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The intersubject and intrasubject reproducibility of FMRI activation during three encoding tasks: implications for clinical applications

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Abstract The goal of the present study was to evaluate the inter- and intrasubject reproducibility of FMRI activation for three memory encoding tasks previously used in the context of presurgical functional mapping. The primary region of interest (ROI) was the medial temporal lobe (MTL). Comparative ROIs included the inferior frontal and fusiform gyri which are less affected by susceptibility-induced signal losses than the MTL regions. Eighteen subjects were scanned using three memory encoding paradigms: word-pair, pattern, and scene encoding. Nine subjects underwent repeat scanning. Intersubject reproducibility of FMRI activation was evaluated by examining the percent of subjects who showed activation within a given ROI and the range to which individual laterality indices (LIs) varied from the mean. Intrasubject test-retest reproducibility was evaluated by examining the LI test-retest correlation, the average difference between LIs from two separate imaging sessions, and concordance ratios of activation volumes (R_{volume} and $R_{overlap}$). For scene encoding the reproducibility of activation volume and LIs within the MTL were as good as or better than the reproducibility within the fusiform and inferior frontal ROIs. For pattern encoding and word-pair encoding, the reproducibility of activation volume and LIs within the MTL tended to be worse compared to the fusiform and inferior frontal ROIs. The differences in FMRI reproducibility appeared more dependent on the task than the susceptibility effects. The results of this study suggest that FMRI-based assessment of the neural substrates of memory using a scene encoding task may be a useful clinical tool.

Keywords Brain mapping · Reproducibility · Memory · Encoding · Neurosurgical planning

Introduction

Anterior temporal lobectomy eliminates or improves seizure control in 80–90% of patients with medically intractable medial temporal lobe (MTL) epilepsy [1]. However, the decision to pursue surgery must be considered in the context of a risk for cognitive morbidity including declines in memory. In temporal lobe epilepsy (TLE), presurgical evaluation of memory function is useful in predicting the relative risk of postsurgical memory deficits as well as postsurgical seizure outcome, and confirmation of the side of seizure focus [2–6]. Currently, the Wada test, or the intracarotid amobarbital procedure (IAP), is considered to be the gold standard in the assessment of the lateralization of memory function. The IAP requires a unilateral injection of a short-acting barbiturate (typically amobarbital) into one internal carotid artery [7]. The barbiturate temporarily anesthetizes the ipsilateral hemisphere, theoretically mimicking the effects of surgery on that hemisphere. The IAP is an invasive procedure associated with some degree of risk, which makes the evaluation of test-retest reproducibility difficult [8].

Functional MRI (FMRI) is a technique which detects a signal dependent on blood oxygenation level, and is therefore an indirect indicator of neuronal activity associated with performance of a specific task. FMRI offers the potential to assess the lateralization and localization of cognitive functions in a noninvasive way. Previous FMRI studies have shown that the formation of new memory representations for novel stimuli (encoding) is associated with neural activation within medial temporal structures, along with other areas including the inferior frontal gyrus [9–17]. MTL structures including the hippocampal formation and parahippocampal regions (parahippocampal and perirhinal cortices) are essential to the ability to acquire and retain new information [18–20]. Only a few studies to date have examined the lateralization of memory functions using FMRI in individuals with epilepsy [9, 21–27]. It has been proposed that abnormal patterns of FMRI activation (e.g. atypical asymmetry) within MTL structures may serve as a proxy for assessing the functional integrity or organization of these brain regions. Jokeit et al. [21] showed that active retrieval of spatial information produced interhemispheric differences in MTL structures that corresponded to the side of seizure onset in 90% of 30 patients with unilateral TLE. Similarly, Detre et al. [9] found that memory asymmetries as shown with FMRI concurred with IAP-based memory asymmetries in all nine patients tested. In both of these studies memory tasks that tended to produce bilateral and largely symmetrical activation of MTL structures were used in healthy control subjects with the idea that asymmetric activation would signal unilateral mesiotemporal dysfunction. An alternate approach used by Golby et al. [14, 22] employed material-specific memory encoding tasks that produce asymmetric activation in healthy control subjects with the goal of looking for an abnormal or reversed pattern of asymmetry in clinical populations. These authors found that in eight of nine TLE patients, lateralization of memory encoding was concordant with that obtained from an IAP. Further, group analyses demonstrated right medial temporal activation during encoding word-pairs by the left TLE group, and left medial temporal activation during encoding of nonverbal material in the right TLE group; patterns which were the reverse of those in healthy controls. Such findings are consistent with the reorganization of memory function to the contralateral mesiotemporal region and emphasize the possible clinical utility of material-specific memory encoding tasks [28].

