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Medial Demons Registration Localizes The Degree of Genetic Influence Over Subcortical Shape Variability: An N= 1480 Meta-Analysis

Boris A. Gutman¹, Neda Jahanshad¹, Christopher R.K. Ching², Yalin Wang³, Peter V. Kochunov⁴, Thomas E. Nichols⁵, and Paul M. Thompson¹

¹Imaging Genetics Center, Keck School of Medicine, University of Southern California, Marina del Rey, CA

²University of California, Los Angeles, Los Angeles, CA

³Department of Computer Science and Engineering, Arizona State University, Tempe, AZ

⁴Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD

⁵Department of Statistics, University of Warwick, Coventry, UK

Abstract

We present a multi-cohort shape heritability study, extending the fast spherical demons registration to subcortical shapes via medial modeling. A multi-channel demons registration based on vector spherical harmonics is applied to medial and curvature features, while controlling for metric distortion. We registered and compared seven subcortical structures of 1480 twins and siblings from the Queensland Twin Imaging Study and Human Connectome Project: *Thalamus*, *Caudate*, *Putamen*, *Pallidum*, *Hippocampus*, *Amygdala*, and *Nucleus Accumbens*. Radial distance and tensor-based morphometry (TBM) features were found to be highly heritable throughout the entire basal ganglia and limbic system. Surface maps reveal subtle variation in heritability across functionally distinct parts of each structure. Medial Demons reveals more significantly heritable regions than two previously described surface registration methods. This approach may help to prioritize features and measures for genome-wide association studies.

Index Terms

shape registration; medial curves; heritability; spherical demons; meta-analysis

1. Introduction

Subcortical shape analysis is a key field of research within the family of morphometric techniques developed to analyze brain anatomy. The major subcortical structures are generally easier to parcellate than cortical regions and have a set of clearly distinct functional roles, but structures within the basal ganglia and limbic system present additional challenges. The basic approach of simply measuring the volume of each structure overlooks subtleties of shape that affect the variability in volume. These subtleties may be necessary to fully explain the biological effect of interest and may also provide for more powerful biomarkers of disease. Yet, local analysis of subcortical surfaces is hampered by the lack of

clearly identifiable surface landmarks; such landmarks tend to be easier to identify on cortical surfaces.

The quest to identify variations in our DNA that influence brain structure is known as imaging genetics, and aims to identify mechanisms of diseases that affect the brain. Genetic analysis of brain scans may eventually help to identify drugs that influence the link between genes and brain biomarkers. Large consortia such as ENIGMA have discovered genetic variants that consistently affect structure volumes on brain MRI, but until now such efforts have required analysis of MRI data from tens of thousands of individuals [1]. Even so, simple volumetric measures for a structure may not provide detailed information on neuroanatomical pathways, cell types, or connections that may be genetically influenced. A detailed surface-based evaluation of the shape of the region may also help localize the effect of genes within the structure and help distinguish genes targeted to particular neuroanatomical pathways and cell types from those that affect structure globally. Subcortical volumes are highly heritable: 40-80% of the observed population variance in the individual volumes is due to additive genetic effects [1]. However detailed maps of surface wise heritability are not yet available. Classical behavior genetics approaches use family based models of twins, siblings or pedigrees to break down the observed population variance and determine the overall genetic component. For surface-based metrics, this is done on a vertex-wise level, and accurate registration of surfaces is critical [2].

