Statistical Issues in Imaging Studies

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2 Faculty Members
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5 Postdoctor Fellows
2 Visitor Scholars
4 Past members
UNC Biostatistics and Imaging Analysis Lab

UNC Gillings School of Global Public Health

UNC BIOSTATISTICS AND IMAGING ANALYSIS LAB (BIA)

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PEOPLE
GRANTS
PUBLICATIONS
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GROUP MEETING
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About Us

We have diverse interest in solving methodological issues in statistics. Our past and present statistical projects include diagnostic measures, stochastic approximation algorithm, structural equation models, mixed effect models, spline regression, missing data problems, variable selections, empirical likelihood, mixture models and regression tree.

We have developed methods and software for the analysis of the data from a state-of-the art magnetic resonance imaging (MRI) technique including MRI, functional MRI, and diffusion tensor image. We have developed and enhanced tools in data mining, Monte Carlo method, statistical modeling, and applied them to scientific problems to understand the function and structure of the brain. Our collaborators and we work closely to study healthy and neurologically disordered children and adults.

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Outline

- **Evaluating** Imaging Sequence Accuracy
- **Imaging Sequence** Optimization
- **Reconstructing** Diffusion Tensor Images
- **Smoothing** Diffusion Tensor Field
- Analyzing Tract-based Diffusion Tensor Statistics
- Multiscale Adaptive Regression Models
- Brain Connectivity Analysis
Evaluating Imaging Sequence Accuracy

Statistical Methods in Diagnostic Medicine

ARFI Beam Sequence Performance as Evaluated by Trained Readers: Plaque Detection
PI. Caterina M. Gallippi
Methods of Acoustic Radiation Force Impulse (ARFI) Ultrasound

1. ARFI Excitation Pulse (~70μs) induces axial displacement
2. Conventional B-Mode pulses track induced displacement
3. Displacements are calculated to create a displacement profile for every pixel within the image.
Methods of Shear Wave Elasticity Imaging (SWEI)

(1) ARFI Excitation Pulse (~70μs) induces axial displacement
(2) Tracking Away From Region of Excitation Tracks ARFI-induced Shear Waves
(3) Displacement Profiles Are Created
Hypothesis

Select ARFI/SWEI beam sequences will yield higher sensitivity and specificity for atherosclerotic plaque detection in peripheral arteries.
General Methods: Beam Sequences

- 3 Types of Excitation
  - Single F/1.5 (SP1.5)
  - Single F/3 (SP3)
  - Double F/1.5 (DP)

- 3 Types of Tracking
  - Single A-line RX (SRx)
  - 4:1 Parallel RX (ParRx)
  - SWEI

- Combine for 9 Total Sequences

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Reader Study

• Automatically Generated Images
  ♦ Lumen masking & Color scaling

• 12 Trained Readers
  ♦ Various levels of experience with ARFI
  ♦ Only 6 evaluated each Image Set

• Validation
  ♦ Phantom results compared with known truth
  ♦ Ex vivo results compared with pathologist rating of spatially matched histology

• Statistics
  ♦ Latent Variable Models to compare ordinal responses
  ♦ Generated receiver operating characteristic (ROC) curves
  ♦ Calculated mean area under the curve (AUC)
Custom Phantom Structure

- ~4mm Layer
- Hard or Soft Inclusions
  - ~110 kPa & ~190 kPa
- 2.5 or 5mm Width
- Imaging in 3 Locations
  - Centered (0mm Offset)
  - -3mm Lateral Offset
  - -6mm Lateral Offset
- 2 Acquisitions
- 250 Total Image Sets
Results: Phantom, All Locations

Area Under ROC Curve vs. Beam Sequence

** p<0.02
*** p<0.005

AUC

0.942 0.910 0.906 0.903 0.887 0.879 0.660 0.604 0.598

Beam Sequence

DP ParRx SP1.5 ParRx SP3 ParRx SP3 ParRx DP SRx SP1.5 SRx SP3 SWEI DP SWEI SP1.5 SWEI

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Results: Phantom, -6 mm Lateral Offset

Area Under ROC Curve vs. Beam Sequence

Beam Sequence

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Conclusions

- Robust Method for Statistically Comparing Beam Sequences
- Plaque Detection was better when tracking in ROE
  - Both in Phantoms and Ex Vivo
  - Even when accounting for optimal positioning
- Ranking of sequence performance remained consistent between phantom and ex vivo studies
  - SP1.5-SRx
  - SP3-SRx
  - SP3-ParRx
  - DP-SRx
  - DP-ParRx
  - SP3-SWEI
  - SP1.5-SWEI
Imaging Sequence Optimization

