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Discussion of "LESA: Longitudinal Elastic Shape Analysis of Brain Subcortical Structures"

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The brain surfaces including both cortical and subcortical structures including hippocampus have been analyzed for more than a decade using publicly available software packages such as FreeSurfer (Dale and Fischl 1999) and SurfStat (Worsley et al. 2009; Chung et al. 2010). Zhang et al. (2022) proposes an elastic shape metric based method for performing longitudinal shape analysis on brain subcortical structures. However, the demonstrated applications are limited to global summary measures such as the total surface area and principle component (PC) scores significantly limiting the impact of the study. For analyzing total surface area, we do not even need to align structures using LESA. PC scores loose richer vertex-based local information and it is unclear what parts of the hippocampus are responsible for longitudinal change. A more effective approach is to perform local shape analysis using the Deformation-based Morphometry (DBM) and Tensor-based Morphometry (TBM) after obtaining deformation in LESA (Ashburner et al. 1998; Ashburner, Good, and Friston 2000; Thompson et al. 2000). Considering elastic methods put severe constraints on the Jacobian determinant of image deformation (Chung et al. 2001), it is not clear LESA can be effectively used in local shape analysis. We contrast shape analysis done in Zhang et al. (2022) against DBM and TBM in a longitudinal hippocampus study (Chung et al. 2011).

The DBM uses the deformation field obtained through nonlinear image registration (Ashburner et al. 1998; Chung et al. 2001). In DBM, it is possible to detect local shape differences within the hippocampus and identify exactly what subregion of hippocampus is responsible for the most growth (Figure 1). Given surface $\mathcal{M}$, the *deformation* is given as a three-dimensional vector field $d(x)$ at vertex $x \in \mathcal{M}$. The deformation can be represented in the Lagrangian coordinate system as $d(x) = x + U(x)$, where $U = (U_1, U_2, U_3)$ is the *displacement* in the elastic deformation theory and measures a relative movement of vertex x (Chung et al. 2001). The longitudinal change over time t can be then modeled as $\frac{\partial U}{\partial t}(x,t) = L(U) + \Sigma^{1/2}(x)\epsilon(x)$. If the change is assumed to follow a diffusive behavior, then L is the Laplacian. If the morphological changes follow a fluid dynamics model or elastic deformation, L becomes the Navier–Stokes or elastic operator (Chung et al. 2001). Σ is the symmetric positive definitive covariance matrix allowing correlations between components of the deformations. The error vector field ϵ is assumed to be zero mean and unit standard deviation possibly Gaussian (Worsley et al. 1996).

In contrast to DBM, TBM quantifies the differential qualities called the displacement tensor $\frac{\partial U}{\partial x} = (\frac{\partial U_i}{\partial x_j})$ (Thompson et al. 2000; Chung et al. 2001). Suppose surface $\mathcal{M}$ is parameterized by $x = X(v)$ with parameters $v = (v^1, v^2) \in \mathbb{R}^2$. The partial derivatives $X_i = \partial X / \partial v^i$ forms the basis in the tangent space. The Riemannian metric tensor $g = (g_{ij})$ is then given by the inner product $g_{ij} = \langle X_i, X_j \rangle$, which measures the amount of the deviation from the flat Euclidean plane. Unlike analyzing the total surface area $\int_{X^{-1}(\mathcal{M})} \sqrt{\det g} \; du$ as in Zhang et al. (2022), we can analyze the local *area element* $\sqrt{\det g}$ at the vertex resolution, the generalization of the Jacobian determinant, often used in TBM (Chung et al. 2003). Often DBM and TBM provide complimentary local shape information (Chung et al. 2001).

Since Zhang et al. (2022) only analyzed single summary measure per surface, it does not have multiple comparisons. The multiple comparisons across all the vertices is traditionally handled through the random field theory (Worsley et al. 1996). The random field theory is implemented in most brain imaging tools such as SPM (Ashburner et al. 1998) and SurfStat (*https://laplcebeltrami.github.io/SurfStat*) (Worsley et al. 2009; Chung et al. 2010). SurfStat is the most widely used MATLAB package for building both fixed- and mixed-effects models for brain surface data. Mixed-effect model parameters are estimated using the restricted maximum likelihood (REML). SurfStat uses a model formula approach similar to R and we can simply set up a mixed-effect model used in Figure 1 as

```
lm = 1+ Sex + Age + Group + Age*Group
     + random(Subject) + I;
```

making variable `Subject` into a random effect. Identity matrix `I` is added to allow for independent noise in every subject. Then the corrected p-value of test statistic T is reported as $P\big(\sup_{x\in\mathcal{M}} T(\mathbf{x}) \geq y\big)$. Figure 1 displays the output of SurfStat.

