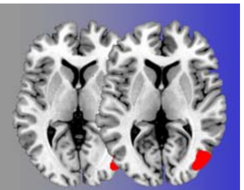


A Bayesian Hierarchical Framework for Spatial Modeling of fMRI Data

DuBois Bowman
Department of Biostatistics and Bioinformatics
Emory University

Mathematics in Brain Imaging
Institute for Pure & Applied Mathematics
University of California at Los Angeles
July 18, 2008

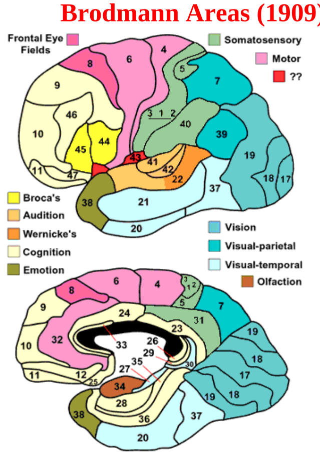
OUTLINE

I. Introduction

Functional Specialization (Localization): Specific mental processes link to particular brain regions
[Gall, 1796; Broca, 1861; Brodmann, 1909]

Functional Integration: Interactions between specialised neuronal populations

Brodmann Areas (1909)



52 anatomically distinct regions

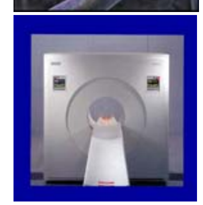
Imaging Modalities

Functional Neuroimaging
- Noninvasively measures localized *brain activity* using correlates of blood flow

Modalities

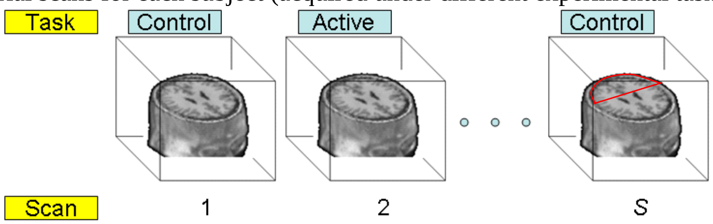
Vascular methods
- **fMRI:** Functional Magnetic Resonance Imaging
- **PET:** Positron Emission Tomography
- **SPECT:** Single photon emission computed tomography

Electrophysiological methods
- **EEG/MEG**: electro-/magneto-encephalogram

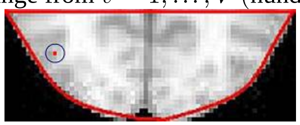


Data Representation

- Serial scans for each subject (acquired under different experimental tasks)



- Voxels $v = (x, y, z)$ range from $v = 1, \ldots, V$ (hundreds of thousands)



Data Representation

General Data Characteristics

Response

- Localized measurements of "brain activity" (BOLD response)
  - Temporally and spatially correlated

Design Matrix

- Experimental conditions
- Covariate adjustments
  - Motion parameters
  - Low frequency trends, e.g. due to artifacts from scanner

Pre-processing

- Realignment - motion correction
- Spatial normalization - warping brains to a standard space (Talairach)
  - Provides exact coordinates for anatomical locations
- Spatial smoothing*

II. Conventional Analyses

Functional Specialization: Activation Studies*

- To identify specific regions of the brain that are more active under one experimental condition relative to another
  - Voxel-level
    - Stage 1 (individual) model
    - Stage 2 (group) model
    - Thresholding (Bonferonni, FDR, RFT)
  - Region of Interest (ROI)
    - Average data over voxels within ROI

Functional Integration: Connectivity Studies

- *Functional* connectivity - correlations between distinct brain regions
  - Local correlations
  - Long-range correlations
- *Effective* connectivity - the influence one neural system exerts over another

[Friston, 1993]

III. Experimental Data

fMRI Study of Inhibitory Control in Cocaine Addicts

- $n = 28$ subjects ($n_p = 12$ cocaine addicts, $n_c = 16$ controls)
- Study Conditions: Inhibitory Control
  - ▹ Correctly inhibiting a prepotent response
    - ∘ Response primed with frequent occurrence of "go cues"
    - ∘ "Stop signal" is an auditory tone signaled after a "go cue"
- Sessions: Two Sessions (170 scans per subject in each session)
  - ▹ Addicts: Pre- and Post-Treatment
  - ▹ Controls: Baseline and Follow-up
- 176 million measurements per subject! 4.9 billion for all subjects!!
- Objective: Treatment-emergent neural processing changes related to response inhibition in cocaine-addicts

