Published in final edited form as:
Hippocampus. 2009 June ; 19(6): 517–525. doi:10.1002/hipo.20620.

Structure Specific Analysis of the Hippocampus in Temporal Lobe Epilepsy

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Abstract

The hippocampus is a major structure of interest affected by temporal lobe epilepsy (TLE). Region of interest (ROI)-based analysis has traditionally been used to study hippocampal involvement in TLE, although spatial variation of structural and functional pathology have been known to exist within the ROI. In this article, structure-specific analysis (Yushkevich et al. (2007) Neuroimage 35:1516–1530) is applied to the study of both structure and function in TLE patients. This methodology takes into account information about the spatial correspondence of voxels within ROIs on left and right sides of the same subject as well as between subjects. Hippocampal thickness is studied as a measure of structural integrity, and functional activation in a functional magnetic resonance imaging (fMRI) experiment in which subjects performed a memory encoding task is studied as a measure of functional integrity. Pronounced disease-related decrease in thickness is found in posterior and anterior hippocampus. A region in the body also shows increased thickness in patients' healthy hippocampi compared with controls. Functional activation in diseased hippocampi is reduced in the body region compared to controls, whereas a region in the tail showing greater right-lateralized activation in controls also shows greater activation in healthy hippocampi compared with the diseased side in patients. Summary measurements generated by integrating quantities of interest over the entire hippocampus can also be used, as is done in conventional ROI analysis.

Keywords

structure-specific; hippocampus; temporal lobe epilepsy; fMRI; shape analysis

INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common form of epilepsy that presents with focal seizures (Wiebe, 2000) often arising within the hippocampus and surrounding medial temporal lobe structures. Hippocampal sclerosis is a well-known structural biomarker of disease-related atrophy in TLE that is often visible in magnetic resonance images (Berkovic et al., 1991).

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Hippocampal volumetry has proven to be a useful technique to study such atrophy, as well as to lateralize the disease in unilateral TLE patients (Cendes, 1993; Bernasconi et al., 2003; Seidenberg et al., 2005). However, conventional volumetry cannot be used to study spatial variation of atrophy within the hippocampus, which has been reported in TLE patients (Bernasconi et al., 2003). The origin of focal seizures is also known to vary, and does not always colocalize with regions of greatest structural atrophy (King et al., 1997). Similarly, asymmetric functional activation during language and memory-related cognitive tasks that activate the hippocampus has been widely reported in TLE patients (Rabin et al., 2004), and has been reliably used to lateralize language function (Binder et al., 1996; Rutten et al., 2002), although memory lateralization using functional magnetic resonance imaging (fMRI) remains challenging (Powell et al., 2008). Again, group differences as well as interhemispheric asymmetry in functional activation within different subregions of the hippocampus in TLE may provide valuable information about the disease process, and how they relate to structure.

Region of interest (ROI)-based analysis of structural as well as functional data can help increase sensitivity of population studies in neuroimaging and allow structure-specific hypotheses to be tested. However, even within the ROI, spatial variation of structural properties such as local folding and tissue thickness may convey useful information. These variations may coexist with functionally distinct subregions, often composed of different cell types, for example in the subfields of the hippocampus (Hogan et al., 2004). This can give rise to heterogeneity of brain function within ROI that can in turn undermine the sensitivity of a traditional ROI-based analysis for detecting meaningful effects. One advantage of a *structure-specific* approach (Yushkevich et al., 2007) is the availability of *point-by-point correspondence* within the structure modeled. Quantities of interest such as functional activation as well as morphometric variables are mapped onto a common shape-based coordinate system across subjects, and between hemispheres in the same subject. In this article, we apply the structure-specific analysis framework based on continuous medial representations (cm-rep) (Yushkevich et al., 2006) to study group differences in local tissue thickness as well as functional activation *within the hippocampus* in TLE.

Medial representation-based structural analysis in the hippocampus has been used in clinical studies (Styner et al., 2004; Thompson et al., 2004), as well as other studies that derive thickness measures from shape modeling (Bouix et al., 2005). However, this study is the first to apply such techniques to analyze both structural and functional data in TLE.

MATERIALS AND METHODS

Imaging

All scans were obtained from a 3 Tesla Siemens Trio scanner using an eight-channel head coil and body coil transmitter. The T1-weighted structural MRI scans used the MP–RAGE sequence with the following parameters: TR = 1620 ms, TE = 3.87 ms, TI = 950 ms, flip angle = 15°, and voxel size 0.9375 × 0.9375 × 1 mm. For the fMRI experiment, the memory encoding task consisted of viewing of complex visual scenes in a blocked design experiment with alternating blocks of scene encoding or control. Subjects were instructed to remember the scenes for a subsequent recognition task. Passive viewing of randomly scrambled scenes was used as control condition. BOLD fMRI images were obtained using a gradient echo echoplanar (EPI) sequence with TR = 3000 ms, TE = 30 ms, and 3-mm isotropic voxels. Further details of the experimental protocol can be found in Rabin et al., 2004. Twenty patients with TLE participated in the study, out of which 12 had their Intracarotid Amobarbital Testing (IAT) scores dichotomized according to hemispheric dominance for memory for comparison with fMRI data. Twenty healthy volunteers also participated in the study. Both structural and functional imaging data were obtained for the healthy volunteers in the same way as that for patients. The EPI data were motion corrected, aligned to the structural image, and smoothed

