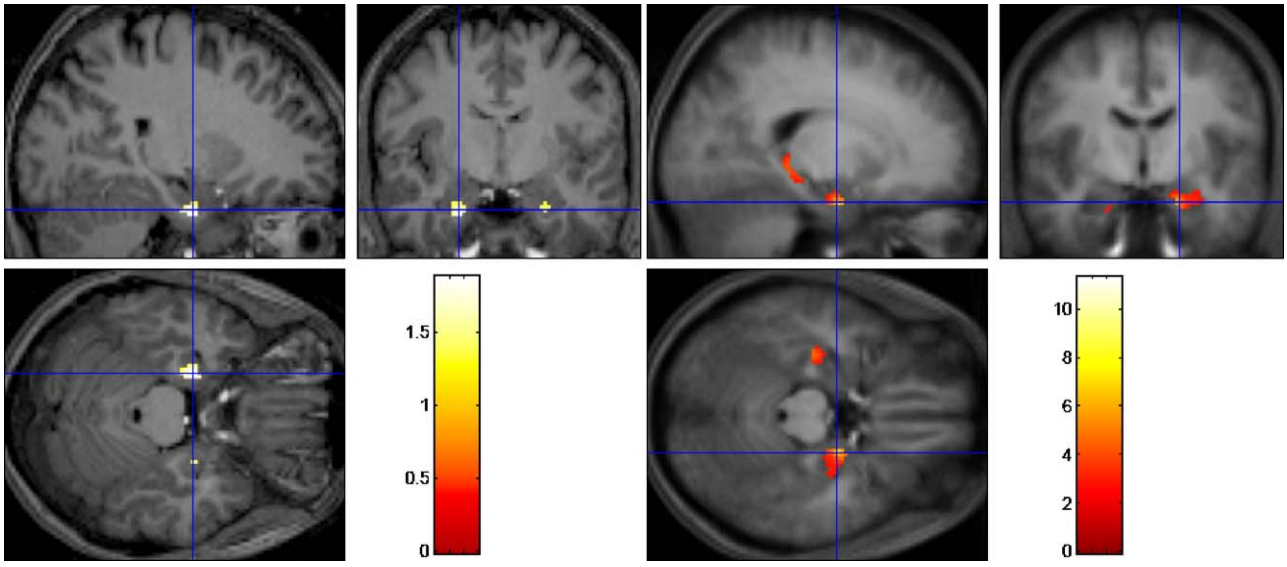

Fig. 2. Activations in the anterior hippocampus. Left panel: activations of a healthy subject encoding scenes overlaid on subject's own structural T1 image. Crosshairs indicate stronger activations on the right hippocampus. Right panel: random-effects activations for the combined effect of patterns, scenes, and words encoding overlaid on average T1 image obtained from all subjects. Crosshairs indicate stronger activations on the left hippocampus.

