

Analysis of Multiple Sclerosis Lesions via Spatially Varying Coefficients

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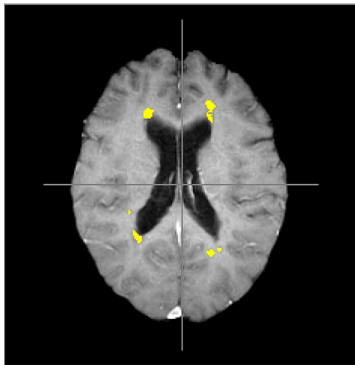
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Multiple Sclerosis

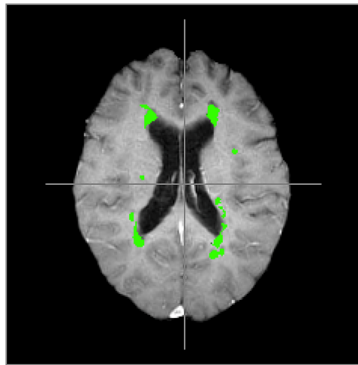
- An autoimmune disease of the central nervous system
- Neuronal demyelination and lesions in the brain and spinal cord

Multiple Sclerosis

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T1 black-hole lesions



T2 lesions

Multiple Sclerosis

- An autoimmune disease of the central nervous system
- Neuronal demyelination and lesions in the brain and spinal cord
- Symptoms - almost any neurological symptom or sign
- Disability measures
 - Expanded Disability Status Scale (EDSS) - overall score of 7 functional systems subscores
 - Paced Auditory Serial Addition Test (PASAT) - auditory speed/flexibility + calculation ability
- Clinical subtypes - clinically isolated syndrome (CIS); relapsed-remitting (RLRM); primary progressive (PRP); secondary chronic progressive (SCP); progressive relapsing (PRL)
- Imaging - T1, T2, Gadolinium-enhanced T1, DTI, etc

Quantitative Analysis of Classical T1/T2 Images

- Segmented, registered to standard template, thresholded to binary images that mark the exact location of lesions
- Compare lesion probability maps cross-sectionally or longitudinally [e.g., [Holland et al., 2012](#); [Filli et al., 2012](#)]
 - hard to associate lesion locations with certain covariates of interest
- Voxel-based lesion-symptom mapping (massive univariate method) [e.g., [Bates et al., 2003](#)]
 - ill suited to the binary nature of the data and cannot account for the spatial structure
- Smooth lesion masks by a Gaussian kernel [e.g., [Charil et al., 2003, 2007](#); [Kincses et al., 2011](#)]
 - does not completely eliminate the non-Gaussian nature of the data and requires an arbitrary choice of smoothing parameter (different kernels might give different results)

- To appropriately model binary lesion maps
- To determine the relationship between local lesion incidence and subject specific covariates (e.g., age, gender, disease duration, disability scores, etc)

The Spatially Varying Coefficient Model

- Voxel-wise generalized linear mixed model (Probit regression)

$$\Phi^{-1}[\Pr(Y_i(s_j) = 1 \mid \cdot)] = \mathbf{x}_i^\top [\boldsymbol{\alpha} + \boldsymbol{\beta}(s_j)] + w(s_j)\gamma$$

- Subject $i = 1, \dots, N$; voxel $s_j, j = 1, \dots, M$
- Outcome $Y_i(s_j) \in \{0, 1\}$
- Φ - the cumulative distribution function for the standard normal distribution
- \mathbf{x}_i - subject specific covariates (e.g., age, gender, etc);
 $w(s_j)$ - spatially varying covariates (e.g., atlas white matter probability image)
- $\boldsymbol{\alpha}$ and γ - spatially constant coefficients (spatial fixed effects);
 $\boldsymbol{\beta}(s_j)$ - spatially varying coefficients (spatial random effects)

Multivariate Markov Random Field

- View the spatially varying coefficients as latent spatial processes
- Multivariate Conditional Autoregressive (MCAR) model prior [Besag, 1993; Mardia, 1988]

$$[\beta(s_j) \mid \beta(s_{-j}), \Sigma] \sim \text{MVN} \left(\frac{\sum_{s_r \in \partial s_j} \beta(s_r)}{n(s_j)}, \frac{\Sigma}{n(s_j)} \right)$$

- $s_j \sim s_k$ - neighboring voxels; ∂s_j - the set of neighbors of s_j ;
 $n(s_j)$ - the number of neighbors of s_j
- Σ - positive definite matrix (learn from data)
- Other priors
 - $\pi(\alpha) \propto 1$ and $\pi(\gamma) \propto 1$
 - Wishart prior – $\Sigma^{-1} \sim W(\nu, \mathbf{I})$

Application and Implementation

- Dimensionality of the data set
 - 250 subjects, 5 clinical subtypes, 3D T2-lesion images, 274,596 whole-brain in-mask voxels
 - Subject specific covariates - age, gender, disease duration, EDSS, PASAT (associated with spatially varying coefficients)
 - Spatially varying covariates - white matter probability image
 - Random intercept for each subtype
 - **Approximately 70 million observed outcomes and 2.5 million spatially varying coefficients!**
- Implementation (computation completed under 8 hours)
 - Latent variable representation [Albert and Chib, 1993]
 - Gibbs sampler
 - GPU and parallelization (50 times faster than using a CPU)