with an isotropic Gaussian kernel (6-mm FWHM). A general linear model (GLM) was used to generate activation maps that measure the correlation between smoothed EPI time series and a boxcar task function convolved with a canonical model of the hemodynamic response function using Statistical Parametric Mapping (SPM5) software (Friston et al., 1994). The resulting contrast images were used for ROI-based analysis as described below.

Structure-Specific Analysis

Each subject's hippocampi are segmented by an expert using a semiautomated protocol that uses landmark-driven diffeomorphic normalization to a disease-specific template with a fully labeled hippocampus (Pluta et al., 2009). The deformable cm-rep model (Yushkevich et al., 2006) is then fitted to each hippocampus. The model imposes a 3D coordinate system on the interior of the hippocampus. The 2D medial manifold forms the *skeleton* of the ROI, and is parameterized by $u = (u_1,u_2)$. u_1 and u_2 denote two axes of the cmrep coordinate system. For every location on the medial manifold, two line segments, called *spokes*, emanate and reach the boundary of the structure. These line segments are orthogonal to the boundary; they completely span the structure's interior, and thus provide the third axis in the cmrep coordinate system denoted by ξ. ξ varies from 0 at every point on the medial manifolds to −1 and +1 at points where the two spokes reach the boundary. Therefore, any point $\boldsymbol{x}$ within the hippocampal volume is represented by the vector (u_1,u_2,ξ). On the one hand, this provides a consistent set of coordinates between left and right hippocampi in the same subject as well as across subjects, thus making spatial correspondence information available. On the other hand, because the axes are based on the medial geometry of hippocampus, location of a point along the axes naturally annotates different subregions and its position relative to the shape of the structure. Since the spoke length is also the distance from the boundary to the medial manifold, it provides a measure of the local tissue thickness.

Let $C_L(x)$ and $C_R(x)$ be the fMRI contrast images for left and right hippocampus respectively, where $x=(u_1,u_2,\xi)$ denotes the cmrep coordinate of a point. A functional asymmetry map over the ROI can be computed as $A_f(x) = (C_L(x) - C_R(x))/(|C_L(x)| + |C_R(x)|)$. Examples of asymmetry maps are shown in Figure 1. We define the functional asymmetry index over the whole ROI as $AI_f = \frac{1}{V}\int_{x\in\Omega} A_f(x)dV$ where dV is the volume element at the cmrep coordinate x, V is the volume of the ROI and Ω is the cmrep domain.

Conventionally, the asymmetry index is calculated as $(N_L - N_R)/(N_L + N_R)$ where N_L and N_R are the number of suprathreshold voxels in the statistical parametric map within the hand-drawn ROIs in the left and right hemispheres, respectively (Golby et al., 2002). This measure is sensitive to the threshold chosen, and since the information about the distribution of the locations of suprathreshold voxels within the ROI is not used, we do not know if one subregion has more asymmetric activation than another. For comparison, we also calculated asymmetry index as $(M_L - M_R)/(|M_L| + |M_R|)$, where M_L and M_R are mean contrast images over the hand-drawn left and right ROI, respectively. For each of the three asymmetry measures, one way analysis of variance (ANOVA) is conducted to determine if asymmetry index as calculated from fMRI is predictive of memory lateralization as given by IAT.

We also study local morphological information in the form of local hippocampal thickness, $T(y)$, as measured at every boundary surface point y. Similar to functional asymmetry, thickness-based structural asymmetry maps can be generated by computing relative thickness difference as $A_s(y) = (T_L(y) - T_R(y)) / (T_L(y) + T_R(y))$ where $T_L(y)$ and $T_R(y)$ denote the thickness maps of the left and right ROI, respectively (Fig. 1). A thickness-based structural asymmetry index for a subject can be computed as $AI_s = \frac{1}{S}\int_{y\in\Psi} A_s(y)dS$ where dS is the surface element at the

boundary location with cmrep coordinate y, S is the total surface area of the ROI and Ψ is the domain of all boundary surface points.