Experimental Design

How to design an optimal imaging acquisition scheme to achieve the best signal-to-noise ratio for a given scan time?
**Acquisition Scheme**
(Imaging Parameters)

**Noisy Images**

**Images Reconstruction**

Pulled-gradient spin-echo (PGSE) sequence
Gradient orientations & b factors

Design Criterion

Global Optimization

\[ S \approx S_0 e^{-bg^T Dg} = f(x, \theta) \]

\[ p(S, b, g \mid S_0, D) \]

Gradient directions (Hasan & Narayana, 2005, MedicaMundi)
Hasan & Narayana (2005), MedicaMundi.


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Conventional gradient schemes (a) and optimized schemes (b) based on LS and WLS estimation for uniform fiber case.


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Reconstructing Diffusion Tensor Images

Estimation Theory

How to obtain accurate estimates of diffusion tensor and its derived quantities?
$$\{ (S_i(v), b_i, g_i) : i = 1, \ldots, n; v \in V \}$$

$$S_i(v) = S_0(v) \exp(-b_i g_i^T D(v) g_i) + \text{noise}$$

$$\hat{D}(v)$$

$$\{ (\hat{\lambda}_k, \hat{e}_k) : k = 1, 2, 3 \}$$
Sorting Bias

\[
\hat{D}(v) = \hat{\lambda}_1 \hat{e}_1 \hat{e}_1^T + \hat{\lambda}_2 \hat{e}_2 \hat{e}_2^T + \hat{\lambda}_3 \hat{e}_3 \hat{e}_3^T
\]

\[
P(\hat{\lambda}_1 > \hat{\lambda}_2 > \hat{\lambda}_3) = 1
\]

\[
E(\hat{\lambda}_1) > \lambda_1
\]

\[
E(\hat{\lambda}_3) < \lambda_3
\]

\[
E(\hat{\lambda}_2) \approx \lambda_2
\]

True Diffusion Tensor

\[
D(v) = \lambda_1 e_1 e_1^T + \lambda_2 e_2 e_2^T + \lambda_3 e_3 e_3^T
\]

\[
\lambda_1 \geq \lambda_2 \geq \lambda_3
\]

\[
D = \text{diag}(0.7, 0.7, 0.7)
\]
\[ \theta \in [0, 2\pi] \text{ and } \phi \in [0, \pi] \text{ are associated with the spherical coordinate } (1, \theta, \phi) \text{ of } e_1. \]

\[ SNR = S_0 / \sigma = 22 \]
\[ \text{SNR} = S_0 / \sigma = 22 \]
\[ D = \text{diag}[0.9, 0.7, 0.5] \]
Quantifying Uncertainty by using bootstrap methods

Gold Standard

Repetition Bootstrap

Wild Bootstrap

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Smoothing Diffusion Tensor Field

Nonparametric Regression

How to smooth diffusion tensor along fiber tracts or in 3D volume?
Data \((x_1, S_1), \cdots, (x_n, S_n)\)

$M = \text{Sym}(m)^+$

- Inner product $<< Y_D, Z_D >>$
- Geodesic
- Riemannian exponential/logarithm maps
  - Affine invariant metric
    $$<< Y_D, Z_D >>_{D,R} = \text{tr}(Y_D D^{-1}Z_D D^{-1})$$
  - Log-Euclidean metric
    $$<< Y_D, Z_D >>_{D,L} = \text{tr}(R_D(Y_D)R_D(Z_D))$$

$$R_D : T_D M \rightarrow T_{I_m} M$$
Local polynomial kernel regression to nonparametrically estimate an intrinsic mean of S given x.

Local linear regression performs better than local constant regression.

Statistical inferences depend on a specific inner product defined on the tangent space.
Local Polynomial Kernel Regression

\[
\log_{D(x_0)}(D(x)) \in T_{D(x_0)}\text{Sym}^+(m)
\]

\[
\phi_{D(x_0)}(.) : T_{D(x_0)}\text{Sym}^+(m) \rightarrow T_{I_m}\text{Sym}^+(m)
\]

\[
Y(x) = \phi_{D(x_0)}(\log_{D(x_0)}(D(x)))
\]

\[
\log_{D(x_0)}(D(x))) = \phi_{D(x_0)}^{-1}(Y(x)) \approx \phi_{D(x_0)}^{-1}(Y(x_0)) + \sum_{k=1}^{K} Y^{(k)}(x_0)(x - x_0)^k
\]

\[
D(x) = \exp_{D(x_0)}(\phi_{D(x_0)}^{-1}(Y(x))) \approx \exp_{D(x_0)}(\phi_{D(x_0)}^{-1}(\sum_{k=1}^{K} Y^{(k)}(x_0)(x - x_0)^k))
\]
Simulation Studies

