Spatial Correspondence Based Asymmetry Analysis in Hippocampus: Application to Temporal Lobe Epilepsy

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Abstract. Quantification of functional and structural asymmetry in the brain can provide clinically useful information. In the study of temporal lobe epilepsy (TLE), such analyses are often carried out within the hippocampus. Functional asymmetry is typically expressed in terms of differences in the number of suprathreshold voxels activated, normalized to total activation, within the structure of interest, while the subjects perform a cognitive task in a functional magnetic resonance imaging (fMRI) experiment. Structural asymmetry is usually expressed in terms of normalized, relative hippocampal volume differences between hemispheres. We introduce methodologies for carrying out asymmetry analysis for region of interest (ROI) based studies that take into account information about spatial correspondence of voxels on two sides of the brain. We apply this methodology to make determination of hemispheric specialization during a memory encoding task in patients with refractory TLE. Memory lateralization is an important step in the presurgical evaluation of such patients for temporal lobectomy. Our functional asymmetry scores in hippocampus are found to have a strong correspondence with hemispheric dominance given by Intracarotid Amobarbital Testing (IAT), which is the widely accepted gold standard for determining laterality. We also use local thickness measurements to study structural asymmetry within hippocampus. Regional variation in thickness differences between different subgroups are revealed using the correspondence based approach.

1 Introduction

If segmentations of structures of interest are available, region of interest (ROI) based analysis of structural as well as functional data can help increase sensitivity of population studies and allow structure-specific hypothesis to be tested.

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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 [6]. 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 model based structure-specific approach such as the continuous medial representation (cmrep) [7] is the availability of a common shape based coordinate system within the volume of each structure modeled. Any quantity of interest – functional activation [5], as well as morphometric variables – mapped onto this common coordinate system has a natural point-by-point correspondence. For functional asymmetry analysis, this allows us to have a local measure of asymmetric activation at each point of the ROI, instead of having to rely on a global measure of asymmetric activation within the whole ROI, as is done conventionally where no such point-to-point correspondence information is available. Similarly, local structural measurements such as tissue thickness can also be studied using this coordinate system.

In this paper, we make use of continuous medial representation based shape modeling for asymmetry analysis within the hippocampus, a critical region for memory function. Analyzing functional data using this framework provides an asymmetry map over the entire volumetric ROI that can be informative about the variability of asymmetric activation within different subregions. Asymmetry indices generated by integrating such maps may provide a more powerful statistical measure than conventional voxel count based indices.

Intracarotid Amobarbital Testing (IAT) is an invasive procedure used for lateralizing language and memory function in patients. Lateralization of language function, however, has been reliably performed using fMRI [8]. In contrast, use of fMRI for memory lateralization hasn’t been shown to be as reliable, despite a lot of promise as potentially being a noninvasive alternative to IAT [9]. In section 3, we show that correspondence based measures of asymmetry in hippocampus as introduced here has a strong concordance with hemispheric dominance as reported by IAT in a cohort of TLE patients.

Medial representation based structural analysis in the hippocampus has been used in clinical studies [3, 4], as well as other studies that derive thickness measures from shape modeling [2]. We construct thickness maps in hippocampus using the cmrep coordinate system. Structural asymmetry indices [10] are computed using these thickness maps. Subregions within hippocampus that are thinner in TLE patients compared to controls, as well as within the affected hemisphere compared to the healthy one in patients, are revealed.

2 Materials and Methods

2.1 Imaging

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 scene was used as control condition. Bold fMRI images were obtained from a 3 Tesla Siemens Trio scanner, using a gradient echo echoplanar (EPI) sequence with TR = 3000ms, TE = 30 ms, and 3 mm isotropic voxels. A high resolution (voxel size 0.9375 x 0.9375 x 1.5 mm) T1-weighted structural MRI scan was also obtained. Further details of the experimental protocol can be found in [11]. 20 patients with TLE participated in the study, out of which 12 had their IAT dichotomized according to hemispheric dominance for memory for comparison with fMRI data. Structural MRI data from 14 healthy volunteers were also obtained.

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 timeseries and a boxcar task function convolved with a canonical model of the hemodynamic response function using Statistical Parametric Mapping software [12]. The resulting contrast images were used for ROI based analysis as described below.

2.2 Region of Interest Analysis

Each subject’s hippocampi are segmented by an expert using a protocol described in Pluta et al. [13]. The deformable cm-rep model [7] is fitted to each hippocampus. The model imposes a 3D coordinate system on the interior of the structure of interest, hippocampus in this case. 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. Let the medial manifold be parameterized by \( u = (u_1, u_2) \) and let \( x \) be the location of any point within the hippocampal volume. In the cmrep coordinate system, \( x \) is represented by the vector \( (u_1, u_2, \xi) \) where \( \xi \in [-1, 1] \). For every location \( u \) on the medial manifold (where \( \xi = 0 \)), two line segments, called spokes, emanate and reach the boundary of the structure, as \( \xi \) varies from 0 to -1 and 0 to 1, respectively (Figure 1). These line segments are orthogonal to the boundary of the structure, and they completely span the structure’s interior. Thus, for every point on the boundary, the length of the spoke on which the point lies provides a measure of the local tissue thickness as measured from the boundary to the medial surface.