Cluster Analysis

Group-wise cluster-based analysis (Nichols and Holmes, 2002) of quantities of interest is performed in the cmrep coordinate space. All analyses are carried out and visualized on the boundary mesh. The structural quantity of interest, thickness, is mapped to every boundary point y, and equals the length of the corresponding spoke, $T(y)$. Functional quantities of interest, including fMRI task contrast $C(x)$ and local asymmetry index $A_f(x)$, are defined at every interior point x within the ROI. These quantities are mapped to the boundary points y by taking a maximum intensity projection along the corresponding spoke. For a quantity $F(x)$ to be mapped as $F'(y)$, we write $F'(y) = \max_{\xi \in [0,b]} F(x)$ where $b = 1$ or $b - = 1$ since y is a boundary point. Once structural and functional features maps are thus defined over the boundary manifold, we study group differences using nonparametric cluster-based analysis with family-wise error rate (FWER) correction (Nichols and Holmes, 2002). A t-statistic is first computed at every boundary point y either for two-sample or pair wise comparison. Given an arbitrary threshold t_0, corresponding to a p-value p_0, the set of clusters with $t > t_0$, $p < p_0$ is extracted, where a cluster $C \in \Omega$ is defined as a simply connected subset in the domain of the boundary mesh that satisfies $t(y = \{u_1, u_2, b\}) \geq t_0 \forall y \in C$. The cluster mass of each cluster C is defined as $\int_C t(y)\, dA$ where dA is the area element at y. A histogram of maximum cluster masses obtained from a large number of identical experiments in which the labels of the subjects are randomly permuted is then constructed. The relative position of each cluster mass in the experiment with the correct labeling with respect to this maximum cluster mass histogram yields a permutation corrected p-value for each cluster.

RESULTS

Structure-Specific Maps of Thickness and Functional Activation

Structure-specific maps defined over a common coordinate system make it easier to visually compare spatial variation of quantities of interest across subjects as well as between left and right ROIs in the same subject. Figure 1a,b show fMRI task contrasts for the left and right ROI, respectively, for a TLE subject, rendered on the boundary surface of the cmrep model of the hippocampus. Although the right ROI seems to have more task-related activation overall, different subregions have different levels of *relative activation.* Spatial variation of interhemispheric activation asymmetry can be seen in the asymmetry maps $A_f(x)$ in Panels c and d. The asymmetry map in Panel c is from a subject with left lateralized IAT memory score, while that in Panel d is that of a right lateralized one. Despite the spatial variations in the respective asymmetry maps, the difference in overall asymmetry consistent with the IAT laterality can be clearly observed.

Similarly, thickness maps of the left and right hippocampi of a subject with left-sided TLE is shown in Figure 1e,f. The right hippocampus is thicker, as one would expect. Panels g and h show the thickness asymmetry maps $A_S(y)$ of two subjects with right and left-sided TLE, respectively. Again, the spatial variation of thickness as well as thickness-based structural asymmetry across the ROI can be visualized in this fashion, and entered into group analysis, which we describe in the following sections.

Group Differences: Structure

Structural atrophy is conventionally studied using ROI-based volumetric measurements. Here we use local thickness derived from the medial representation instead as a surrogate of structural integrity. Figure 2 summarizes group differences in thickness between different

subject groups, with left column showing average thickness differences and right column showing the corresponding *t*-statistic maps. Average difference map in thickness between all control hippocampi (both left and right) and patients' hippocampi on the seizure side show that control ROIs are thicker on average across most of the hippocampus (Panel a). Most severe reduction in thickness is found in the tail. Most significant clusters of thickness difference are in the anterior (S1) and posterior (S2) hippocampus.

Figure 2b shows average thickness difference across the hippocampal ROI between the left and right sides for controls. There is no significant difference in thickness between the two sides, as one would expect (although Bernasconi et al., 2003 found greater right hippocampal volume in the head region). In contrast, the ipsilateral ROIs in patients show severe atrophy compared with the contralateral side (Panel c). Large swath of the ROI is significantly thinner in the ipsilateral side (S3) with the most significant difference found in the tail (S4).

The structural differences presented in Panels a and c yielded significant clusters of thickness differences only in one direction consistent with hippocampal volumetry in literature: i.e., thinner regions in ipsilateral ROIs compared with controls, and thinner ipsilateral ROIs compared with the contralateral side in patients. However, in comparing contralateral patient ROIs to control ROIs, significant thickness differences are found in both directions (Fig. 2d). Significant clusters where control ROIs are thicker are found in regions similar to that found in Panel a (compare S5 to S1 and S6 to S2), although they are smaller. Interestingly, one cluster in the body of the hippocampus is found where contralateral patient ROIs are thicker than control ROIs (S7).

Group Differences: Functional Activation

Figure 3 presents group differences in functional activation between pairs of subgroups. Again, average group differences are shown on the left, and the corresponding *t*-statistic maps are shown on the right in each panel. Although control ROIs are on average more active than diseased hippocampi in patients during the scene encoding task, the biggest difference is in the body of the hippocampus (Cluster F1, Panel a), rather than in the head or tail, where the most significant structural differences occur. On the other hand, in comparing activation difference between control ROIs and the healthy hippocampi in patients, some regions in the healthy ROIs in patients are on average more active during scene encoding than control ROIs (Fig. 3d), even though no significant clusters could be found.