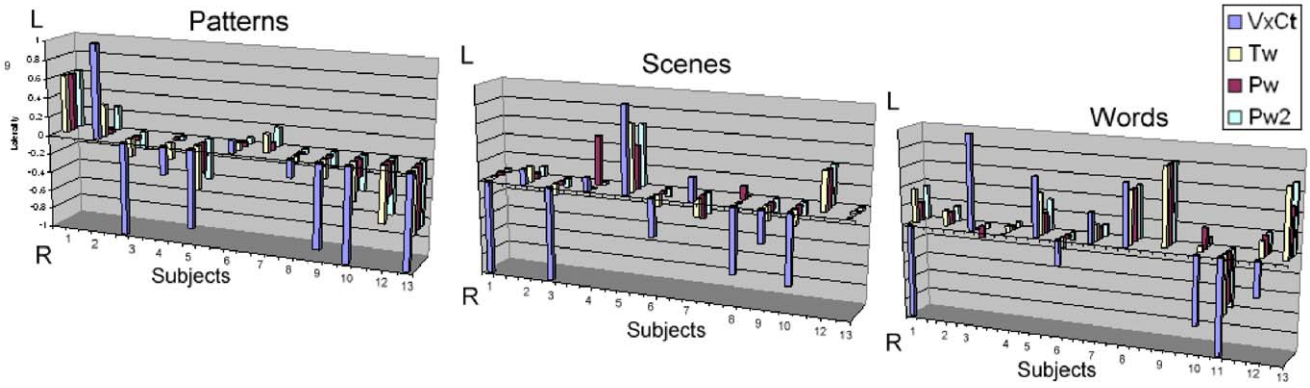

Fig. 3. Laterality indices in the normal subjects for patterns, scenes, and words. The 4 techniques used to estimate LIs are presented. Note the overall tendency of lateralization to the right for patterns, to the left for words, and intermediately for scenes. Also note that the blue bars indicating LIs obtained with the VxCt10 technique are usually bigger and can indicate opposite lateralizations if compared to the weighted LIs.

means (and SDs) produced by FFX analysis using VxCt10, Tw, Pw, and Pw2 were 0.18 ± 0.56, 0.10 ± 0.22, 0.06 ± 0.14, and 0.09 ± 0.19, respectively.

Second-level RFX analysis was performed for patterns, scenes, words, and the combination of the three material types. LIs obtained from RFX analysis are displayed in Table 2.