Let \( x \) be the location of a point within the hippocampal volume in the cmrep coordinate system, and \( C_L(x) \) and \( C_R(x) \) be the fMRI contrast images for left and right hippocampus respectively. 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 2. We define the functional asymmetry
index over the whole ROI as

\[ AI_f = \frac{1}{V} \int_{x \in \Omega} A_f(x) dV, \]  

(1)

where \( dV \) is the volume element at the cmrep coordinate \( x \), \( V \) is the volume of the ROI and \( \Omega \) is the cmrep domain.

Conventionally, 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 [11]. 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 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 surface point \( y \), with the help of the cmrep coordinate system. 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 map of the left and right ROI respectively. A thickness based structural asymmetry index for a subject can be computed as

\[ AI_s = \frac{1}{S} \int_{y \in S} A_s(y) dS, \]  

(2)

where \( dS \) is the surface element at the surface location with cmrep coordinate \( y \), \( S \) is the total surface area of the ROI and \( S \) is the domain of all surface points. Group differences in spatial variation in thickness, for example, between hippocampi in the diseased and healthy side in patients, or between patient and control population – can be visualized in the cmrep coordinate system. In
addition, summary measures like average thickness over the entire hippocampus, can also be computed and compared between different subgroups of subjects.

3 Results

Figure 2 shows results of ROI based functional asymmetry analysis using the cmrep model. Panels (a) and (b) show fMRI task contrasts for a subject rendered on the surface of the cmrep model of the hippocampus for the left and right ROI respectively. We can observe that while the right ROI seems to have more task related activation overall, different subregions have different levels of relative activation. Normalization to a shape based coordinate system allows us to capture the spatial variation of asymmetric activation over the ROI. This can be seen in the asymmetry maps in panels (c) and (d). Note that the asymmetry map in panel (c) is derived from a subject with right lateralized IAT memory score, while that in panel (d) is that of a left 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.

Asymmetry index for each subject is computed using equation 1. Asymmetry indices are also computed using conventional method [11] as well as mean contrast. Figure 3 shows the difference in asymmetry indices for subjects with left and right-lateralized IAT. IAT laterality is more strongly correlated with spatial correspondence based asymmetry indices with a clear separation between the two groups.

We use local thickness measurements mapped on the hippocampal surface points as an example of a morphological quantity that can be studied utilizing the cmrep coordinate system. Thickness based structural asymmetry indices are computed using equation 2 for all subjects in patient subgroups with left and right sided seizure foci as well as those in the control group. Figure 4 shows the distribution of these indices within each subgroup. As expected, since thickness can be considered a surrogate measurement for local volume, results are similar to those based on volumetry based structural asymmetry measurements [10, 14]. 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.

We visualize spatial variation of thickness within different subgroups using the cmrep coordinate system (Figure 5). Panel (a) shows average thickness differences between patients and controls. Patients have reduced thickness in most subregions, yet, there is considerable variation in the amount of reduction which can be observed in the cmrep template space. A two sample t-test is performed at each surface location. Permutation based correction is used to determine a significant threshold with corrected $p$-value $< 0.05$ [15]. Most significant atrophy is found in regions of the anterior hippocampus as well as in the tail (regions within black contours in panel (b)). These findings are consistent with hippocampal volumetry [14]. Similarly, variation of average difference in thick-
Fig. 2. All panels show maximum intensity projection of quantities of interest inside the hippocampus computed in the cmrep coordinate system. (a) and (b) show fMRI task contrast maps in the left and right hippocampus of a subject (blue is less contrast, red is more). (c) and (d) show asymmetry maps for two subjects with right and left lateralized memory functions in IAT respectively. Blue means more activation in the right, red means more activation in the left.

ness between the diseased and healthy hippocampi in patients is shown in panel (c). Most significant differences (panel (d)) are in the tail of the hippocampus in this case.

4 Discussion

We have introduced methods for asymmetry analysis in structures of interest that make use of spatial correspondence of voxels. Structure specific analysis uses normalization of data to a shape based coordinate system. This allows for the construction of structure specific asymmetry maps. These can help visualize regional differences in structural and functional asymmetry and can be integrated to generate summary statistics.

We have shown these spatial correspondence based functional asymmetry measures to be useful for presurgical memory lateralization in TLE patients. 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.

Spatial correspondence based structural asymmetry analysis using local thickness measures available from the geometric model has been shown to replicate existing results that rely on hippocampal volumetry. Availability of point correspondence will allow structural asymmetry studies at a finer spatial scale. For
Fig. 3. 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 over the ROI. A positive asymmetry index implies higher activation in the left ROI and vice versa. Group separation is much more significant using cmrep (p=0.0005) than using conventional voxel count (p=0.03) as well as mean contrast based (p=0.04) asymmetry analysis.

Fig. 4. Box plot showing 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.

example, in combination with high resolution imaging and subfield labeling [6], one can test subfield-specific clinical hypothesis.

Finally, the ability to map structural and functional data and asymmetry measurements in 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.

Ongoing work will validate these methodologies on a larger dataset of patients and include structure specific analysis on ROIs such as the parahippocampal gyrus. The asymmetry scores will be regressed against neuropsychological measures to assess their value for predicting surgical outcome. One could also further
extend the idea of using correspondence in the time domain. Instead of using contrast images as produced by a GLM, one could directly compare the activity of corresponding voxels at the same time points.

References