Contralateral hippocampi may have greater functional activation than corresponding ipsilateral ones in patients, because of possible reorganization of memory encoding function to the unaffected side (Golby et al., 2002). This is what we find in our data as well (Fig. 3c). Note that most of the hippocampus has positive activation difference values as well as positive *t*-values, indicating greater activation on average in the contralateral side. A very significant cluster (F4, $p < 10^{-6}$) in the tail overlapping with a cluster signifying structural asymmetry in Figure 2(c) (cluster S4) is observed. A second significant cluster (p 5 0.02) in the body of the hippocampus (F3) also overlaps with the bigger region showing thickness difference in Figure 2c (cluster S3), but perhaps more interestingly nearly coincides with the significant cluster (F1) showing greater activation in controls compared with ipsilateral ROIs in panel a.

Figure 3b presents average task contrast differences between left and right ROIs in controls. A significant cluster in the tail (F2) is found where right hippocampi are more active than the left. Table 1 lists the clusters of significant differences in thickness and functional activation described above and shown in Figures 2 and 3.

Asymmetry Maps and Summary Measurements

Thickness-based structural asymmetry indices AI_S are computed for all subjects in patient subgroups with left- and right-sided seizure foci as well as those in the control group. Figure 4(right) shows the distribution of these indices within each subgroup. As expected, since thickness can be considered an equivalent measurement for local volume, results are similar to volume-based asymmetry measurements (Cendes, 1993;Bernasconi et al., 2003). Asymmetry indices for left- and right-sided patient subgroups are centered around values with opposite signs, consistent with the diseased side having a thinner hippocampus. The control group, on the other hand, is more symmetric, and has less variation in the asymmetry index.

Similarly, functional asymmetry index AI_f is computed for each subject by integrating the asymmetry maps $A_f(x)$. Asymmetry indices are also computed using conventional method (Rabin et al., 2004) as well as mean contrast. Figure 4 shows the difference in asymmetry indices for subjects with left and right-lateralized IAT. IAT laterality is correlated with spatial correspondence-based asymmetry indices with a separation between the two groups that has statistical significance comparable with conventional indices.

DISCUSSION

Contribution

In this work, we present a clinical application of methods for point-wise structure-specific analysis that uses normalization of data to a shape-based coordinate system. This allows for the construction of structure-specific group difference as well as normalized asymmetry maps and can be integrated to generate summary statistics. These can (1) help visualize regional differences in structural and functional asymmetry in hippocampus in TLE, (2) may lead to a better understanding of the underlying pathology and structure-function relationships. Also, summary measures such as structural and functional asymmetry indices may have potential clinical use.

Structural Differences

Hippocampal volume loss in TLE patients compared with controls has been well documented in the literature (Cendes, 1993; Seidenberg et al., 2005). However, the presence and extent of atrophy in different subregions of the hippocampus have been studied in relatively few imaging studies. Bernasconi et al. (2003) found volumetric asymmetry in all three subregions (head, body, and tail) in the ipsilateral ROIs compared with controls, greatest in the head region. In contrast, a similar study by King et al. (1997) found greater atrophy in posterior segments, despite seizure onsets being more prevalent in the anterior regions in the same patient cohort. In our study, control hippocampi were thicker on average than ipsilateral ones across most of the ROI, yet most pronounced differences occur in anterior as well as posterior hippocampus (Fig. 2a). Even though this pattern of atrophy is consistent with known pathology, it is hard to generalize these patterns, as is evident from the somewhat conflicting findings reported in the literature.

We found clusters of significantly reduced thickness in the contralateral ROI in patients as compared to controls as well (Fig. 2d), although these clusters are relatively small. Atrophied contralateral hippocampus in TLE has been reported by others using volumetry (Jokeit et al., 1999;Bernasconi et al., 2003). Hogan et al. (2004) did not find volume reductions in the contralateral hippocampus, even though shape changes in the head were reported. Our data also show a cluster of increased thickness in contralateral hippocampi in the anterior portion of the hippocampal body when compared with our control cohort. This is a surprising finding, and we speculate that this may indicate disease-related plastic changes in the contralateral hippocampus.

Pairwise comparison of thickness maps between the ipsilateral and contralateral hippocampi in patients show that almost the entire ROI is thinner in the diseased side (Fig. 2c) on an average. A very significant cluster is observed in the tail ($P < 10^{-6}$), and a larger but less significant cluster encompasses almost the entire ROI except the anterior region of the head. Atrophy in the hippocampal head is a common finding (Bernasconi et al., 2003;Sencer et al., 2003)—and our results show reduced thickness in the head in the ipsilateral side when compared with controls (Fig. 2a). However, the head also shows reduced thickness in the contralateral side compared to controls (Fig. 2d). This might be one reason why group difference in thickness between the two sides in patients in the head region, even though present on average, does not yield a significant cluster in permutation-based cluster analysis.