If FMRI is going to provide a means for assessing the functional substrates of memory in clinical populations, it must first be demonstrated that activation patterns associated with particular memory tasks are reproducible. That is, FMRI parameters such as laterality indices (LIs) and volume of activation should be similar within a given subject over repeat scans (e.g. test-retest reproducibility). Only one published study has evaluated test-retest reproducibility of FMRI activation for a memory encoding task [12]. This study found relatively poor test-retest reproducibility related to the volume of activation for a visual scene encoding task. Unfortunately, the reproducibility of a measure of the pattern or laterality of the activation was not examined. Further, it is important to understand the degree of intersubject reproducibility associated with various FMRI indices in healthy, right-handed individuals, in order for us to begin to recognize when findings for a given individual fall outside the normal range. For example, what is the normal range of LIs in healthy subjects and when do measures of asymmetry become outside the normal range?

The goal of the present study was to evaluate the inter- and intrasubject reproducibility of FMRI activation for three memory-encoding tasks that have been used in the context of presurgical functional mapping. We evaluated the reproducibility of FMRI generated LIs and activation volume. We were particularly interested in evaluating the reproducibility of FMRI activation within the MTL region, since this region is critical in the evaluation of surgical candidates for temporal lobectomy. One problem with FMRI-based assessment of memory has been the relative difficulty in consistently activating MTL structures, possibly due to the susceptibility-induced FMRI signal losses [29–31]. Therefore, we also evaluated the reproducibility of FMRI activation within other regions (inferior frontal and fusiform gyri) which are less affected by susceptibility-induced signal losses in order to compare the reproducibility within these regions to that of the MTL. An inferior frontal region of interest (ROI) was chosen because of its known association with encoding tasks [9–17] and a fusiform ROI was chosen because activation in this area is associated with a wide variety of visually based cognitive tasks [32–39] including visual encoding paradigms [9–13, 15–17]. If decreased inter- or intrasubject reproducibility is consistently seen within the MTL ROI across different encoding tasks as compared to the other two regions, this would suggest that the reduced FMRI signal in the MTL regions may play a role in the decreased reproducibility.

Methods

The study was approved by the UC Davis Human Subjects Protection Committee and written informed consent was obtained from all participants. The study group comprised 18 healthy subjects, 15 of whom were female. Their average age was 32.1 years (SD 9.5 years) ranging from 18 to 49 years. All participants were right-handed as measured by the Edinburgh Handedness Inventory [40]. Nine of the subjects returned for a second imaging session (average time between sessions 9.5 weeks, range of 1 to 14 weeks).

Tasks were incorporated into block design paradigms with experimental conditions lasting 12 to 30 s alternating with baseline conditions of similar durations. Visual stimuli were projected onto a screen located at the end of the

scanner patient table using the Presentation software package ("http://www.neurobs.com") and the subject viewed the screen via a mirror on top of the head coil. The subject's head was restrained using a moldable air bag (Vac-Fix, Bionix, Toledo, Ohio).

Three different encoding tasks were used, each designed to tap memory for various types of information as described by Golby et al. [14]. Memory for verbal material was assessed using word-pairs and memory for nonverbal information was assessed using abstract patterns. In the third task, the stimuli comprised complex visual scenes which were likely to be encoded using both verbal and nonverbal strategies. For the participants undergoing repeat scanning, different stimuli were used for the second imaging session. Before each encoding task subjects were explicitly instructed to remember the stimuli for a later test. The stimuli were presented every 4 s for 3.5 s. For the experimental condition of the scene encoding task, color photographs of indoor and outdoor scenes were presented. To encourage adequate processing of the stimuli, subjects were instructed to make a covert decision regarding whether the photographs depicted indoor or outdoor scenes. An abstract color noise image was repeated for the baseline condition of the scene encoding task [9]. During the experimental condition of the pattern encoding task, subjects viewed novel color images of abstract designs and were instructed to make a decision as to whether the pattern was symmetric or asymmetric. During the experimental condition of the word-pair encoding task, pairs of common words (nouns, verbs and adjectives) were presented visually and subjects were instructed to generate a sentence silently using both words. For the pattern and word-pair tasks, the same pattern or word-pair was repeated throughout the baseline condition. For the repeating word-pairs, subjects were told to generate the same sentence each time.

Scanning and data analysis

During the memory encoding tasks, 24 contiguous 5-mm axial slices were acquired with a gradient echo, echo-planar imaging (EPI) sequence (TR 2 s, TE 40 ms, flip angle 90°, FOV 22 cm, matrix 64×64) using a 1.5-T GE Signa NV/I MRI system, LX version 8.2.5. In each functional scan, a data set consisting of 196 image volumes was acquired over 384 s. The first four image volumes were removed from the data set to insure that image intensity variations due to magnetization approach to dynamic equilibrium were not included in the functional analysis. High-resolution structural images were obtained for use as anatomical references using a 3D T1-weighted fast SGPR sequence (slice thickness 1.2 mm, FOV 22 cm, 256×256×124, TE 1.8 ms, TR 8.7 ms, flip angle 15°, bandwidth 15.63 kHz).

