comparison between LSE and the sparse estimation. The sparse method shrinks the estimated coefficients toward zero.

Basically, the sparse regression approach penalizes insignificant low degree LB-coefficients while the LSE does not. Then only about 5-6% nonzero coefficients were used to reconstruct the surface. As a result, the sparse regression smooth out the resulting statistical map whereas LSE does not. Therefore, LSE probably needs an additional pre-smoothing step to guarantee the smoothness for the random field theory.

7.7.2 *Effect of Aging on Hippocampus Shape*

The sparse shape modeling framework can be used in determining the effects of age and gender on the shape of amygdala and hippocampus. Here, we demonstrate that the proposed L_1-penalty approach can detect the localized anatomical difference within the subcortical structures while the traditional method cannot.

Image Processing. We have high-resolution T1-weighted inverse recovery fast gradient echo MRI, collected in 124 contiguous 1.2-mm axial slices (TE=1.8 ms; TR=8.9 ms; flip angle = $10°$; FOV = 240 mm; 256×256 data acquisition matrix) of 52 middle-age and elderly adults ranging between 37 to 74 years (mean age = 55.52 ± 10.40 years). There are 16 men and 36 women in the study. Trained raters manually segmented the amygdala and hippocampus structures from T1-weighted images. Brain tissues in the MRI scans were automatically segmented using Brain Extraction Tool (BET) (Smith, 2002). Then we performed a nonlinear image registration using the diffeomorphic shape and intensity averaging technique with the cross-correlation as the similarity metric using Advanced Normalization Tools (ANTS) (Avants *et al.*, 2008). Using the deformation field obtained from warping the individual image to the template, we aligned the amygdala and hippocampus binary masks to the template space. The normalized masks were then averaged to produce the subcortical structure template. The isosurfaces of the subcortical structure template were extracted using the marching cube algorithm (Lorensen and Cline, 1987).

Surface Displacement. The displacement vector field is defined on each voxel, while the vertices of mesh are located within a voxel. So we linearly interpolated the vector field on mesh vertices from the voxels. The length of the displacement vector at each vertex is computed and used as a feature to measure the local shape variation with respect to the template space. Since the lengths of displacement defined on mesh vertices are expected to be noisy due to errors associated with image acquisition and preprocessing, it is necessary to smooth out the noise and increase the signal-to-noise ratio (SNR) (Chung *et al.*, 2003c, 2010d). Further, smoothing is desirable in satisfying the assumptions of the random field theory, which is used in correcting for multiple comparisons (Adler, 2000; Worsley *et al.*, 1996b). Gaussianness and sufficient smoothness of random fields are needed. Therefore, it is crucial so smooth the displacement along the subcotical surfaces. Many previous surface data smoothing approaches have used heat diffusion type of smoothing to reduce surface noise (Andrade *et al.*, 2001; Chung *et al.*, 2003b; Malladi and Ravve, 2002; Perona and Malik, 1990; Sochen *et al.*, 1998; Tang *et al.*, 1999; Taubin, 2000). However, such approaches tend to have numerical instability that has been amply discussed in previous chapters.

Volume Difference. In the traditional approach, the volume of a structure is simply computed by counting the number of voxels within the binary mask. In order to account for the effect of inter-subject variability in brain size, the brain volume excluding cerebellum was estimated and covariated in a general linear models (GLM). The brain volume is significantly correlated with the amygdala (p-value < 0.0001) and the hippocampus volumes (p-value < 0.00001). Since amygdala and hippocampus volumes are related to the brain volume, it is crucial to factor out the brain volume in GLM. So we model `Volume` of amygdala and hippocampus as

$$\texttt{Volume} = \beta_1 + \beta_2 \cdot \texttt{Brain} + \beta_3 \cdot \texttt{Age} + \beta_4 \cdot \texttt{Gender} + \epsilon,$$

where `Brain` is the total brain volume, `Age` and `Gender` are age and gender of subjects. We did not find a significant age effect on the amygdala and hippocampus at $\alpha = 0.05$. However, we found a significant gender effect on the left hippocampus (p-value $= 0.04$), Since the results are based on the whole volume of the amygdala and hippocampus, it is still unclear if the there are any localized shape differences within the parts of the subcortical structures. Therefore, we performed a localized deformation-based morphometry (DBM) on the surfaces of the substructures.