Functional Activation Differences

Activation asymmetry between the two hippocampi reflecting some lateralization of memory function in TLE patients has been widely reported in the literature (Golby et al., 2002; Rabin et al., 2004; Powell et al., 2008). Widespread activation asymmetry is observed in our data as well (Fig. 3c), with a significant cluster in the body (F3) that overlaps with the cluster of activation difference between controls and ipsilateral ROIs (F1), and one in the tail (F4) that coincides with a significant cluster of greater right hippocampal activation in controls (Fig. 3b, F2). Greater right hippocampal activation in controls has been reported in the literature in visual memory encoding (Figueiredo et al., 2008), and in visual scene encoding in particular (Golby et al., 2001). The posterior location of this cluster in controls is consistent with published data (Powell et al., 2005; Figueiredo et al., 2008). Its colocalization with cluster F4, which is very strongly lateralized ($P < 10^{-6}$), may indicate some transfer of normal visual encoding function to the posterior regions in the contralateral side for TLE patients. Note that the patient cohort included roughly equal number of left and right TLE patients.

Summary Measurements of Asymmetry

Structural asymmetry measurements based on hippocampal volumetry have been extensively used to study disease related atrophy in TLE (Cendes, 1993; Bernasconi et al., 2003). Structural asymmetry indices generated by spatial correspondence-based structural asymmetry maps replicate these findings as shown in Figure 4. On the other hand, we have shown that spatial correspondence-based functional asymmetry measures are useful for presurgical memory lateralization in TLE patients (Fig. 4). This has the potential for further improving the reliability and power of asymmetry analysis, hopefully taking us closer to be able to use fMRI as a noninvasive alternative to IAT (Baxendale, 2002).

Methodological Considerations

Establishing spatial correspondence of anatomy across subjects is a prerequisite for any population study in neuroimaging, including normalization methods for whole brain analysis (Christensen et al., 1997). However, often such analyses are exploratory in nature, and can suffer from low sensitivity, as discussed by other researchers (Miller et al., 2005), particularly when clinically meaningful effects are confined to a small region of interest. Thus, ROI-based analysis techniques have become popular where summary measurements averaged in some fashion over the ROI are used in order to increase sensitivity. However, specificity of effects within the ROI is lost and sensitivity may also suffer if there is enough heterogeneity of structure and function within ROI. The ability to establish spatial correspondence across ROI can, therefore, be a valuable tool when (1) such heterogeneity within ROI is known to exist, (2) when study of asymmetry in structure and function between hemispheres within the subject and between different populations can provide clinically meaningful information, and (3) when the structure(s) of interest in the clinical application can be reliably described using geometric shape modeling. In this sense, structural and functional asymmetry analysis in the hippocampal

ROI in TLE is an appropriate application area for the structure-specific methodologies used here, and similar ones proposed by other researchers (Hogan et al., 2004; Styner et al., 2004; Thompson et al., 2004; Bouix et al., 2005; Miller et al., 2005). However, many of these methodologies have only been used to study structural changes (Hogan et al., 2004; Styner et al., 2004; Thompson et al., 2004; Bouix et al., 2005) or functional activation (Zeineh et al., 2003), and to our knowledge, none have used such structure-specific analysis to study both structural and functional differences within the hippocampus in TLE. The advantages of this approach in fMRI analysis have been described in Yushkevich et al. (2007). Here we have presented the first application of this framework in the study of TLE.

Limitations

The ultimate goal of this research is to be able to make predictions of functional localization and postsurgical outcome for individual TLE patients. Toward this end, it is imperative for any methodology to first achieve robust group level predictions. Even though we have been able to reproduce several known group level results, a major hurdle to move toward single-subject level analysis is the relatively small size of our dataset. Imaging related limitations such as image resolution and distortion also pose a significant challenge.

Future Work

Ongoing work will validate these methodologies on a larger dataset of patients and include structure specific analysis on other medial temporal lobe ROIs such as the parahippocampal gyrus and amygdala. Correlation of neuropsychological measures with asymmetry maps will be performed to assess their value for predicting surgical outcome. Improvement in image acquisition protocols, including refinement of fMRI task design to elicit more robust activation in the temporal lobe is another direction of our future work that has the potential to further increase the power and reliability of statistical analysis, in combination with correspondence-based methods.

Finally, the ability to map structural and functional data and asymmetry measurements to a *common* coordinate system opens up possibilities for testing clinical hypotheses that relate structure and function in a diseased population. For example, in combination with hippocampal subfield labeling, one could try to answer questions like whether there is a correlation between observed atrophy specific to a subfield and functional activation within that region.

Acknowledgments

This publication was made possible by grant numbers R21 NS061111, K25 AG02778, K24 NS058386, P30 NS045839 and T32 EB000814 from NIH.