The echo-planar images were reconstructed using standard Fourier transformation combined with image phase correction [41, 42] to reduce the N/2 ghost artifact. The images were registered to the third image in the FMRI time-series with a 3D registration algorithm [43]. All statistical analyses were performed with the AFNI analysis and display software package [44]. Statistical maps were generated using a multiple regression algorithm with a boxcar (6 s lag) reference waveform, and linear trends were included as covariates. Activation maps were created by applying a *P*-value and cluster size threshold [45, 46] to the statistical maps. The program AlphaSim within AFNI was used to estimate the cluster size necessary to achieve a significance level less than 0.05 with an individual voxel threshold of $P<1\times10^{-4}$. The statistical maps were transformed to Talairach coordinates [47] with linear interpolation [44] using the transformation derived from the 3D anatomical images acquired during the same scanning session as the functional images used to generate the statistical maps.

ROIs for the inferior frontal gyrus (Brodmann areas 44–47), fusiform gyrus (BA 20/37), and the MTL, consisting of the hippocampus and parahippocampal gyrus, were

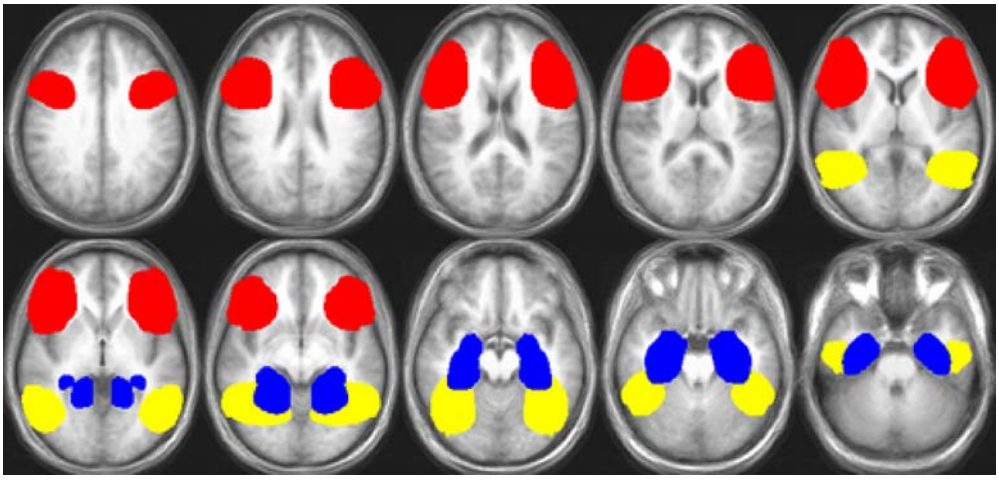

Fig. 1 Regions of interest (*red* inferior frontal ROI, *blue* MTL ROI, *yellow* fusiform ROI)

hand drawn according to Talairach coordinates utilizing the Talairach atlas [48]. Figure 1 shows the ROI locations overlaid on the group averaged anatomical reference image. The volume of activation within each ROI for the three tasks was calculated by counting voxels above the given threshold. Analysis of variance (ANOVA) was used to determine the main effect of task on the total activation detected within each ROI. In order to reduce the influence of potential laterality differences, a second analysis was performed on the total activation (left and right hemisphere) within each ROI.

LIs were calculated for each ROI using the F statistic of each voxel generated from the regression analysis. The sum of the F statistics from voxels above a given threshold in the right ROI was subtracted from the sum in the left ROI and then dividing by the sum from both ROIs: $LI=(F\text{-}SUM_{left}-F\text{-}SUM_{right})/(F\text{-}SUM_{left}+F\text{-}SUM_{right})$. Intermediate LIs were calculated for a range of *P*-value thresholds starting at a $P<0.01$ threshold and progressing to $P<1.0\times10^{-6}$. The final LI assigned to each ROI was the average of the intermediate LIs over the range of thresholds. The LIs ranged from 1.0 to −1.0 and LIs less than −0.2 were classified as right lateralized, LIs greater than 0.2 were classified as left lateralized and all LIs in between ($-0.2\leq LI\leq 0.2$) were classified as bilateral [49, 50]. It was expected that the three tasks would yield different LIs. ANOVAs were used to determine the task effect on the average LIs generated from each ROI.

Intersubject reproducibility

The intersubject reproducibility of FMRI activation was evaluated by determining (1) the percent of subjects who showed activation within a given ROI for each encoding task [46, 51–54] and (2) the range of variation from the group mean of the individual scores (as measured by standard deviation in the LI). Differences in the standard deviation of the LIs between tasks and between ROIs were compared using F-tests for variance.