**Data model**

\[ S_i = C(x_i) \exp(E_i) C(x_i), \quad E_i \sim MN(0, \Omega) \]
\[ x_i \sim N(0, 0.25) \]
\[ D(x) = C(x)^2 \]
\[ C(x) = \begin{pmatrix} -0.1x & 0.2x & \sin(x) \\ 0.2x & 0.6x & -0.4x \\ \sin(x) & -0.4x & 0.5x \end{pmatrix} \]

**Correlation**

\[ \Sigma_1 = \begin{pmatrix} 0.3 & 0.049 & 0.052 \\ 0.049 & 0.2 & 0.0424 \\ 0.052 & 0.0424 & 0.1 \end{pmatrix}, \quad \Sigma_2 = 2\Sigma_1, \quad \Sigma_3 = 4\Sigma_1, \quad \Sigma_4 = 8\Sigma_1 \]

**Data**

\[ \{(x_i, S_i) : i = 1, \ldots, n\} \quad \text{for} \quad n = 50 \quad \text{or} \quad 100 \]
Fig. 1. Ellipsoidal representations of the true (the first row) and simulated SPD matrix data along the design points under the four different noise distributions (the second to the fifth rows: $\Sigma_1-\Sigma_4$) colored with FA values.
Fig. 2. Ellipsoidal representations of the true (the first row) and estimated SPD matrix data along the design points under the four different noise levels colored with FA values. The second to the fifth rows (Log-Euclidean metric): $\Sigma_1-\Sigma_4$, the sixth to the ninth rows (the Riemannian metric): $\Sigma_1-\Sigma_4$. 

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Simulation 1.

• Compare the performance of the **local linear** with the **local constant**

• Assess the performance using the Average Geodesic Distance (AGD) for each replication $j=1, \ldots, N$ with $N$ as the number of replications, denoted by

$$\text{AGD} = (nN)^{-1} \sum_{j=1}^{N} \sum_{i=1}^{n} d(\hat{D}_j(x_i), D(x_i))$$

where $\hat{D}_j(x_i)$ and $D(x_i)$ are, respectively, the estimated and true diffusion tensors at $X_i$. 

Fig. 3. Boxplots of the AGD using the intrinsic local constant and linear estimators under the log-Euclidean (the first row) and Riemannian (the second row) metrics based on 100 replications under the three covariance matrices (a)-(b) $\Sigma_1$, (c)-(d) $\Sigma_2$, and (e)-(f) $\Sigma_3$. C50 and C100 represent the intrinsic local constant estimators at sample sizes 50 and 100, respectively. L50 and L100 represent the intrinsic local linear estimators at sample sizes 50 and 100, respectively.
Fig. 4. The LAGD curves at each sample point using the intrinsic local constant (solid line) and linear (dash-dotted line) estimators under the three covariance matrices $\Sigma_1$, $\Sigma_2$, $\Sigma_3$ for sample sizes 50 (the top two rows) and 100 (the bottom two rows). The first and third rows correspond to the log-Euclidean metric while the second and fourth rows correspond to the Riemannian metric.
Simulation 2. High noisy level

Compare the performance of the local linear under two metrics

Riemannian (dashed) Log-Euclidean (solid)

**Fig. 5.** (a) Boxplots of the AGD’s using the linear regressions based on 100 replications under the covariance matrix $\Sigma_4$, under the Log-Euclidean and Riemannian metrics, respectively. (b) and (c) LAGD curves at each sample point using the local linear regressions under the affine invariant (dash-dotted line) and Log-Euclidean (solid line) metrics under the the covariance matrix $\Sigma_4$ at sample size 50 (b) and 100 (c), respectively. LL50 (LR50) and LL100 (LR100), respectively, represent the local linear regressions under Log-Euclidean (Riemannian) metrics at sample sizes 50 and 100.
Simulation 3.