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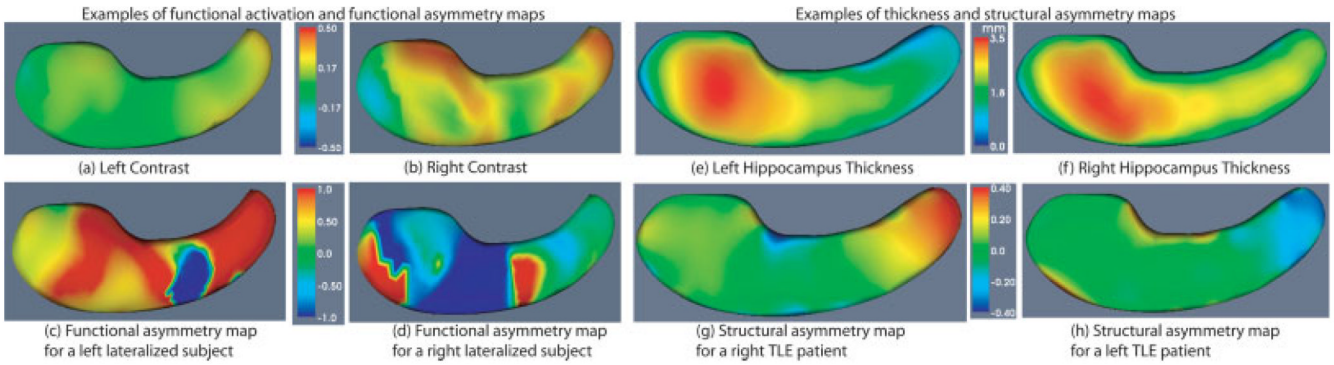

FIGURE 1.

Panels a and b show fMRI task contrast maps in the left and right hippocampus of a subject (blue is less contrast, red is more). Panels c and d show asymmetry maps for two subjects with left- and right-lateralized memory functions in IAT, respectively. Blue means more activation in the right, red means more activation in the left. All four Panels (a–d) show maximum intensity projection of quantities of interest inside the hippocampus computed in the cmrep coordinate system. Panels e and f show left and right hippocampus thickness maps of a subject (blue is thinner, red is thicker). Panels g and h show thickness asymmetry maps of two patients with right- and left-sided disease, respectively (blue means right is thicker, red means left is thicker). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