Several approaches exist to register subcortical surfaces. SPHARM [3], a popular method during the early days of subcortical shape analysis, applies a rigid transformation to a spherical parameterization based on the ellipsoid formed by first degree spherical harmonics. This approach works well for rough global surface alignment, but depends heavily on the chosen spherical parameterization. Among the more recent surface registration approaches are those based purely on the concept of metric distortion minimization, such as the conformal [4] or near-isometric [5] mappings. These approaches often achieve reasonable correspondence, but they ignore higher-order geometric information, such as curvature. Shi et al. [6] partially resolved this by fluidly registering curvature in the flat parametric domain after conformal parameterization. However, the registration is no longer guaranteed to be angle-preserving, and requires identifying artificial curve landmarks to map to domain boundaries. An alternative approach exploits the intrinsic shape features based on the Laplace-Beltrami operator [7]. Surfaces are mapped directly without explicit parameterization, by embedding each shape into a high-dimensional space via its LB spectrum. A pair of surfaces is then brought into correspondence by varying the scale of the metric tensor to reduce distance between embeddings. Another class of methods [8, 9] place the shape registration problem in a Riemannian setting, defining a metric on smooth maps from the 2-sphere to space that is invariant to reparameterization. The use of the Riemannian machinery leads to a number of useful abilities, such as computing Karcher means and shape geodesics; however, ultimately the shape metric is still based on the embedding of a shape in space, possibly heuristically normalized for translation and size, rather than on the intrinsic properties of the shape itself. It is unclear that the use of such a metric defines appropriate correspondences for anatomical shapes or that the perceived distance between anatomies does not encapsulate nuisance factors. The latter problem

diminishes the statistical power of such metrics for sensitive tests such as heritability analysis.

Our approach extends a previously validated fast spherical demons algorithm [9] for cortical surface registration to shape features of subcortical boundaries. Yeo et al's. [10] original adaptation of the Euclidean demons registration to the 2-sphere was further improved in [11] by using vector spherical harmonics to significantly speed up the convolution step of the demons method. We use mean and Gaussian curvature to drive the initial registration by demons, followed by a registration based on the shape medial model [12]. The metric distortion is controlled by the distortion-minimizing initial spherical parameterization [13], and the regularization of the demons algorithm. To compare shapes in a point-wise manner, we apply two complementary local measures: radial distance mapping or “shape thickness,” and the log of the Jacobian determinant [14]. We applied our pipeline to seven subcortical structures and used SOLAR <http://solar.txbiomedgenetics.org/> [15] to model heritability in 440 twins and siblings from the Human Connectome Project cohort, and 1040 twins from the Queensland Twin IMaging study (QTIM). Our registration algorithm provides a unique and stable matching between datasets, allowing us to efficiently and effectively meta-analyze heritability across datasets.

2. Initial Surface Registration

Our shapes are extracted using the FreeSurfer 5.3 parcellation, followed by a topological correction and mild smoothing based on the topology-preserving level set algorithm [16]. Our initial spherical parameterization is based on the robust conformal and area-preserving mapping by Friedel [13]. Our version of the spherical demons algorithm, previously described in [11], is based on the standard 2-step formulation [17]. In this formulation, the first step represents a search for the update direction of the current warp, and the second – the regulation of the new warp resulting from this update. Adapting the demons approach to (fixed and moving) spherical images $S, T: \mathbb{S}^2 \rightarrow \mathbb{R}$, we optimize over $\mathbf{u}, \mathbf{g}, \mathbf{G}: \mathbb{S}^2 \rightarrow T_x \mathbb{S}^2$, and following Yeo's convention [10], define $T * \mathbf{g}$ using the Lagrangian frame $T * \mathbf{g}[p(x, \mathbf{g}\{x\})] = T[x]$, where

$$p(x, \mathbf{g}\{x\}) = x \sqrt{1 - \|\mathbf{g}\{x\}\|^2} + \mathbf{g}\{x\}. \quad (1)$$

The optimized field $\mathbf{g}$ is the warp bringing the two images into correspondence (Fig. 1). The inverse of this field parameterization is given by $\mathbf{g}\{x\} = -\mathcal{G}^2(x)p(x, \mathbf{g}\{x\})$, where $\mathcal{G}$ is the cross-product matrix, as suggested in [10]. The coupled optimization problems may be written as

$$\mathbf{u} = \arg \min_{\mathbf{u}} \left(\|S - T * \{\mathbf{g} * \mathbf{u}\}\|_2^2 + \frac{1}{\sigma} \text{dist}(\mathbf{g}, \{\mathbf{g} * \mathbf{u}\}) \right), \quad (2)$$