Intrasubject reproducibility

Intrasubject reproducibility of FMRI activation was evaluated using test-retest reproducibility measures. Test-retest reproducibility of the LI was evaluated by examining the test-retest correlation (Pearson *r*) and the average difference between LIs from two separate imaging sessions. Test-retest reproducibility of the volume of activation was evaluated by calculating two concurrence ratios for activation, denoted R_{volume} and $R_{overlap}$ [12, 55–61]. R_{volume} measured only the volume of activation while

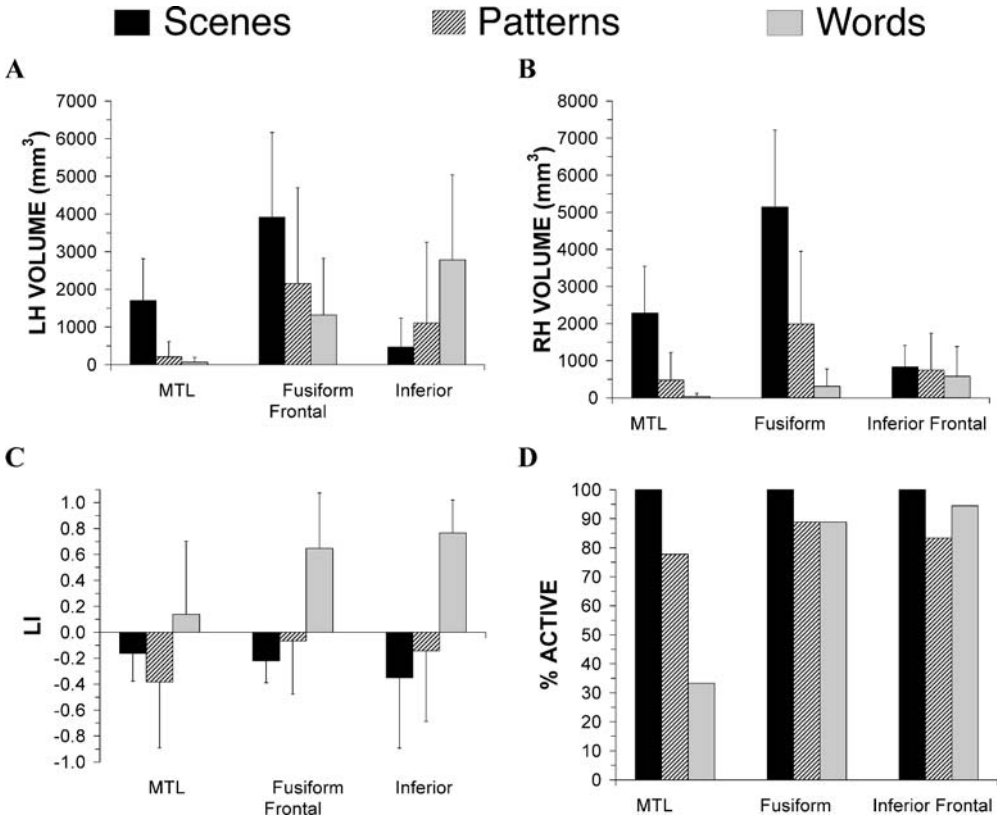

Fig. 2 Intersubject variability. **a** Activation volumes (mean and SD) within the left hemisphere ROIs; **b** activation volumes (mean and SD) within the right hemisphere ROIs; **c** LIs (average and SD); **d** percentage of subjects in whom activation was detected within each ROI

$R_{overlap}$ combined location of activation and volume of activation into one test-retest reproducibility variable. The concurrence ratios for volume and overlap (in percentage) were calculated within the ROIs using the formulas from Rombouts et al. [62]:

$$R_{volume} = 2 \times \frac{VOL_{min}}{VOL_1 + VOL_2}$$

$$R_{overlap} = 2 \times \frac{VOL_{overlap}}{VOL_1 + VOL_2}$$

where VOL_1 and VOL_2 are the activation volumes within the given ROI for the first and second session, respectively, VOL_{min} is the smallest volume of activation between sessions, and $VOL_{overlap}$ is the overlap of activation between sessions. All volumes were calculated from the spatially normalized data sets.