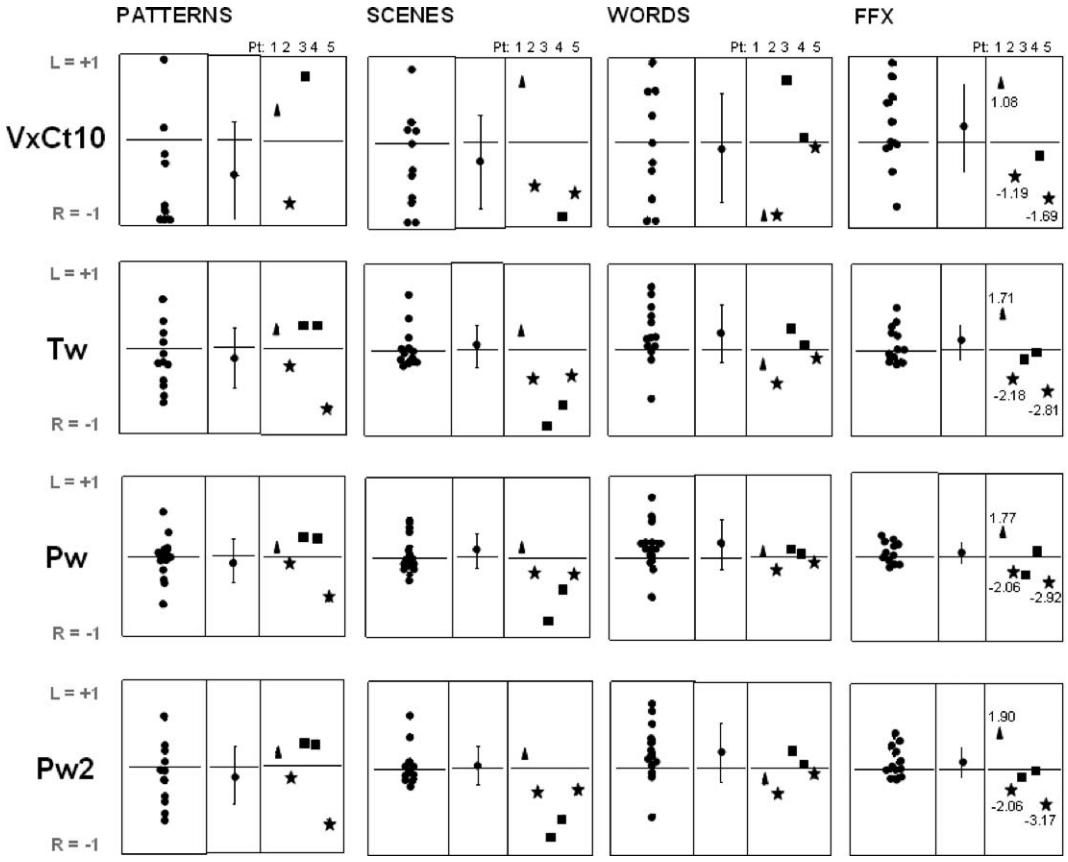

Fig. 4. Laterality indices in all subjects for patterns, scenes, and words (individually) and all modalities combined (FFX) (columns), calculated with four different techniques (rows). The left part of each graph represents the individual laterality indices for each control (dots); the middle, the group mean laterality index (LI_m); and the right, the individual laterality indices for patients. Patients identified by a star had a right-lateralizing IAP and lesion in the left MTL; patient identified by a triangle had a clear IAP to the left and normal MRI; and patients identified by squares had a slightly left-lateralizing IAP and normal MRI. Points above *x* axis indicate left lateralization, and points below indicate right lateralization. Bars represent one standard deviation (SD). Note the decrease in LI variability (SD) when either of the weighted techniques is used compared to that when the simple suprathreshold voxel count methodology is used. Also note that the weighted techniques preserve the overall distribution of lateralization obtained by using VxCt10, but with less variability. The numbers adjacent to patients 1, 2, and 5 (which had clear IAP results) on the FFX column indicate the difference in SDs from the healthy group's average. Note that when using either of the weighted techniques, there is a better basis for differentiating the patients from the healthy population's mean laterality—this is mainly due to decreased inter-subject variability in the control group compared to simple suprathreshold voxel count methodologies. It is also noteworthy that the combined effect of patterns, scenes, and words is much better in differentiating patients from the normal group than any of the material types independently.

Table 2
Laterality indices obtained from random-effects (RFX) analysis in healthy subjects

	Patterns	Scenes	Words	FFX analysis across materials
VxCt10	−0.05435	−0.06852	0.271186	0.027545
Tw	−0.03461	0.033	0.382604	0.072973
Pw	−0.0344	−0.00901	0.365937	0.007793
Pw2	−0.03738	−0.03023	0.423085	0.011701

Using all analytical methods, there is a continuum of lateralization from right to left for patterns, scenes, and words. FFX analysis across materials in the healthy subjects is slightly to the left.

During the post-scan recognition session, words were significantly better recollected than both patterns [$t(23) = 2.85$, $P < 0.005$] and scenes [$t(23) = 3.92$, $P < 0.0\ 005$]. The average number of correct hits and their SDs for patterns, scenes, and words were, respectively, 27.5 ± 10.62, 25.33 ± 10, and 34 ± 9.47.

Patients

IAP memory lateralization was clearly to the right in two patients (patients 2 and 5) and to the left in one (patient 1). In the other two (patients 3 and 4), IAP memory lateralization was inconclusive and slightly to the left (Table 1). Only the two patients with right lateralizing IAPs had lesions in the MTLs (on the left). Functional MRI lateralizations for patients are presented in Fig. 4 and compared to the control group in terms of standard deviations (SD) from the normal group mean.

In the two patients with right-lateralizing IAPs and lesions in the left MTL, all LI techniques produced right lateralizations for the three stimulus modalities, the VxCt10 tending to yield the strongest lateralizations, but also having a stronger tendency of yielding no activation at all, as happened in patient 5 for patterns (due to no activated voxels below $P = 0.1$). Also, VxCt10 was the only technique to produce a lateralization to the left of the group mean (words in patient 5), although we would expect it to be to the right of the mean (given IAP and structural MRI results). FFX analysis for patterns, scenes, and words combined also produced lateralizations to the right using all four techniques. In both patients, the distance (in terms of SD) between their LIs and the group mean LI was clearly larger when we used the weighted distributions. The largest distances for patient 2 were found using VxCt10 (−0.57), Tw (−1.56), Tw (−1.71), and Pw2 (−2.06), respectively, for patterns, scenes, words, and FFX. For patient 5, they were found at Pw (−1.93), Tw (−1.57), Pw2 (−0.77), and Pw2 (−3.17). Only the weighted techniques yielded deviations greater than 2 SDs, which happened when the three material types were conjointly analyzed (FFX).

Patient 1, who had a clearly left-lateralizing IAP, but no lesion on MRI, had lateralizations for patterns and scenes greater than 1 SD from the control group mean for VxCt only (1.19 and 1.72 SDs, respectively). All weighted distributions presented lateralization to the left of the mean, but smaller than 1 SD (excepting Tw for patterns, which yielded an LI of 1.03 SD). As for words, this patient's lateralization was unexpectedly to the right of the control group mean, with VxCt yielding again an LI greater than 1 SD (−1.3). FFX analysis, however, correctly resulted in LIs to left of the group average LI, with Pw2 yielding the most robust differentiation (1.90 SD).