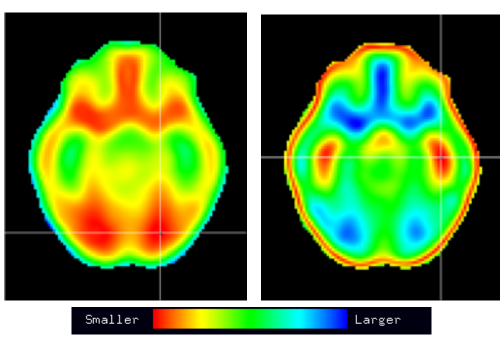
IV. Spatial Modeling

- Key Considerations
  - ▹ Correlation as a function of *Distance*
    - ∘ Local correlations
    - ∘ Long-range correlations due to neurophysiology
  - ▹ Volume of data (billions of voxel pairs!)
  - ▹ Complexity of neuroanatomy (billions of axons!)
- Approaches:
  - ▹ **Model 3**: Spatial Bayesian Hierarchical Model (BHM) [Bowman et al., 2008]
  - ▹ **Model 2**: Spatial Modeling using Functional Distances [Bowman, 2007]
  - ▹ **Model 1**: Cluster-based Spatial Autoregressive Model [Bowman, 2005]

Exploring Spatial Associations

- Define *functional* distance between activity in voxels i and j

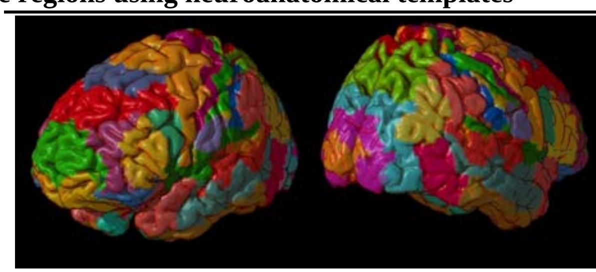
$$d_{ij} = \left[(\boldsymbol{\mu}_i - \boldsymbol{\mu}_j)'(\boldsymbol{\mu}_i - \boldsymbol{\mu}_j)\right]^{1/2}, \quad \boldsymbol{\mu}_i \text{ is a summary statistic.}$$



Spatial Modeling Approaches

Spatial Bayesian Hierarchical Model

- **Define regions using neuroanatomical templates**



$G = 116$ (Anatomical regions); $G = 52$ (Brodmann regions)

[Tzourio-Mazoyer et al., 2002] [Brodmann, 1909]]

NOTE: Also considered alternative partitions of the V voxels into G regions such as data-driven clustering methods based on the functional distances d_{ij}.

[Bowman et al., 2004; Bowman and Patel, 2004; Bowman, 2005]

Model

Stage I

$$\boldsymbol{Y}_{ig}(v) = \boldsymbol{X}_{igv}\boldsymbol{B}_{ig}(v) + \boldsymbol{H}_{iv}\boldsymbol{\nu}_{ig}(v) + \boldsymbol{\varepsilon}_{ig}(v)$$

where

$\boldsymbol{Y}_{ig}(v)$	$(S \times 1)$	serial brain activity at location v (e.g. BOLD) (within *cluster g*)
$\boldsymbol{X}_{igv}$	$(S \times q)$	design matrix containing independent variables (common to all v)
$\boldsymbol{B}_{ig}(v)$	$(q \times 1)$	parameter vector containing individualized effects
$\boldsymbol{\varepsilon}_{ig}(v)$	$(S \times 1)$	random error about k^{th} subject's individualized mean
$\boldsymbol{H}_{iv}$	$(S \times m)$	contains other covariates, e.g. high-pass filtering

Model Assumptions

- $\boldsymbol{\varepsilon}_{ig}(v) \sim N\left(0, \tau_{gv}^2 \mathbf{I}_S\right)$
- Brain activity measurements from different scans are independent

Spatial Modeling Approaches

Stage II: Spatial Bayesian Hierarchical Model

1. $B_{igj}(v)|\mu_{gj}(v), \alpha_{igj}, \sigma_{gj}^2 \sim N\left(\mu_{gj}(v) + \alpha_{igj}, \sigma_{gj}^2\right)$ — *Data*
2. $\mu_{gj}(v)|\lambda_{gj}^2 \sim N\left(\mu_{0gj}, \lambda_{gj}^2\right),$ — voxel means
   $\sigma_{gj}^{-2} \sim G(a_0, b_0)$ — common voxel variances
   $\boldsymbol{\alpha}_{ij}|\boldsymbol{\Gamma}_j \sim N(\mathbf{0}, \boldsymbol{\Gamma}_j), \quad \boldsymbol{\alpha}_{ij} = (\alpha_{i1j}, \ldots, \alpha_{iGj})'$ — subj-spec. random effects
3. $\lambda_{gj}^{-2} \sim G(c_0, d_0)$ — variances of voxel means
   $\boldsymbol{\Gamma}_j^{-1} \sim W\left((h_0 \boldsymbol{H}_{0j})^{-1}, h_0\right)$ — spatial covariance matrix