Results

Laterality and volume of activation

Figure 2 displays the average volume of activation and the average LI within each ROI. With the exception of the right hemisphere inferior frontal ROI, there was a significant task effect for the volume of activation within each ROI ($P \leq 0.005$). Paired *t*-tests were used to further evaluate the task effect within the ROIs. Within the MTL ROIs of both the right and left hemisphere scene encoding produced significantly more activation than the other two tasks ($P \leq 3.3 \times 10^{-7}$). This same pattern was also observed within the right and left hemisphere fusiform ROIs. Within the inferior frontal ROI the volume of activation across the three tasks differed as a function of hemisphere. Within the left inferior frontal ROI word-pair encoding produced significantly more activation than the other two tasks ($P \leq 5.5 \times 10^{-4}$), while scene and pattern encoding produced less but equivalent activation. Within the right inferior frontal ROI the scene encoding task produced significantly more activation than the word-pair encoding task. In terms of laterality, the LIs within each ROI were not significantly different from a normal distribution according to the Kolmogorov-Smirnov test for normality. There was a significant task effect for the LIs within each ROI ($P \leq 0.005$).

Intersubject reproducibility

Figure 2 also shows the percentage of subjects who showed some degree of activation for each task within the three ROIs. The scene encoding task was the only encoding task to produce activation within the three ROIs for all 18 subjects. Alternatively, pattern encoding (77.8%) and word-pair encoding (33.3%) were associated with MTL activation in a much lower percentage of the subjects.

The LI SDs (Fig. 2) provide a measure of the degree of dispersion in these values from subject to subject. The LIs for scene encoding were associated with the smallest standard deviation within the MTL (0.22) and fusiform (0.17) ROIs and these standard deviations were significantly less than the other two tasks ($P \leq 4.9 \times 10^{-4}$).

To further illustrate the dispersion in the LIs within the ROI of primary interest—the MTL ROI—Fig. 3 shows the number of subjects with different LI ranges within the MTL. Scene encoding was bilateral or mildly right lateralized in all of the subjects while the LIs for the other two tasks were more widely distributed, especially for word-pair encoding.

Intrasubject reproducibility

Figure 4 shows the LI test-retest correlations, the average LI differences between sessions and the average concurrence ratios for each task within the three ROIs. Scene encoding and pattern encoding both produced adequate LI test-retest correlations within the MTL ROI ($P < 0.05$). Word-pair encoding was the only task associated with adequate test-retest correlations within the fusiform ROI and was also associated with the strongest test-retest correlations within the inferior frontal ROI. Finally, scene encoding was associated with the smallest average difference between LIs calculated from the two imaging sessions within the MTL ROI (average LI difference 0.14±0.11).

In terms of the volume of activation, encoding scenes produced the highest average R_{volume} within all of the ROIs; suggesting that compared to the other two tasks, a higher proportion of voxels within the same ROI were detected across sessions for scene encoding. Scene encoding also produced the highest average $R_{overlap}$ within the MTL and fusiform ROIs, suggesting that scene encoding yielded a significantly higher proportion of overlapping voxels across sessions. Within the inferior frontal ROI, scene encoding produced the highest average