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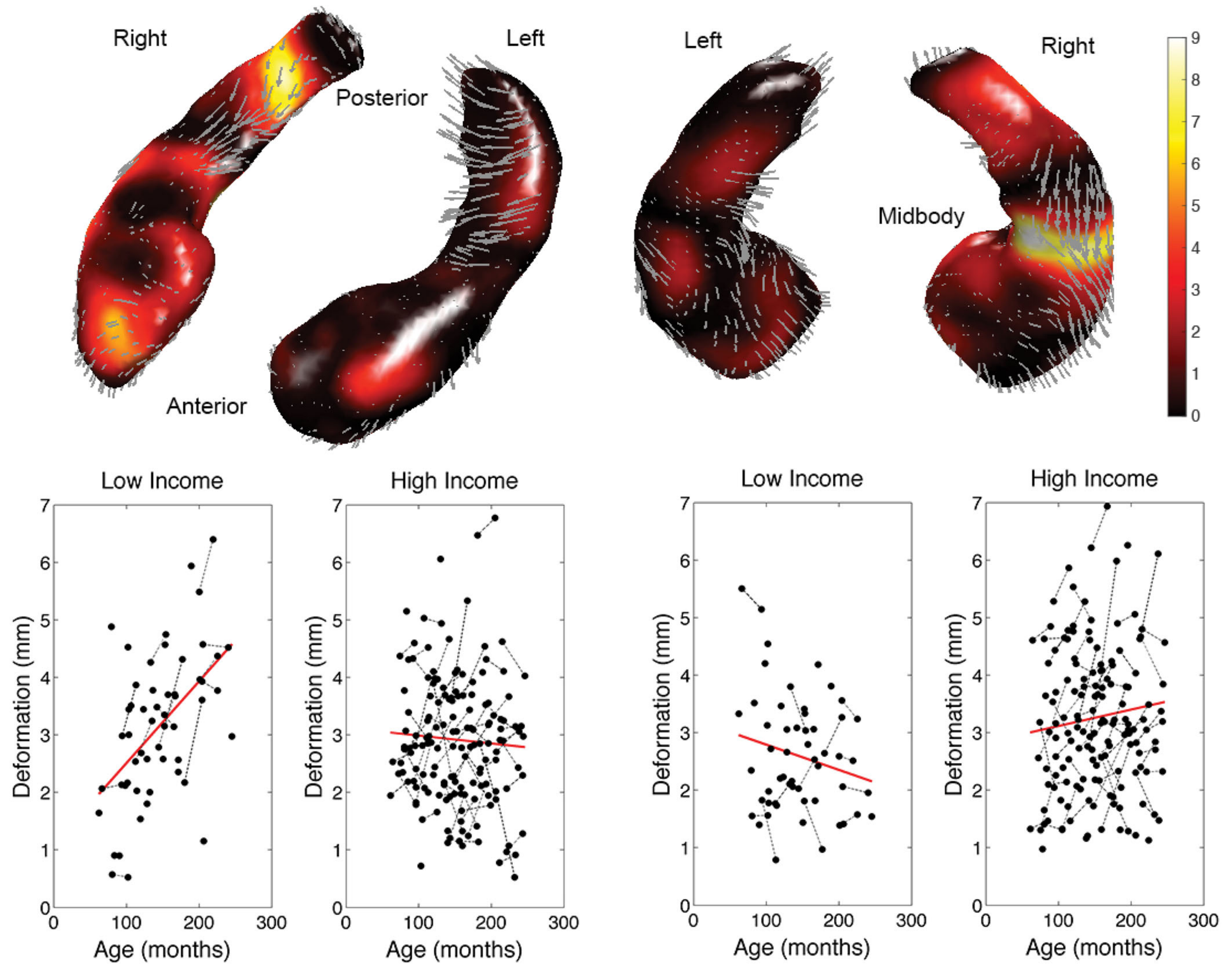

Figure 1. Hippocampus longitudinal study of 124 children showing localized growth pattern difference between high-income (above $75,000) and low-income (below $35,000) families (Chung et al. 2011). The F-statistics map on testing the interaction between income and age while controlling for sex in a mixed-effects model is computed in SurfStat. The arrows are the average displacement differences between high and low income families. The posterior region is enlarging while the midbody and the anterior parts of right hippocampus are shrinking in low-income families (corrected p-value < 0.03). The developmental pattern is the opposite for high-income families.

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