where $\mathbf{u}$ is a “hidden” transformation, and the regularization

$$\mathbf{G} = \arg \min_{\mathbf{G}} \left(\frac{1}{\sigma_{\mathbf{G}}} R(\mathbf{G}) + \frac{1}{\sigma} \text{dist}(\mathbf{G}, \{\mathbf{g} * \mathbf{u}\}) \right), \quad (3)$$

with the update $\mathbf{g}_{t+1} = \mathbf{G}_t$. The regularization term $R(\mathbf{G})$ is generally taken as a norm of a differential operator, so that the minimization can be achieved with a convolution. A well-known example, minimizing the harmonic energy in $\mathbb{R}^n$ is equivalent to a Gaussian smoothing of the displacement field $\mathbf{G}$ [18]. Likewise, the second term in the first equation (2) can be interpreted as a penalty on the harmonic energy of $\mathbf{u}$, as well as its norm, and can be smoothed with a heat kernel. Smoothing the displacement field is often termed “diffusion-like regularization,” [11] and smoothing the update, “fluid-like regularization” [18]. The unique advantage of the demons family of algorithms is precisely the separation of the two optimization problems: each cost can be optimized very efficiently with either a linear approximation or a fast convolution. Lastly, a more recent modification of the demons framework [18] introduced the idea of maintaining diffeomorphic warps by passing each update step $\mathbf{u}$ through the exponential $\mathbf{u} \rightarrow \exp(\mathbf{u})$, thus ensuring invertibility. Since diffeomorphisms form a Lie group under composition, this approach guarantees a smooth invertible final warp $\mathbf{g}$. In solving the first optimization problem (2), we deviate from [10], who optimize the problem directly in the original image space, and follow [18] more closely: we reformulate the problem as

$$\mathbf{u} = \arg \min_{\mathbf{u}} \left(\|S - [T * \mathbf{g}] * \mathbf{u}\|_2^2 + \frac{1}{\sigma} \|\mathbf{u}\|^2 \right). \quad (4)$$

This leads to a straightforward linear problem, following the linearization of $\|S - T * \{\mathbf{g}\} * \{\mathbf{u}\}\|_2^2$, which can be solved separately for every point on $\mathbb{S}^2$.

$$\mathbf{u}\{p\} = \frac{S\{p\} - [T * \mathbf{g}] * \mathbf{u}\{p\}}{\|\vec{\nabla}[T * \mathbf{g}]\{p\}\|^2 + \frac{1}{\sigma^2\{p\}}} \vec{\nabla}[T * \mathbf{g}]\{p\}, \quad (5)$$

A key difference between our demons adaptation and [10] lies in the optimization of the second demons problem (3). In [10], the authors recursively apply an explicit brute-force kernel. Such an approach becomes computationally infeasible for larger kernels. We replace this with vector heat kernel smoothing via the Vector Spherical Harmonic (VSH) transform, which eliminates the limitation on the kernel size and speeds up the process considerably. Vector spherical harmonics satisfy $\mathbf{A}_{lm} = l(l+1)\mathbf{A}_{lm}$, where $\mathbf{A}_{lm}$ is the **vector** spherical Laplacian. They can be defined as the gradient of the scalar harmonics Y_{lm} , and its orthogonal complement [19].

$$\mathbf{B}_{lm} = \frac{1}{\sqrt{l(l+1)}} \left[\frac{\partial Y_{lm}}{\partial \theta} \mathbf{e}_{\theta} + \frac{1}{\sin \theta} \frac{\partial Y_{lm}}{\partial \varphi} \mathbf{e}_{\varphi} \right], \mathbf{C}_{lm} = -\mathbf{e}_r \times \mathbf{B}_{lm}. \quad (6)$$

The harmonic decomposition of a spherical vector field is then $\mathbf{v} =$

$$\sum_{\substack{l=1 \\ |m| \leq l}}^{\infty} [\mathbf{B}_{lm} f^B(l, m) + \mathbf{C}_{lm} f^C(l, m)], f^A(l, m) = \langle \mathbf{v}, \mathbf{A}_{lm} \rangle_{L^2(\mathbb{T}\mathbb{S}^2)} \quad (7)$$