On FFX analysis for patient 3, who had an inconclusive IAP, lateralizations deviated to the right of the control group mean for weighted techniques (SD = −1.07, −1.98, −1.24, respectively, for Tw, Pw and Pw2) whereas VxCt10 was not able to yield an LI. This patient also had epileptic activity from the left MTL on EEG. For the other patient with inconclusive IAP (patient 4), deviations on FFX were −0.66, −0.55, +0.08, and −0.42, respectively, for VxCt10, Tw, Pw, and Pw2. This patient had bilateral abnormal EEG activity in the MTL, greater on the left.

Memory performance during the fMRI recognition run for patients 1–4 is presented in Table 1. It was not possible to perform the recognition task for patient 5.

Discussion

A good technique for calculation of LIs should produce robust results (that do not vary with parameters such as threshold), should permit consistent inter-subject comparison, and should be reproducible (Nagata et al., 2001). The methodology of weighted distributions described here was primarily developed to improve robustness and consistency, as we did not want to rely on specific thresholds to calculate LIs, and we sought to differentiate patients from healthy subjects. Importantly, whereas it can be difficult to obtain robust fMRI results from single subjects (and patients in particular) and from the MTL, we were able to demonstrate that this methodology produced results that consistently agreed with IAP lateralizations in patients—the clinical gold standard.

LIs calculated from weighted distributions were more consistent, with standard deviations in the control group approximately 50% smaller than those using VxCt10. Moreover, the weighted distributions were able do identify deviations greater than 2 SDs using FFX analysis for the two patients with clearly right-lateralizing IAPs and lesions in the left MTL, whereas VxCt10 deviations remained smaller than 2 SDs. For patterns in patient 5, despite no activated voxels below $P = 0.1$, the weighted distributions were all able to extract a correct lateralization from the remaining voxels, and it also showed this lateralization to be more than one SD from the control group's mean LI (Fig. 4). This finding demonstrates that weighted distributions can produce more robust lateralizations even when there are small numbers of activated voxels in the ROIs. LIs calculated this way are also independent of arbitrary threshold setting.

Whereas this approach may be very successful, we do not suggest that using whole voxel distributions is adequate for situations other then laterality assessment (such as the elaboration of activation maps), as these voxels would hardly produce meaningful activation maps. Nevertheless, weighting voxels by their statistical significance and subsequently utilizing the distribution for comparison across the cerebral hemispheres result in an adequate estimation of laterality consistent with IAP testing results.

Naturally, LIs calculated using whole voxel distributions will tend to approach zero as we also incorporate poorly activated voxels (as illustrated in our results). However, this effect tends to make the resulting LIs more homogeneous across subjects, and thus more consistent. A patient's LI that is clearly different from the mean LI of the normal group when calculated by these methods will be very likely to be truly different, as it has withstood this tendency towards zero. The technique is thus more

specific. A simple VxCt approach, by the same token, can produce stronger LIs, but because variability in the normal group is large using this method (as illustrated in our results), it becomes more difficult to distinguish a patient from the control group, and the method is therefore less sensitive, as happened for words in patient 5.

Other strategies have been proposed that do not assume any threshold selection and are thus expected to be more robust. One of these methods relies on the magnitude of the task-induced mean signal change (MSC) of voxels in a specific ROI (Benson et al., 1999; Adcock et al., 2003). One advantage of the MSC approach is that it relies on the correlation between the signal intensity fluctuation and the behavioral task timing rather than on *t*-tests for changes in mean intensities, which would better respect the signal time course (Cohen and DuBois, 1999). This method has been compared to simple VxCt at a specific threshold and shown to be more stable (Cohen and DuBois, 1999). Nevertheless, Adcock et al. (2003) have found that MSC can be more prone to produce ambiguous lateralizations when compared to the standard VxCt procedures. The likely explanation is that MSC sensitivity relies on the appropriate selection of voxels that are included into the analysis, eventually demanding that other kinds of thresholds be established. Previous reports have selected voxels for MSC analysis on basis of the degree of correlation between voxels' signals and the behavioral model (Benson et al., 1999; Cohen and DuBois, 1999), or the participation of such voxels in functional ROIs previously defined by a simple VxCt approach (Adcock et al., 2003). Whereas the former demands a "correlational" threshold, the latter demands a "significance" threshold. Once again, arbitrary parameters are applied.