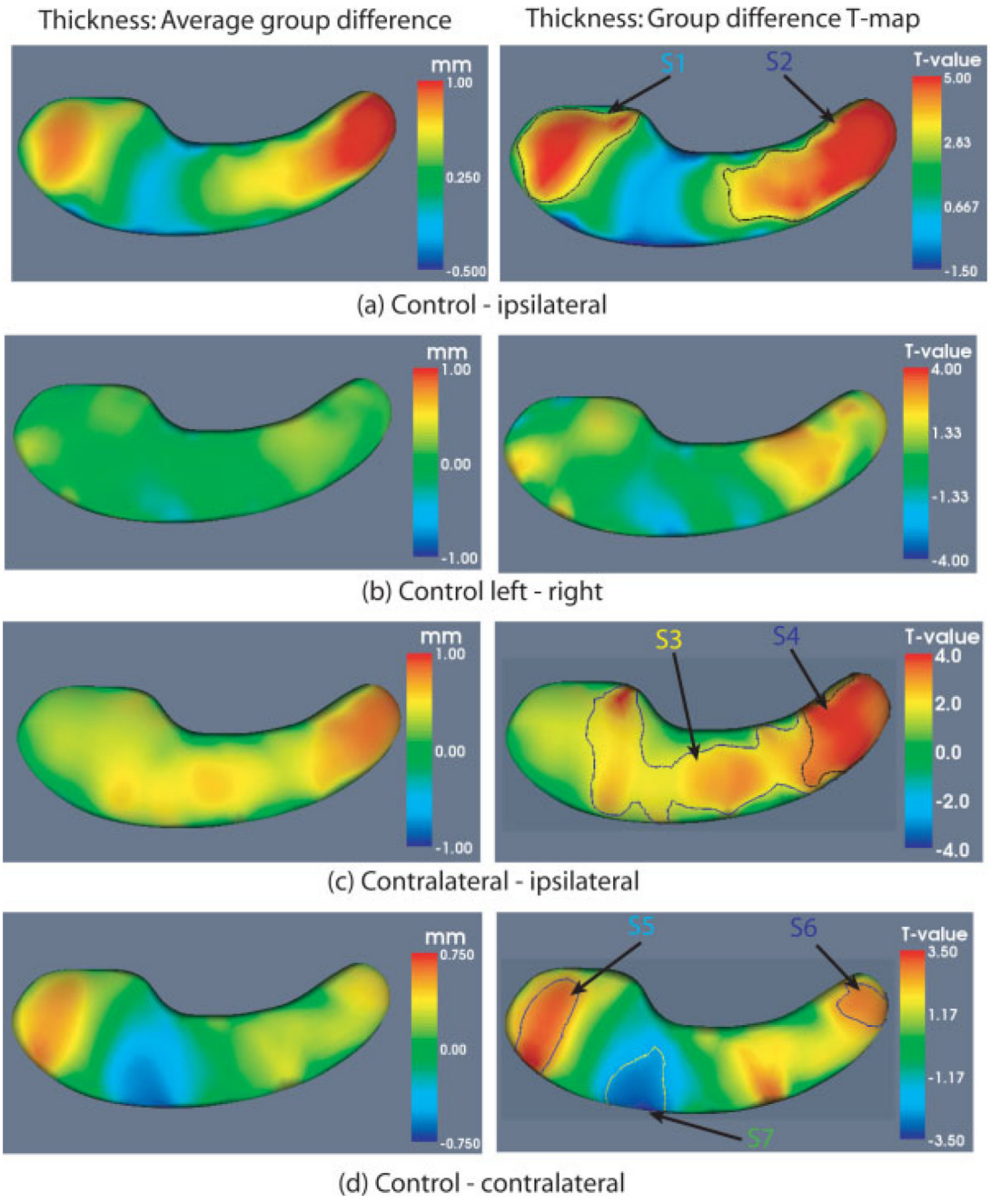

FIGURE 2.

Group difference in thickness between different pairs of subgroups of subjects is shown in each of panels (a–d). Left column of each panel shows the average group difference whereas the right column shows the corresponding *t*-statistic map. Significant clusters of group difference are depicted with contours on the *t*-maps, and are also listed in Table 1. See text for discussion. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

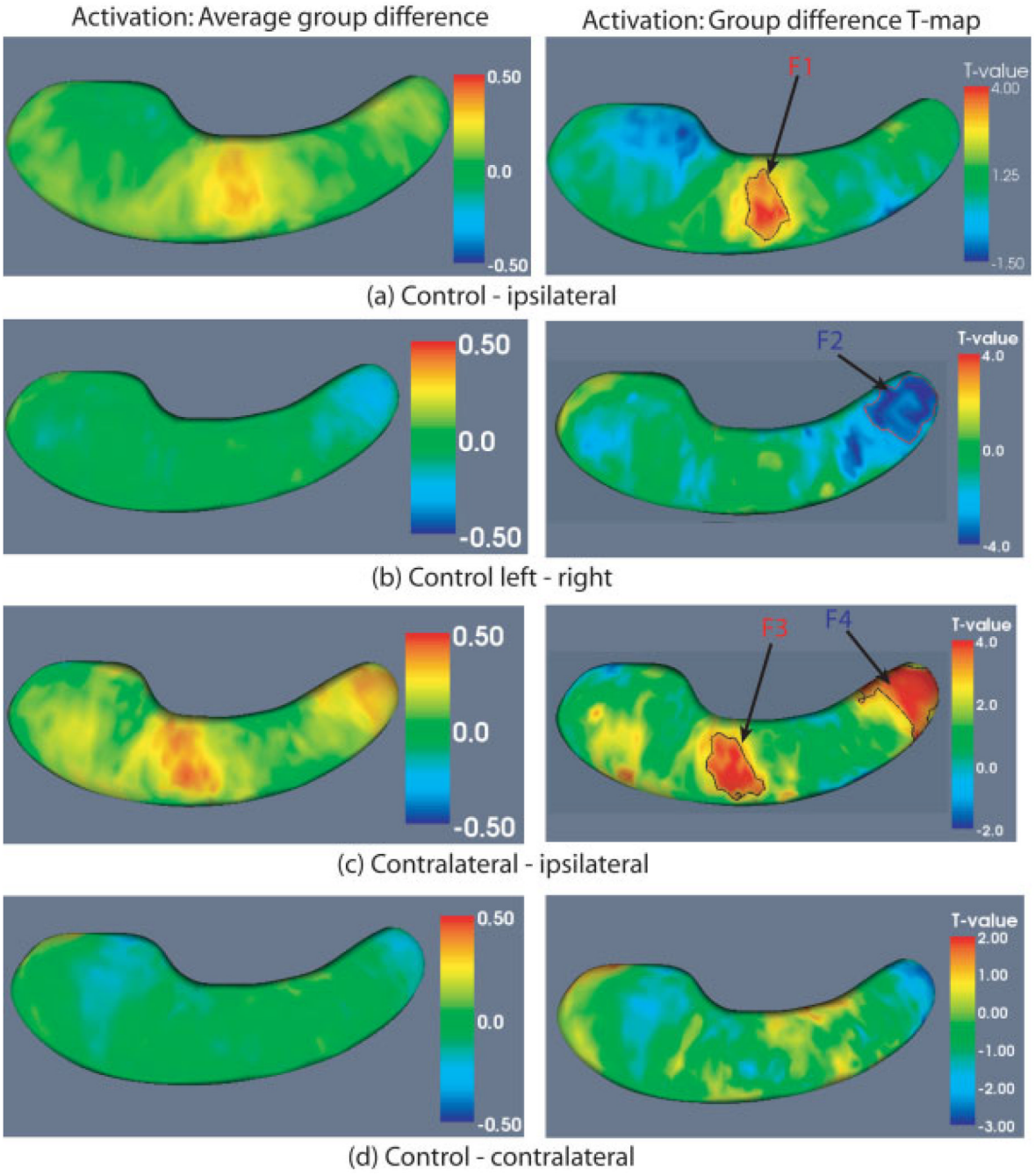

FIGURE 3.