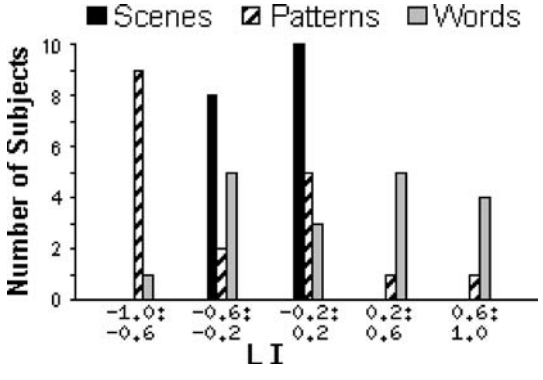

Fig. 3 Histogram of LIs within the MTL ROI

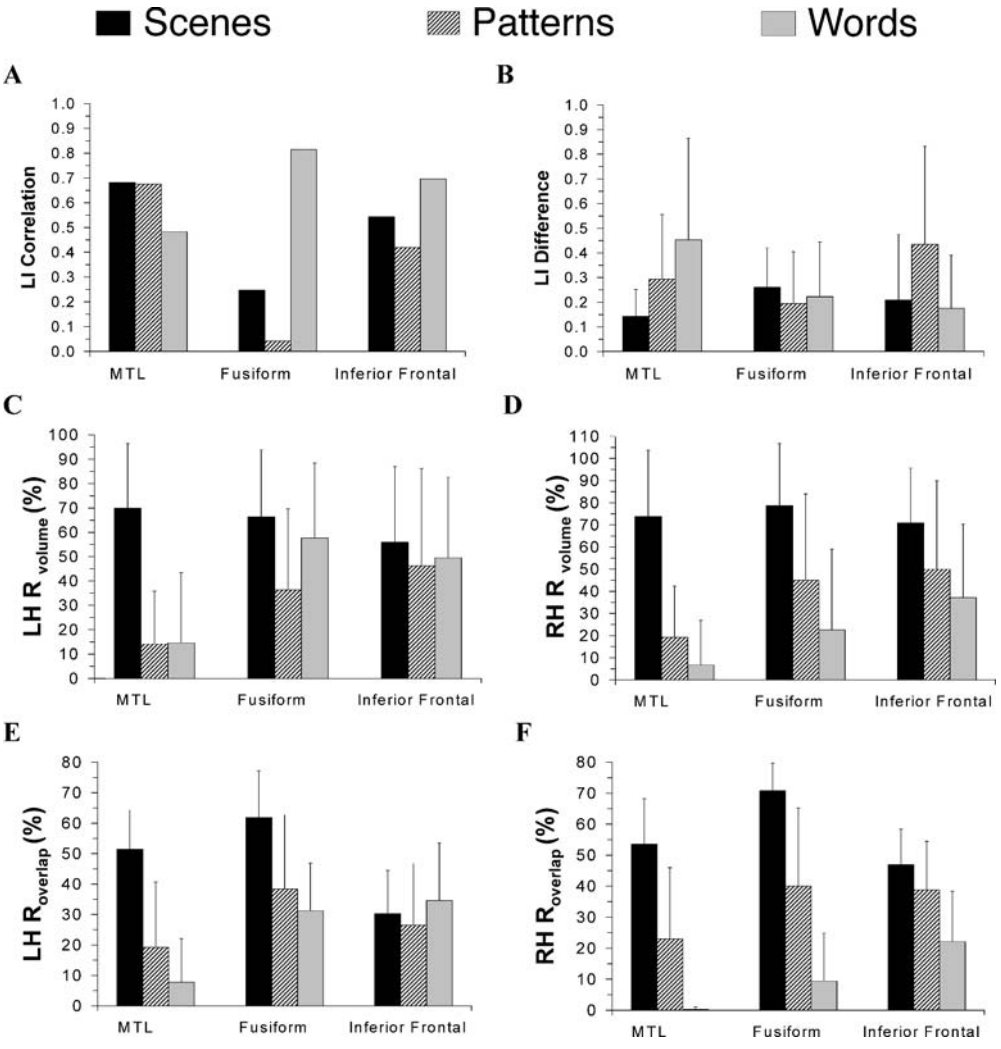

Fig. 4 **a**, **b** LI test-retest correlation (**a**) and average LI difference (plus SD) (**b**) between sessions. **c**, **d** R_{extent} for the left (**c**) and right (**d**) hemisphere ROIs (average plus SD). **e**, **f** $R_{overlap}$ for the left (**e**) and right (**f**) hemisphere ROIs (average plus SD)

$R_{overlap}$ in the right hemisphere but word-pair encoding produced the highest $R_{overlap}$ in the left hemisphere. Figure 5 illustrates the activation, including the overlap of activation, for the scene encoding task in an example subject. Table 1 shows the reproducibility indices for the individual subject in Fig. 5.

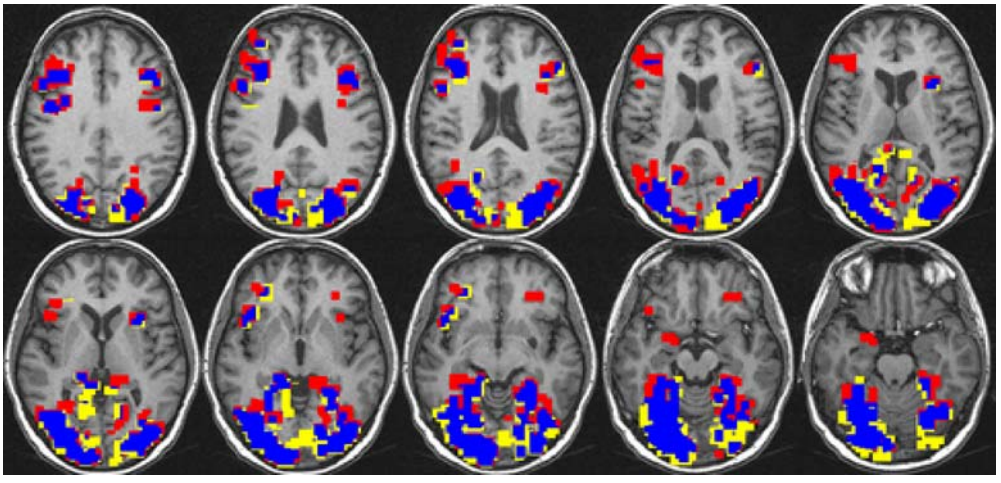

Fig. 5 Scene encoding overlap (example subject) showing activation and overlap for the scene encoding task (*yellow* session 1 only, *red* session 2 only, *blue* overlap between sessions). See Table 1 for activation information. Extent and concordance ratios are for the right hemisphere ROIs

Table 1 Test-retest results for scene encoding (same subject as in Fig. 5) (volume and concordance ratios are for the right hemisphere ROIs)