An attempt to extract language LIs from traditional *t*-test distributions without selecting a threshold was carried out by Nagata et al. (2001). In this work, it was found that a reference function $(1/z \text{ score})^4$ was highly correlated with the number of activated voxels above each *z* score in expressive language areas of interest. Scatter diagrams in which the *x* axis contained $(1/z \text{ score})^4$ values and the *y* axis contained the respective number of voxels above each *z* score were analyzed by regression. Because the resulting curves were approximately linear, they serve as an estimate of monomial regression curves whose coefficients proved to be valid for an LI calculation that was independent of the threshold. One of the drawbacks to this approach, however, is that the $(1/z \text{ score})^4$ function was empirically derived and has to be independently validated for other ROIs, other subjects, and other paradigms. Also, the concave *z* score versus activated voxel count curves, from which the $(1/z \text{ score})^4$ was extracted, were extended only to a minimum *z* score of approximately 0.8. It is not clear if this function would hold if the plots were extended to $z = 0$. Finally, a regression line is always an approximation and is thus subject to errors and data loss. The method suggested here, however, uses all positively correlated voxels and does not rely on fitting data to estimated curves, being simply concerned with comparing entire weighted voxel distributions from both sides of the brain. Therefore, this method is likely to work in other ROIs as well. Nevertheless, Nagata et al. were able to demonstrate that the use of voxel distributions (rather than *z* score suprathreshold voxels) to calculate LIs is a reasonable approach and can produce more robust and consistent lateralizations, as they do not vary with the chosen threshold and are less variable among different subjects. These are important properties when anticipating applications in clinical decision making.

One interesting aspect of our technique is the possibility of selecting statistical distributions (or multipliers derived from them) based on data interpretation. In this study, it was not possible to conclude which distribution (Tw, Pw, or Pw2) is best. We suggest, however, that weighting the voxel distribution by a *P*-like distribution could yield more clinically relevant results than weighting by a *T* distribution, as $1 - P$ values are indicators of probability-to-be-true whereas *T* values are more a measure of dispersion. From the clinical point of view, for example, two voxels at a *P* of 0.001 and 0.05, respectively, are likely to be clinically relevant because their probabilities to be true positives are similar (respectively 99.9% and 95.0%). In terms of *T*, however, their values could be as disparate as 3.15 and 1.656, respectively (for $df = 141$). *T* distributions might be more suitable for cognitive studies with normal volunteers as *T* distributions are more stringent and give less weight to poorly activated voxels than $1 - P$ weighted distributions. Pw2 potentially brings the best of two worlds, as it is based on *P* statistics but behaves as a *T* distribution by suppressing the noisier, lower portion of the voxel distribution.

In this study, we presented five patients with distinct conditions in terms of IAP results, imaging findings and clinical history. Patients 2 and 5 were strongly lateralized to the right by both fMRI and IAP, and both had lesions in the left MTL, which provided further evidence that memory was right lateralized. We regard these two patients as the most suitable in our sample for a comparison between fMRI and IAP results because of unambiguous clinical data and clear-cut IAP results. (Despite low IAP scores for patient 5, he was entirely amnesic during the injection of the left hemisphere, which strongly supports memory lateralization to the right.) Indeed, the correlation between the two procedures was greatest in these two individuals, who were the only ones to obtain fMRI LIs (on FFX analysis) that deviated more than 2 SDs from the control group mean LI. The patient who had a clear left-lateralizing IAP (patient 1) also had a left-lateralizing fMRI. But this patient had no lesion in the right MTL and had a poor memory recognition performance during the fMRI recognition run (Table 1), which was probably caused by little attention to the task, because neuropsychological evaluation was normal. The absence of a lesion suggests that this patient's memory lateralization might be indeed within the normal range of lateralizations of the control group. But the poor performance during the fMRI procedure might also explain why she was not as easily differentiated from the control group (deviations were greater than 1 but smaller than 2 SDs on FFX analysis). This underscores the importance of collecting behavioral data in patients undergoing fMRI for clinical purposes. The same is true of the IAP. The two other patients (patients 3 and 4) were considered to have failed the IAP test, given poor recollection with both injections. In addition, they had no MTL lesions on MRI that could provide further evidence of altered memory lateralization. Because of ill-defined characterization of disease lateralization, we consider these two patients as the least suitable for a comparison between fMRI and IAP LIs. Not surprisingly, the correlation between their IAP and fMRI LIs was less good, with fMRI LIs deviating to the right of the normal group mean LI on FFX analysis, whereas the inconclusive IAPs suggested a slight lateralization to the left side. The presence of abnormal EEG activity in the left MTL in patient 3 might explain the fMRI slight lateralization to the right. Also, considering that this patient essentially failed the IAP, it is possible that the fMRI procedure has been more sensitive and effective in identifying a