Group difference in fMRI task contrast between different pairs of subgroups of subjects is shown in each of Panels (a–d). Left column of each panel shows the average group difference whereas right column shows the corresponding *t*-statistic map. Significant clusters of group difference is depicted with drawn contours on the *t*-maps, and are also listed in Table 1. See text for discussion. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

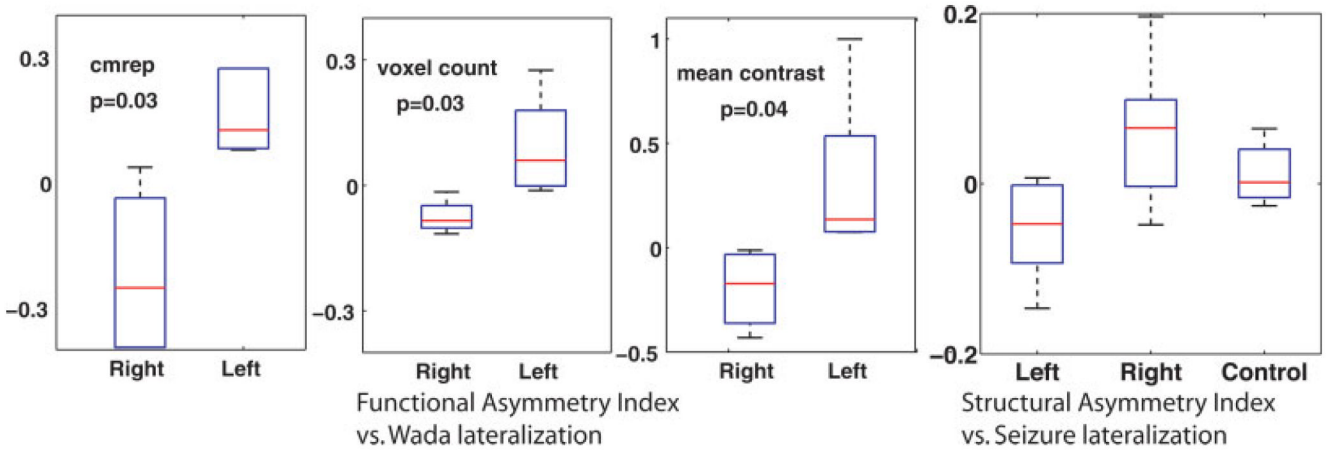

FIGURE 4.

The three left panels show box plots showing asymmetry indices of patients with left and right dominant IAT memory laterality. Asymmetry indices are computed using cmrep (left), voxel count (middle), and mean contrast (right) over the ROI. A positive asymmetry index implies higher activation in the left ROI and vice versa. Group separation is equally significant using cmrep ($P = 0.03$) as using conventional voxel count ($P = 0.03$) as well as mean contrast based ($P = 0.04$) asymmetry analysis. The rightmost panel shows a box plot of thickness based asymmetry indices of patients with left and right lateralized seizures and controls. A positive asymmetry index implies a thicker left hippocampus and vice versa. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE 1

Table Enumerating Clusters of Significant Differences in Thickness and Functional Activation Between Different Pairs of Subject Subgroups as Defined in Column 1 [Color table can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Group Contrast	Cluster	Location	Area (mm^2)	$p_{threshold}$	$\bar{t}$	p_{corr}
Thickness Clusters						
Control > Ipsi	S1	Anterior	118.4	0.002	4.06	0.002
Control > Ipsi	S2	Mid-posterior-to-posterior	290.0	0.002	3.93	<0.0001
Contra > Ipsi	S3	Mid-to-posterior	497.3	0.05	2.42	0.003
Contra > Ipsi	S4	Posterior	173.2	0.005	3.39	<0.0001
Control > Contra	S5	Anterior	67.2	0.01	2.62	0.018
Control > Contra	S6	Posterior	43.4	0.01	2.47	0.032
Contra > Control	S7	Anterior-mid	76.2	0.01	−2.61	0.028
Activation Clusters						
Control > Ipsi	F1	Mid	28.4	0.002	3.15	0.022
Control right > Control left	F2	Posterior	65.3	0.005	−3.19	0.005
Contra > Ipsi	F3	Mid	43.0	0.005	3.50	0.021
Contra > Ipsi	F4	Mid	139.3	0.005	3.34	<0.0001

Clusters annotated with the same colors have significant overlap. Location describes approximate location of cluster along the long axis of the hippocampus. Area is the surface area of the cluster on the medial manifold. Every cluster is defined as a connected region with a $p < p_{thershold}$. $\bar{t}$ is the average value of the t-statistic within the cluster. p_{corr} is the FWER-corrected p-value of the cluster.