Extending Mercer's Theorem [20] to spherical fields, we define the heat kernel as $\mathbf{K}_\sigma(p, q) =$

$$\sum_{l=1}^{\infty} e^{-l(l+1)\sigma} \sum_{m=-l}^l \mathbf{B}_{lm}(p) \otimes \mathbf{B}_{lm}(q) + \mathbf{C}_{lm}(p) \otimes \mathbf{C}_{lm}(q), \quad (8)$$

where $\otimes$ is the tensor product. The kernel in (8) represents Green's function of the vector

isotropic diffusion equation $\frac{\partial \mathbf{v}}{\partial t} = -\Delta \mathbf{v}$, $\sigma = \sqrt{2t}$. Applying the kernel to a field leads to an expression which is similar to the scalar harmonics case [21]:

$$\mathbf{K}_\sigma * \mathbf{v}(p) = \sum_{\substack{l=1 \\ |m| \leq l}}^{\infty} e^{-l(l+1)\sigma} \left[\mathbf{B}_{lm}(p) \int_{\mathbb{S}^2} \mathbf{B}_{lm}(q) \mathbf{v}(q) d\mu(q) + \mathbf{C}_{lm}(p) \int_{\mathbb{S}^2} \mathbf{C}_{lm}(q) \mathbf{v}(q) d\mu(q) \right]. \quad (9)$$

All that is required for an efficient heat kernel smoothing of a spherical field is a forward harmonic transform followed by an $O(n)$ operation and an inverse transform. One additional advantage of having a low-cost smoothing technique for spherical fields is that it enables us to naturally extend the fluid-like regularization of Euclidean demons to the sphere. This modification turns out crucial for improving cortical correspondence accuracy [11].

Similarly to [11], we initially register subcortical shapes with fast spherical cross-correlation [22], followed by a simultaneous registration of the mean and Gaussian curvatures to a pre-computed average template. As in the Euclidean case, minimizing the harmonic energy of the spherical warp fields leads to a mapping that is more nearly harmonic, which is equivalent to the conformity condition for genus zero surfaces [4]. Since the original spherical mapping also incorporates a conformal energy term, the registration reduces metric distortion throughout the entire pipeline. Thus, the framework simultaneously reduces metric distortion and curvature mismatch.

2. Medial Demons Registration

Following our initial non-linear registration, we compute the medial curve-skeletons $\mathbf{c}: [0,1] \rightarrow \mathbb{R}^3$ of each subcortical structure $\mathcal{M}$ as the minimum of a weighted least-squares cost:

$$\int_0^1 \int_{\mathbf{p} \in \mathcal{M}} w(\mathbf{c}(t), \mathbf{c}'(t), \mathbf{p}, \mathcal{M}) \|\mathbf{c}(t) - \mathbf{p}\|^2 d\mathcal{M} dt \quad (10)$$

$$\mathbf{c}(0) \in S, \mathbf{c}(1) \in \mathcal{M}$$

The weight function $w(\mathbf{c}, \mathbf{c}', \mathbf{p}, S)$ defines the medial cost, and has been described previously [12]. The final cost includes the regularization term

$$L(\mathbf{c}(t), \mathcal{M}) = R(\mathbf{c}, \mathbf{c}', \mathcal{M}) + \beta \int_0^1 \|\mathbf{c}''(t)\|^2 dt \quad (11)$$

Solving for the Euler-Lagrange equation of (11), we derive the descent direction for the curve:

$$\frac{d\mathbf{c}}{d\tau} = \int_{\mathbf{p} \in \mathcal{M}} \left[\left(\frac{d}{dt} \frac{dw}{d\mathbf{c}'} - \frac{dw}{d\mathbf{c}} \right) \|\mathbf{c} - \mathbf{p}\|^2 - w(\mathbf{c} - \mathbf{p}) \right] d\mathcal{M} - \beta \mathbf{c}^{(4)} \quad (12)$$

The medial curve model allows us to define the global orientation function (GOF) $G(\mathbf{p}) = \arg \min_t \{\|\mathbf{c}(t) - \mathbf{p}\|\}$, $t \in [0, 1]$. The GOF (Fig. 2) allows us to refine the initial registration, matching GOF's of the average template and each subject in a demons framework in addition to matching the curvatures. Our final deformation model is the mixture of fluid- and diffusion-like diffeomorphic demons, simultaneously registering three channels: mean and Gaussian curvatures, and the GOF.