lateralization consistent with these clinical data than IAP (particularly considering that the weighted LIs deviated more than one SD to the right of the control group mean LI). For patient 3, weighted techniques were able to identify a lateralization on FFX analysis whereas VxCt10 was not, which demonstrates the potential advantage of these techniques.

We believe this study provides good evidence that for a given patient, lateralization index in isolation (i.e., without reference to a normal population) may not be sufficient to determine if a patient has anomalous organization of memory functions in the MTL. Therefore, it would be better to compare a patient's lateralization with those derived from a normal group. In our data, the weighted LIs yield a more clear-cut distinction of patients from the normal group (larger distances in terms of SD from the normal group mean), as weighted LIs tend to yield smaller variability. This effect is stronger if all material types are combined, suggesting that an FFX approach could be better in clinical settings.

For clinical application, we might consider the following strategy to find altered lateralization in patients. First, an FFX VxCt LI should be compared to an FFX Pw2 LI (due to its theoretical advantages over the others). If they both lateralize to the same side, lateralization is clear. If they lateralize to different sides, fMRI results should be regarded as equivocal and activations could be either truly bilateral or biased by artifacts. If lateralizations are consistent between techniques, then it is possible to decide whether they are different or not from the healthy group LIs. They should be compared in terms of SD to the healthy group LI calculated by the same methods and from the same behavioral tasks. If deviations greater than 2 SDs are found for weighted techniques and greater than 1 SD for VxCt (patients 2 and 5), lateralization could be assumed to be clearly different from the healthy group. If deviations are greater than 1 SD for VxCt LIs but not greater than 2 SDs for weighted LIs (patient 1), it means that the difference exists only for highly significant voxels and it is not supported by the whole voxel distribution. It can still be a true difference, but based on a limited amount of data. If deviations are greater than 2 SDs for Pw2, but not greater than 1 SD for VxCt, altered lateralization may still be present because VxCt SDs tend to be large and therefore it is more difficult to find a difference between patients and healthy subjects using this technique.

Future research should be aimed at confirming these findings in a larger sample of patients and normal subjects. Other ways to compare lateralization of patients with healthy group mean lateralizations should be explored because LI distributions are only approximately normal, rendering standard deviation an imprecise measure of variance. Additionally, other statistical distributions or their transforms could be tried. We tested three different alternatives, but others could be tested, such as T^2, $(1 - P)^2$, and $[2(0.5 - P)]^2$, which would give even greater weight to the highly significant voxels. The multiplier $2(0.5 - P)$ was developed to optimize both Tw and Pw advantages, but one must take care, however, when applying new parameters and operators onto the original T or $1 - P$ distributions, which may cause a decrease in robustness. One interesting perspective is the inclusion of negatively correlated voxels, that is, those with negative T values. In designs like ours, where two explicit conditions are compared, it might be equally important to identify asymmetric deactivations as asymmetric activations. Suitable statistical distributions could be then elaborated that would take into account the whole set of voxels, positive and negative ones, into the LI calculation. Other possibilities are the use of nonparametric multipliers or even multipliers developed with supervised learning algorithms, which could be fed by IAP results and/or other clinical variables. The results from such distributions could extend the evidence provided by this study that the use of weighted voxel distributions provides better memory lateralizations by fMRI in patients undergoing pre-operative cognitive evaluation.

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