• Value of developing the LPK smoothing method

• Two different methods for smoothing FA values
  
  M1. Calculate FA values from `noisy' SPDs and then use the local linear method to smooth the FA values
  
  M2. Use the local linear method to smooth SPDs and then calculate FA values from the smoothed SPDs
  
• Calculate the Mean Absolute Deviation Error (MADE):

\[
MADE = (nN)^{-1} \sum_{j=1}^{N} \sum_{i=1}^{n} |\hat{FA}_j(x_i) - FA_j(x_i)|
\]
Fig. 6. Boxplot of the MADE’s using the two smoothing methods based on 100 replications under the covariance matrices (a) $\Sigma_1$, (b) $\Sigma_2$, and (c) $\Sigma_3$ at sample size 50. Smoothed FA curves for the realizations with median MADE under the covariance matrices: (d) $\Sigma_1$, (e) $\Sigma_2$, and (f) $\Sigma_3$. The true FA curve (the solid line), the estimated FA curve using the first method (the dash-dotted line) and the estimated FA curve using the second method (the dashed line). This shows that the more intrinsic approach is much better.
Smoothing DTs along a select tract

Fig. 7. (a) The splenium of the corpus callosum in the analysis of HIV DTI data. (b) The ellipsoidal representation of full tensors on the fiber tract from a selected subject.
Fig. 8. (a) Ellipsoidal representations of the diffusion tensor data and estimated tensors using the intrinsic local linear regression under the (b) log-Euclidean and (c) Riemannian metrics along the fiber tract f1 colored with FA values. The estimated tensors in the middle right part (highlighted in the red line) are more anisotropic using the method under the Log-Euclidean metric.
Fig. 9. (a) FA's, (b) MD's and (c) PE's derived from the raw tensor data (dot line) and estimated tensors using the intrinsic local linear regression under the Riemannian (dash-dot line) and log-Euclidean (dash line) metrics as the function of arc-length along the tract f1. Estimated FA function along the fiber tract f1 by using the standard local linear regression for scalars (solid line).
Smoothing Covariance matrices along age

16 subjects resting state fcMRI
32 ROIs
Analyzing Tract-based Diffusion Tensor Statistics

Multivariate Varying Coefficient Model

How to compare diffusion tensors or tensor quantities along fiber tracts?
Neonatal Brain Development

PI: John H. Gilmore

www.google.com
Early Brain Development

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White Matter Maturation

Week 2
Year 1
Year 2
Week 2
Year 1
Year 2

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Right internal capsule: a collection of axons connecting the cerebral cortex and the brainstem.

**Sample Data**

- **Equation:**
  \[
  Y_i(s_j) = (y_{i,1}(s_j), \ldots, y_{i,m}(s_j))^T
  \]

- **Grids:** \( \{s_1, \ldots, s_{n_G}\} \)

- **Covariates:** \( x_1, \ldots, x_n \)
Tract-based FA as a function of Age
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Multivariate varying coefficient model

$y_{i,k}(s) = x_i^T B_k(s) + \eta_{i,k}(s) + \epsilon_{i,k}(s)$

Weighted least square estimation

$B_k(s_j) = B_k(s) + \hat{\varphi}_k(s_j - s)$

$\Sigma_{\eta,k}(s,t) = \sum_{l=1}^{L} \lambda_{l,k,j} \hat{\psi}_{k,l}(s) \hat{\psi}_{k,l}(t)$

Functional principal component analysis

Resampling methods

Confidence bands

Hypothesis test

Resampling methods

$H_0 : \text{vec}(B(s)) = b_0(s)$

$H_1 : \text{vec}(B(s)) \neq b_0(s)$

$S_n = n \int_0^{\infty} d(s)^T \left[ \Sigma_\eta(s,s) \otimes \Phi^{-1}_Y \right]^{-1} d(s) ds$

$p = G^{-1} \sum_{j=1}^{G} 1(S_n^{(j)} \geq S_n)$
PI: John H. Gilmore

Subjects:
125 healthy infants (75:53 M:F)
Gestational age (298 +/- 17.6 days)

Aims:
Gender Effects
Age Effects

Splenia

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## Global and Local p-values for Gender and Age Effects

<table>
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<th></th>
<th>Right Internal Capsule</th>
<th>Splenium</th>
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<tr>
<td></td>
<td>FA</td>
<td>MD</td>
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<tr>
<td><strong>Gender</strong></td>
<td>.169</td>
<td>.354</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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![Graphs showing p-values for gender and age effects](a) (b)
Functional Principal Components

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Simultaneous Confidence Bands
Multiscale Adaptive Regression Models

Regression Analysis and Nonparametric Smoothing Methods

How to spatially and adaptively compare imaging measures across subjects in 3D volume or 2D surface?
Preprocessed data: single voxel

Design matrix

Parameter estimates

SPMs

Multiple Comparisons
All voxels are treated as independent units.