3. Shape Heritability

Each subcortical template is made by registering a subsample of unrelated individuals to a representative subject. The Euclidean average then serves as the template surface, on which the template medial curve is computed. After registering shapes to templates, we define two point-wise measures of shape morphometry. The first, radial distance, is derived from the medial model as in [12]:

$$D(\mathbf{p}) = \|\mathbf{c}(G(\mathbf{p})) - \mathbf{p}\| \quad (13)$$

The second is based on surface Tensor Based Morphometry (TBM) [14]. Generalizing TBM on Euclidean spaces to surfaces, the Jacobian is replaced by the differential map between the tangent spaces of two surfaces

$$J: T\mathcal{M}_t \rightarrow T\mathcal{M}. \quad (14)$$

In our case, $\mathcal{M}_t$ is the average template, while $\mathcal{M}$ is the surface we wish to study. J is a linear mapping, and can be thought of as the restriction of the standard Jacobian to the tangent spaces of the template and study surfaces. While it is possible to take advantage of the full tensor using Log-Euclidean metrics on SPD matrices [14], such analysis comes at the cost of poorer interpretability. Instead, we simply consider the Jacobian determinant, which represents the surface dilation ratio between the template and the study. Our final TBM measure is the logarithm of the Jacobian determinant, ensuring a more nearly Gaussian distribution.

Variance components method, as implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package (http://www.nitrc.org/projects/se_linux) [23] is used for heritability analysis of vertex-wise features. SOLAR uses maximum likelihood variance decomposition methods to break down the population variance and identify narrow

sense heritability based on the expected kinship of the individuals. The covariance matrix Ω for a pedigree of individuals is given by:

$$\Omega = 2 \cdot \Phi \cdot \sigma_g^2 + I \cdot \sigma_e^2 \quad (15)$$

where σ_g^2 is the genetic variance due to the additive genetic factors, Φ is the kinship matrix representing the pair-wise kinship coefficients among all individuals, σ_e^2 is the variance due to individual-specific environmental effects, and I is an identity matrix. Narrow sense heritability is defined as the fraction of phenotypic variance σ_p^2 attributable to additive genetic factors,

$$h^2 = \sigma_g^2 / \sigma_p^2 \quad (16)$$

Significance of heritability is tested by comparing the likelihood of the model in which σ_g^2 is constrained to zero with that of a model in which σ_g^2 is estimated. Twice the difference between the $\log_e$ likelihoods of these models yields a test statistic, which is asymptotically distributed as a 1/2:1/2 mixture of a χ^2 variable with 1 degree-of-freedom and a point mass at zero. Prior to testing for the significance of heritability, phenotype values for each individual were adjusted for covariates including sex, age, age²; age-sex and age²-sex interactions. Inverse Gaussian transformation was also applied to ensure normality of the measurements. Meta-analysis refers to combining inferences on heritability over multiple cohorts calculated as a weighted meta-analyzed heritability from individual cohorts [24]. We chose one of two methods previously discussed [25] that weights each cohort's estimate by its standard error [26].

$$h_{MA-SE}^2(\mathbf{p}) = \sum_j \text{se}_j^{-2} h_j^2(\mathbf{p}) / \sum_j \text{se}_j^{-2}(\mathbf{p}), \quad (17)$$

where $\mathbf{p} = I$ to N_v indexes vertex, and $j = 1, \dots, 2$ indexes site. SOLAR produces standard errors for the heritability at each vertex via the likelihood's information matrix. A Wald test for heritability then takes the form [27]:

$$Z_{MA-SE}(\mathbf{p}) = \frac{\beta(\mathbf{p})}{SE(\beta(\mathbf{p}))} = \frac{\sum_j \beta_j(\mathbf{p}) \text{se}_j^{-2}(\mathbf{p}) / \sum_j \text{se}_j^{-2}(\mathbf{p})}{\sqrt{1 / \sum_j \text{se}_j^{-2}(\mathbf{p})}}, \quad (18)$$

where, for the SE-weighted meta-analysis, each site's effect is estimated as

$\beta(\mathbf{p}) = Z_j(\mathbf{p}) \times \text{se}_j(\mathbf{p})$ which can be interpreted as z -scores in h^2 SE units.