ROI		Session 1	Session 2
MTL	LI	−0.01	−0.02
	Volume (mm^3)	1,811	2,052
	R_{volume} (%)	93.8	
	$R_{overlap}$ (%)	61.7	
Fusiform	LI	−0.65	−0.37
	Volume (mm^3)	5,732	5,160
	R_{volume} (%)	94.7	
	$R_{overlap}$ (%)	78.1	
Inferior frontal	LI	−0.67	−0.52
	Volume (mm^3)	1,857	4,376
	R_{volume} (%)	59.6	
	$R_{overlap}$ (%)	43.9	

Discussion

The primary aim of this study was to assess the inter- and intrasubject reproducibility of three FMRI encoding paradigms within the medial temporal regions of healthy subjects. Within the MTL ROI, the FMRI activation for the scene encoding task was generally associated with the greatest inter- and intrasubject reproducibility compared to word-pair and pattern encoding. In particular, the inter- and intrasubject reproducibilities for LIs within the MTL were very good for the scene encoding task. Use of the more material-specific stimuli (words and patterns) was associated with lower degrees of inter- and intrasubject reproducibility with both the volume of activation and the LIs. Modifications of the task design may result in an increase in FMRI activation reproducibility for these types of stimuli. However, in their current form the reproducibility of theses two material-specific encoding tasks do not seem to be sufficient to warrant their use in the clinical setting.

As shown in previous studies, scene encoding was associated with largely bilateral activation within the MTL [9, 13, 14, 17, 23, 26, 63] and pattern encoding with mildly asymmetric activation favoring the right MTL [14]. In contrast to the findings of at least one previous study [14] we found the LI for word-pair encoding within the MTL to be primarily symmetrical rather than asymmetrical favoring the left. However, this finding may have been influenced by the extremely low average volume of activation associated with this task within the MTL. In fact, both pattern and word-pair encoding were associated with a significantly lower volume of activation within the MTL than scene encoding, probably making the results less stable overall. If FMRI is to be used for functional mapping in the clinical setting with individual patients, it seems particularly important that a given FMRI task produce activation within a target ROI in all healthy subjects. Only then can one be confident that a lack of activation in the MTL is atypical. In the current study scene encoding was the only task to produce activation in 100% of the subjects within the MTL. Neither the pattern (77.8%) nor word-pair encoding (33.3%) tasks were associated with this degree of consistency in activation within the MTL ROI across subjects.

Also of importance if FMRI is to be used to identify atypical patterns of activation in individual patients is an understanding of the range of scores that should be considered to be within the range of normal variation. When we examined the standard deviations related to the LIs for the three encoding tasks within the MTL ROI, scene encoding showed significantly less dispersion from the group mean than the other two encoding paradigms. Further, when examining the range of LI values for each encoding task within the MTL ROI, scene encoding showed the smallest range of LIs. Alternatively, both pattern and word-pair encoding showed a much wider range of LI scores. Such findings suggest that just about any LI value can be associated with the two latter encoding tasks. Other studies have shown considerable individual variation in FMRI activation for memory retrieval [64] and encoding [53]. However, the encoding of complex visual scenes appears to be consistently bilateral or subtly right lateralized. Thus, the finding of a LI within the MTL greater than two standard deviations from the mean, i.e. strongly right lateralized activation (LI<−0.59) or left lateralization (LI>0.27), likely indicates some atypical organization or function in that individual.

The concurrence ratios for volume and overlap (R_{volume} and $R_{overlap}$) provide a measure of how much the volume of activation within a particular region detected during one imaging session will be reproduced in a second imaging session. The volume of activation produced by scene encoding was more reproducible than the activation for word-pair and pattern encoding. $R_{overlap}$ is particularly valuable in evaluating test-retest reproducibility in FMRI, since FMRI activation maps are often interpreted qualitatively in terms of both location and volume of activation. In scene encoding, about 50% of the activation within the MTL from one session overlapped with activation from the second session in most subjects. Considerable intrasubject variability in FMRI activation volume has been shown in previous studies for a variety of tasks [12, 55, 57–60, 62, 65]. In the only other test-retest study evaluating visual encoding, Machielsen et al. [12] have reported $R_{overlap}$ and R_{volume} averages comparable to those in the current study for a similar scene encoding task. Qualitatively, as depicted in Fig. 5, the non-overlapping region appeared adjacent to and contiguous with the overlapping region, suggesting that the same activation was being detected in both sessions. The non-overlapping regions of activation would be of greater concern if they were composed of largely separate regions of activation detected in one session and not in the other session. However, quantita-

tively the average R_{volume} and $R_{overlap}$ values suggest that improvements in intrasubject reproducibility of activation volume are necessary in order to use the measure of activation volume clinically and that at this point LIs may be a more a reliable measure to use when interpreting at the individual subject level.