Initial smoothing step before the voxel-wise approach often blurs the image data near the edges of activated regions.
Multiscale Adaptive Regression Model

- Learning Voxel Feature
- Local Feature Adaptation
- Adaptive Estimation and Testing
- Automatic Stop
- Nice Asymptotic Results
Identifying homogeneous regions

Drawing a sphere with radius r0 at each voxel

Calculating the similarities between the current voxel and its neighboring voxels.
Being Hierarchical

Drawing nested spheres with increasing radiiuses at each voxel

\[ h_0 = 0 < h_1 < \cdots < h_s = r_0 \]
Model \[ y_i(d) = x_i^T \beta(d) + \varepsilon_i(d) \]

Error \[ \varepsilon_i(d) \sim N(0,1) \quad \varepsilon_i(d) \sim \chi^2(3) - 3 \]

\[ n = 60 \quad \text{or} \quad n = 80 \]

Covariates \[ x_i = (1, x_{i2}, x_{i3})^T \]

\[ x_{i2} \sim \text{Bernoulli}(0.5) \]

\[ x_{i3} \sim \text{Uniform}[1,2] \]

Coefficients \[ \beta(d) = (\beta_1(d), \beta_2(d), \beta_3(d))^T \]

\[ \beta_1(d) = \beta_2(d) = 0 \]

ROIs

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<th>black</th>
<th>blue</th>
<th>red</th>
<th>yellow</th>
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<td>$\chi^2(3) - 3 \quad n = 60$</td>
<td>$\chi^2(3) - 3 \quad n = 80$</td>
<td>$N(0,1) \quad n = 60$</td>
<td>$N(0,1) \quad n = 80$</td>
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<tr>
<td></td>
<td>$h_0$</td>
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Simulation Studies

Table 2. Simulation study for $W_\mu(d, h)$: estimates (ES) and standard errors (SE) of rejection rates for pixels inside the five ROIs were reported at 2 different scales ($h_{0}$, $h_{1.0}$), 2 different distributions ($N(0, 1)$ and $\chi^2(3) - 3$), and 2 different sample sizes ($n = 60, 80$) at $\alpha = 5\%$. For each case, 1,000 simulated data sets were used.

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<th>(\chi^2(3) - 3)</th>
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<td>0.011</td>
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<tr>
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<tr>
<td>$h_{1.0}$</td>
<td>0.08</td>
<td>0.07</td>
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</table>
Infant Brain Development Data

- **Objective:** We want to assess the brain structure change in the early brain development.

- **Subject:** 38 infants.

- **Image:** Diffusion-weighted images and T1 weighted images were acquired for each subject at 2 weeks, 1 and 2 years old.

- **Method:** Voxel-wise imaging analysis and MARM.
New Developments

Adaptive Neighborhoods

Adaptive Weights

Cross-sectional, longitudinal, twin and family studies

Robust Procedure

Parametric and Nonparametric Components

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Brain Connectivity Analysis

Penalized Methods, Multivariate Analysis, and Time Series Analysis

How to spatially and temporally quantify the dynamic association among different functional regions?
Functional connectivity is the mechanism for the coordination of activity between different neural assemblies in order to achieve a complex cognitive task or perceptual process. (Fingelkurts, Fingelkurts, Seppo Kahkonen, Fingelkurts, 2005)

Resting-State Network:
fMRI for finger tapping task; fcMRI: contralateral motor cortex showed activation and low frequency (<0.1 Hz) fluctuations in the signal of the resting brain, revealing a high degree of temporal correlation.

Biswal et al, JCBFM, 17:301-308, 1997
A multivariate network-level approach

(i) network-level correlation using CCA;
(ii) network-level mediation analysis;
(iii) significance detection by resampling methods;
(iv) Network-level correlation pattern.

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Network Definition

Default (DF)

Dorsal Attention (DA)

Frontal-Parietal Control (FPC)

Motor-Sensory (MS)

Visual (V)
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Selective regulation of the two opposing networks during different tasks
Bayesian Covariance Lasso

Flow Cytometry Data
11 proteins
7466 cells

Fig. 5: Networks for 11 proteins from Sachs et al. (2003).
90 ROIs
30 subjects
2-rd fcMRI

Fig. 6: Image plots of the partial correlation matrices for 90 regions of 2-year old children’s brains using the different methods.
Acknowledgements