Deformation-Based Surface Morphometry. The length of displacement vector field on the template surface was estimated using the sparse framework. `Length` is regressed over the total brain volume and other variables:

$$\texttt{Length} = \beta_1 + \beta_2 \cdot \texttt{Brain} + \beta_3 \cdot \texttt{Age} + \beta_4 \cdot \texttt{Gender} + \epsilon.$$

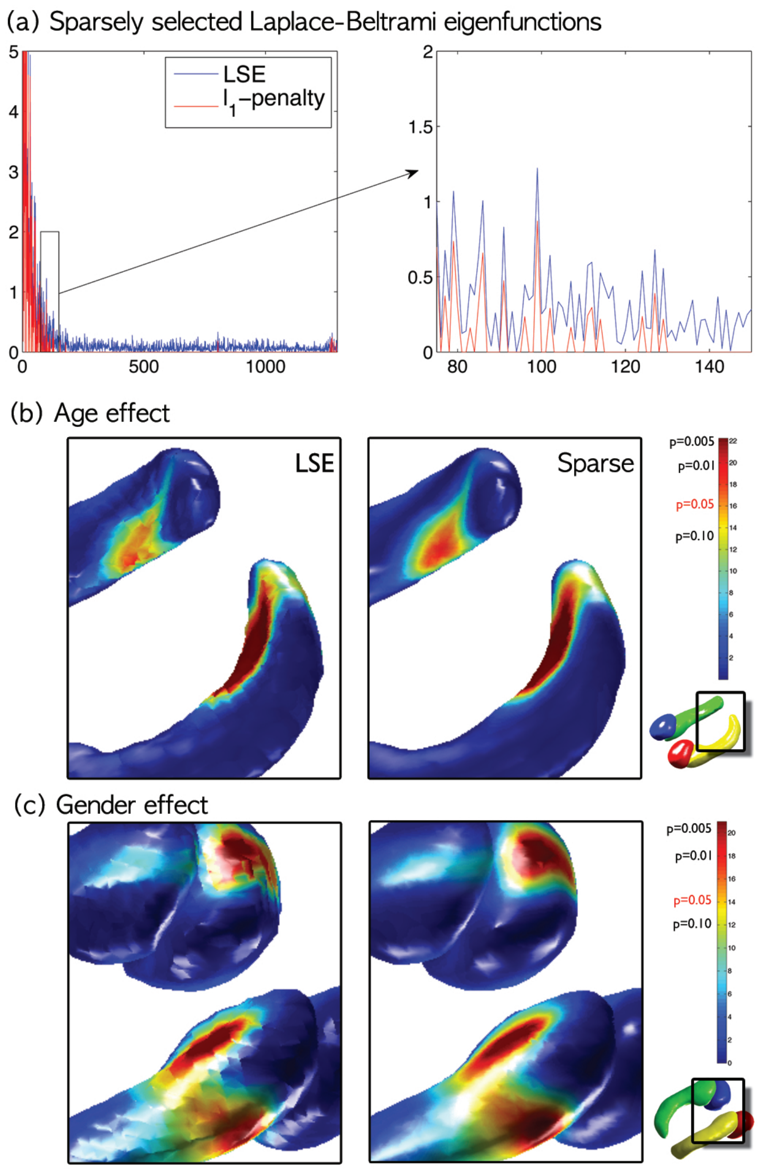

Fig. 7.22 (a) Sparsely selected Laplace-Beltrami eigenfunctions. Absolute values of the corresponding coefficients are shown. Age (b) and gender (c) effects are shown. The details of the study can be found in Kim *et al.* (2012a). The figure was generated by Seung-Goo Kim of Seoul National University.

The age and gender effects were determined by testing the significance of the estimated parameters β_3 and β_4 at $\alpha = 0.05$. The results are displayed in Figure 7.22.

We found the region of significant effect of age on the posterior part of hippocampi (left: max $F = 33.5, p < 0.0002$; right: max $F = 18.5, p = 0.016$). Particularly, on the caudal regions of the left and right hippocampi, we found highly localized effect. It is consistent with other shape modeling studies on hippocampus (Qiu and Miller, 2008; Xu *et al.*, 2008). We did not find any age effects on the amygdala surface at $\alpha = 0.05$. We also found the localize regions of gender effect on the amygdalae (left max $F = 16.90, p = 0.02$; right max $F = 26.41, p < 0.001$) and the left hippocampus (max $F = 25.35, p < 0.002$).