Priors: $(a_0, b_0) = (0.1, 0.005)$
$(c_0, d_0) = (0.1, 0.01)$
$h_0 = G$ ($h_0 \geq G$ to ensure proper posterior, non-informative as $h_0 \to 0$)
$\boldsymbol{H}_{0j} = \hat{\boldsymbol{\Gamma}}_j$ (sample covariance matrix)

[Bowman et al., 2008]

Estimation

- MCMC (Gibbs Sampler)
- Draw samples from the joint posterior distribution of all model parameters
  - Can estimate functions of the model parameters from the joint posterior samples, e.g.
  - Intra-regional *task-related functional connectivity* is given by

$$\rho_{gj} = \frac{\gamma_{gg}^{(j)}}{\gamma_{gg}^{(j)} + \sigma_{gj}^2}.$$

Reflects similarity in brain function between voxels *within* anatomical regions

- Conjugate model specifications lead to *relatively fast* estimation

Results

Treatment-emergent changes in activity related to inhibitory control for patients relative to controls

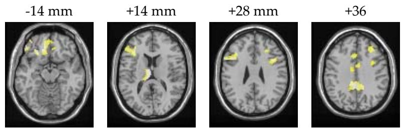
$$A = [(\text{Post-tx} - \text{Pre-tx in Patients}) - (\text{Follow up} - \text{BL in Controls})]$$

Target

- Voxel-Specific Activation Maps
- Regional Activation Maps
- Within-Region Task-Related FC
- Inter-Regional Task-Related FC

Results: Inhibitory Control in Cocaine Addicts

fMRI Voxel-Specific Activation Maps



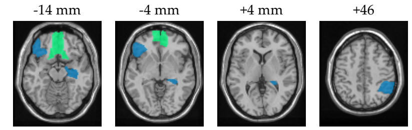
$\Pr(A(v) > 0) \geq 0.70$

Treatment-related changes are probable in

- -14 mm: Medial orbital frontal cortex (OFC) (BA 11)
- +14 mm: Left thalamus and left middle frontal gyrus (BA 46)
- +28 mm: Left and right middle frontal gyrus (BA 9)
- +36 mm: Cingulate gyrus, with most spatially extensive in the posterior cingulate gyrus (BA 31, 32)

Results

fMRI Regional Activation/Deactivation Maps



$\Pr(|A(g)| > 0) \geq 0.80$

Treatment-related changes are probable in

Increases:

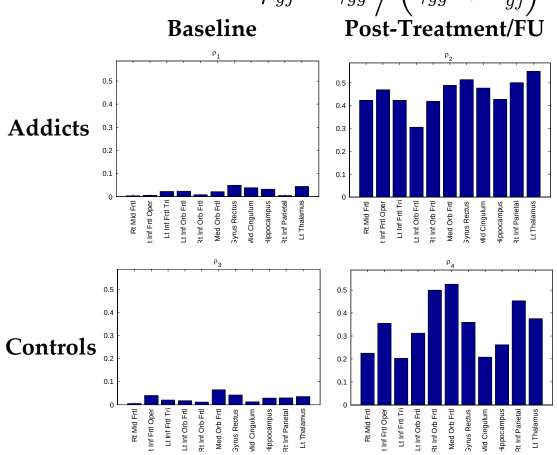
- -14 mm:Gyrus rectus and medial OFC
- -4 mm: Medial OFC

Decreases:

- -14 mm: Left inferior OFC
- -4 mm: Right hippocampus (from -14 to +4) and left inferior OFC
- +46 mm: Right inferior parietal region

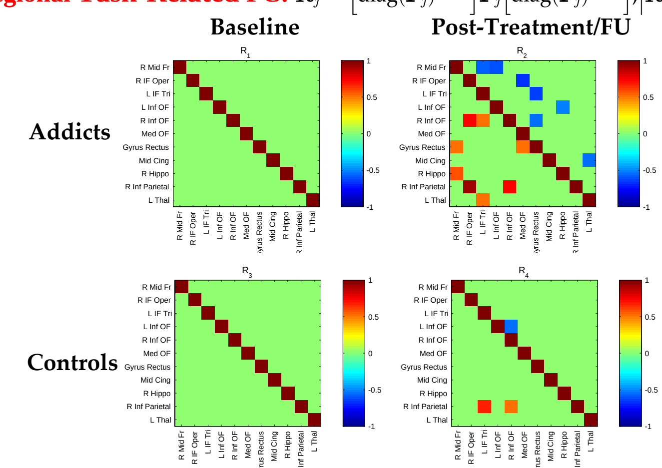
Results

Within-Region Task-Related FC: $\rho_{gj} = \gamma_{gg}^{(j)} \Big/ \left(\gamma_{gg}^{(j)} + \sigma_{gj}^2\right)$