The reproducibility of FMRI activation within the medial temporal regions for each task was also compared with the reproducibility of FMRI activation within inferior frontal and fusiform ROIs, as the latter regions of the brain would be expected to be less effected by the susceptibility-induced signal losses associated with the FMRI signal than medial temporal regions. However, the volume of activation and the differences in the reproducibility of activation between ROIs appeared to be more dependent on the task than the susceptibility effects. The scene encoding task showed very little difference in R_{volume} and $R_{overlap}$ between ROIs. Furthermore, there was no difference in the percentage of subjects who produced activation associated with this task across the three ROIs. Additionally, the LIs associated with scene encoding LI produced a higher test-retest correlation within the MTL ROI compared to the other ROIs. Finally, the amount of dispersion in LIs for individual subjects (as measured by standard deviations) was significantly lower in the MTL ROI than in the inferior frontal ROI. Conversely, in pattern and word-pair encoding, R_{volume}, $R_{overlap}$ and the percentage of subjects active within the MTL ROI were much less than within the other two ROIs. Also, the highest LI test-retest correlation occurred in an ROI other than the MTL ROI. Thus, while it was anticipated that there would be decreased intra- and intersubject FMRI reproducibility within the MTL ROI because of susceptibility-related signal losses, there was only decreased FMRI reproducibility for word-pair encoding and pattern encoding. Scene encoding showed no such decreases and in some cases the FMRI reproducibility for scene encoding was greater within the MTL. Therefore, the decrease in FMRI activation reproducibility within the MTL found with word-pair and pattern encoding cannot be attributed to susceptibility-related signal losses.

One reason for the differences in the degree and consistency of MTL activation across the three encoding tasks may be the subtle differences in the types of baselines that were used. The word-pair and pattern encoding tasks in this study both used repeat stimuli of the same type for the baseline condition. This was based on the hypothesis that more encoding occurs while viewing novel stimuli than repeated stimuli [63, 66, 67]. For the scene encoding task, visual noise (a pixilated image) was used as the baseline. As suggested by Martin [68], this noise image probably contains less encodable information than the repeating pattern or word baselines. Thus, the superior activation for the scene encoding task with the MTL ROI, as compared to the word-pair and pattern encoding tasks, could be because less activation had been subtracted away with the baseline.

The current findings are based on normal controls. It is important to first understand how particular FMRI tasks perform in healthy right-handed controls before examining activation patterns in clinical subjects. In this way one will be able to better judge when atypical cerebral organization may be present. One factor which contributes to the intersubject variability of FMRI activation is variability in neuroanatomy [69]. In the current study, anatomical variability between subjects was reduced by using large ROIs. However, the use of a global ROI (created from a single Talairach image and then applied to all subjects) may have contributed to some of the FMRI variability. In the case of individual clinical patients, many of whom will have structural abnormalities on MRI, individually drawn ROIs will be necessary as the ROI maps created from a 'normal' brain with no pathology would likely not be an adequate fit.

The results of this study suggest that FMRI-based assessment of the neural substrates of learning and memory using a scene encoding task may be a useful clinical tool. This task was associated with largely bilateral activation in normal subjects and thus strongly right lateralized asymmetric activation ($LI \leq -0.6$) or left asymmetric MTL activation is likely to be an indication of unilateral dysfunction and/or reorganization. Whether FMRI is an approach that will offer information regarding the functional adequacy of the MTL structures in an epilepsy patient is yet to be empirically tested. To this end, a better understanding of the relationship between the pattern of MTL FMRI activation using various memory tasks in relation to both the results of IAP and the neuropsychological assessment of memory functioning is necessary. Additionally, the utility of abnormal asymmetries in activation of medial temporal structures in predicting postsurgical memory changes and even seizure outcome are important future directions. Finally, FMRI may provide an approach to further our understanding of how memory functions may be reorganized in individuals with early CNS insults.

In time, FMRI may replace the IAP. However, the two methods attempt to estimate brain function in vastly different ways. FMRI is based on a hemodynamic indicator of neuronal activity, while the IAP measures lateralization and function by suppressing activity on one side of the brain and measuring the extent of remaining ability. The concordance between these two methods, particularly as related to the assessment of memory capacity and laterality, needs further investigation. Demonstration of the reproducibility of FMRI memory paradigms is a critical first step in being able to apply this technique clinically. However, the contribution of FMRI to the prediction of seizure lateralization and postoperative memory function has not yet been the focus of intense investigation. Direct comparisons between the results of IAP-based memory lateralization and FMRI-based lateralization are still needed, and prospective studies examining the ability of

FMRI memory-related activation patterns to contribute to the prediction of postsurgical memory changes are critical.

Conflict of interest statement We declare that we have no conflict of interest.

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