4. Results

We applied the medial demons analysis to two datasets: 440 subjects from the HCP and 1040 subjects from the QTIM cohort. T1-weighted structural MR images were acquired for the HCP cohort and for the QTIM data. As in [1], we used seven subcortical structures in both hemispheres: Thalamus, Caudate, Putamen, Pallidum, Hippocampus, Amygdala, and

Nucleus Accumbens. After computing vertex-wise heritability, h^2 values were mapped back to the shape templates. A lower bound of heritability was computed as $LB(\mathbf{p}) = h^2(\mathbf{p}) - z_{0.05} * SE(\mathbf{p})$, where $SE(\mathbf{p})$ is the standard error of the heritability estimate and $z_{0.05}$ is the lower tail 5% critical value. These results are displayed in Figures 3 and 4 for all 14 structures. Comparing our method to SPHARM [2] in Table 1, we see that the detected heritability averaged over the whole surface is greater when using Medial Demons, which indicated greater sensitivity. We also compare our method's sensitivity to detect heritable subcortical shape features to a previous registration method which only minimizes metric distortion [28]. We show P -maps of Radial Distance heritability, corrected for multiple comparisons with the Bonferroni correction for both methods in Figure 5. Our correction is based on the total number of vertices used to represent all fourteen structures. This is a very severe correction compared to the more frequently used False Discovery Rate method. Several areas found as highly significant using the Medial Demons algorithm are **not found** significant using the registration based on the spherical conformal mapping. The converse however is not true; this indicates substantially greater sensitivity when the Medial Demons registration is used.

5. Conclusion

We developed and applied a framework for studying heritability of subcortical shape. Our framework is based on previously validated surface registration and medial modeling approaches. For the first time, heritability of vertex-wise features of subcortical structures was estimated in multiple cohorts. We were able to localize consistent genetic influences on vertex-wise features describing subcortical region boundary. Nearly all of the surface area of all 14 subcortical regions studied here was found to be significantly heritable using our features. Further, our proposed registration localizes heritable regions with greater sensitivity than a previously described conformal method as well as the SPHARM method.

Shape analysis must play a critical role in genetic association studies (GWAS): it provides a fine-grained map of genetic association, not afforded by the overall volume measure. At the same time, the shape features are still succinct compared to voxel-wise analyses, requiring one to two orders of magnitude fewer points to represent anatomy. An important caveat in heritability analysis relates to the significant variability *between* cohorts. What may be heritable in one population, may not be heritable in another. However, the ability to perform *meta*-analyses of heritability, as done here, allows us detect phenotypes which are likely genetically influenced *across* populations. The heritability study presented here may serve as a template for future vertex-wise GWAS studies, eliminating the few vertices that are not heritable to reduce the multiple comparisons burden, or allowing for more elaborate weighting schemes that use heritability to weight features for genome-wide association in order to find new genetic factors influencing the brain.

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Figure 1.
Mapping a subcortical structure to a template by matching spherical curvature maps.

Figure 2.
(a) Medial curve of a left lateral ventricular surface; (b) The resulting global orientation function.

Figure 3. Lower bound of heritability for the Log Jacobian

Figure 4. Lower bound of heritability for Radial Distance

Figure 5. (A) and (B): lateral and medial views of corrected Log p-values after Medial Demons; (C) and (D): corresponding results after conformal registration. Left: Caudate; Right: Thalamus

Table 1

Mean h^2 values for thickness, using Medial Demons and SPHARM. See text for full subcortical region names.

	Tha	Cau	Put	Pall	Hip	Amy	Accu
Med. Dem	0.40	0.39	0.30	0.27	0.30	0.27	0.18
SPHARM	0.10	0.06	0.09	0.11	0.13	0.11	0.06