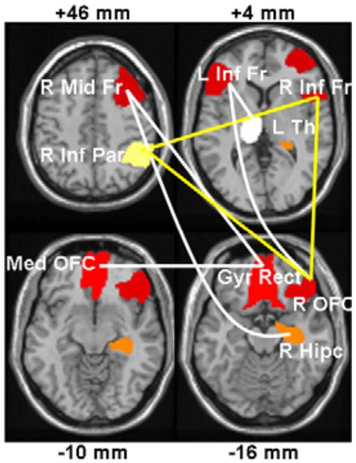
Results

Inter-Regional Task-Related FC: $\boldsymbol{R}_j = \left[\mathrm{diag}(\boldsymbol{\Gamma}_j)^{-1/2}\right]\boldsymbol{\Gamma}_j\left[\mathrm{diag}(\boldsymbol{\Gamma}_j)^{-1/2}\right], \left|\widehat{\boldsymbol{R}}_j(r,c)\right| \geq 0.5$:



Results

Inter-Regional Task-Related FC: Patients Post-Treatment



Yellow: $\widehat{\boldsymbol{R}}_j(r,c) \geq 0.75$:

White: $0.5 \leq \widehat{\boldsymbol{R}}_j(r,c) < 0.75$:

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

Other Considerations

- Sensitivity of results to choice of priors, e.g.

$$\boldsymbol{H}_{0j}^{*} = (1-\omega)\boldsymbol{H}_{0j} + \omega[\text{diag}(\boldsymbol{H}_{0j})], \quad 0 \leq \omega \leq 1$$

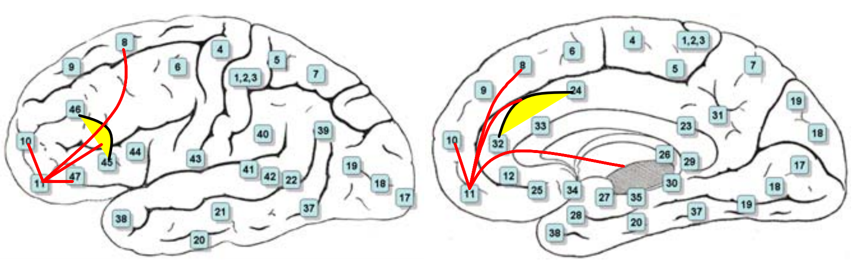
- Convergence diagnostics

- Unified estimation of spatio-temporal model parameters
  - ▹ Computational costs may be *too high*

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

Other Considerations

- Assess changes in task-related FC: treatment-related changes in FC:
  - ▹ $D_{\text{pre}}(r,c) = R_{\text{pats, pre}}(r,c) - R_{\text{ctls, pre}}(r,c)$
    $D_{\text{post}}(r,c) = R_{\text{pats, post}}(r,c) - R_{\text{ctls, post}}(r,c)$
  - ▹ $\Pr\{[D_{\text{pre}}(r,c) - D_{\text{post}}(r,c)] > \delta_0\} \geq \alpha$



EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

V. Summary

Spatial modeling approaches

- *Feasible* for functional neuroimaging data

- Quantifies task-related functional connectivity
  - ▹ Within clusters or neuroanatomical regions
  - ▹ Between neuroanatomical regions (Spatial BHM)

- Allows voxel-specific and regional inferences
  - ▹ Activation inferences account for task-related FC's detected in the data

Project Collaborators

Emory University

- **Clint Kilts**, Ph. D., Department of Psychiatry and Behavioral Sciences
- Gordana Derado, M. S., Department of Biostatistics and Bioinformatics
- Tim Ely, B. A., Department of Psychiatry and Behavioral Sciences
- Robin Gross, B. A., Department of Psychiatry and Behavioral Sciences

Johns Hopkins University

- **Brian Caffo**, Ph. D., Department of Biostatistics
- **Susan Spear Bassett**, M. D., Department of Psychiatry and Behavioral Sciences

References:

- Bowman et al. (2008). Bayesian Hierarchical Framework for Spatial Modeling of fMRI Data. *NeuroImage* 39: 146-156.

- See http://www.sph.emory.edu/bios/CBIS/index.html