Empirical Lesion Probabilities

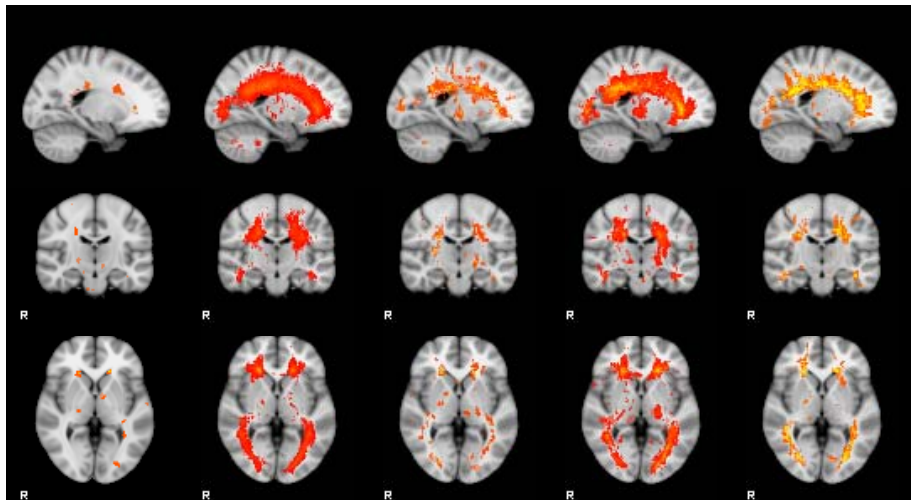
CIS
11 Subj

RLRM
173 Subj

PRP
13 Subj

SCP
43 Subj

PRL
10 Subj



Estimated Lesion Probabilities

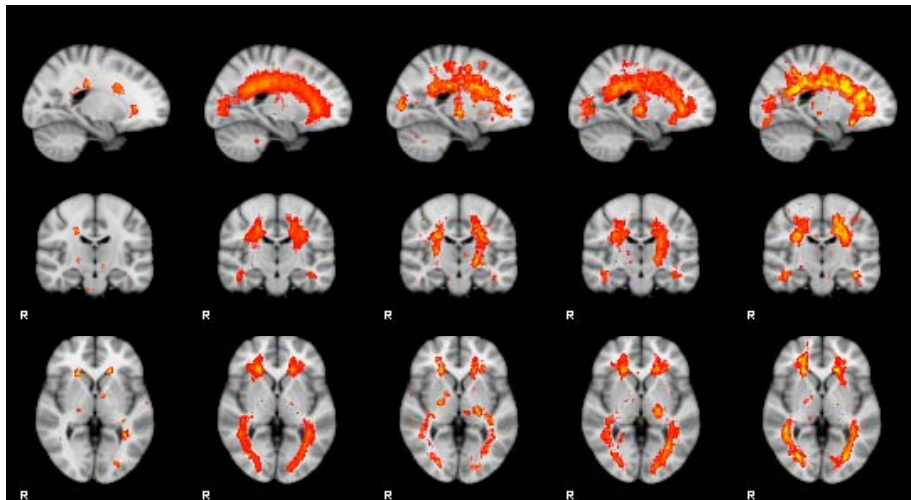
CIS
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Spatially Varying Coefficients

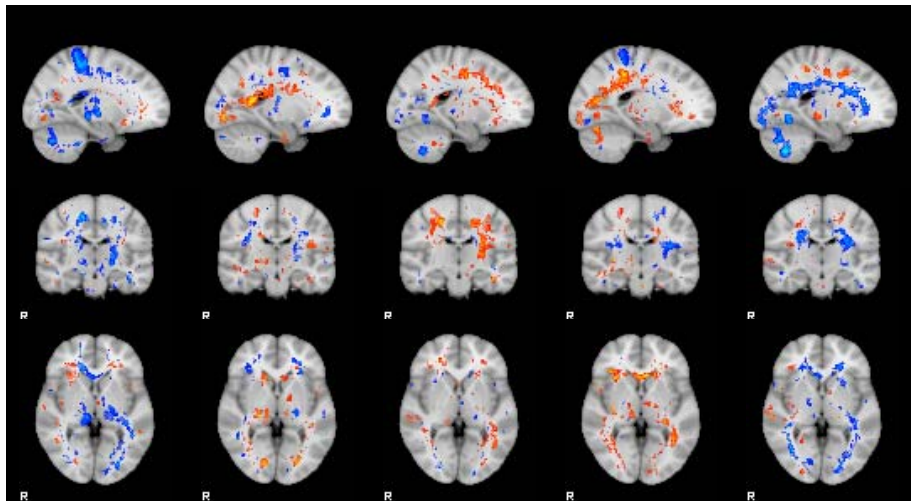
Age

Gender

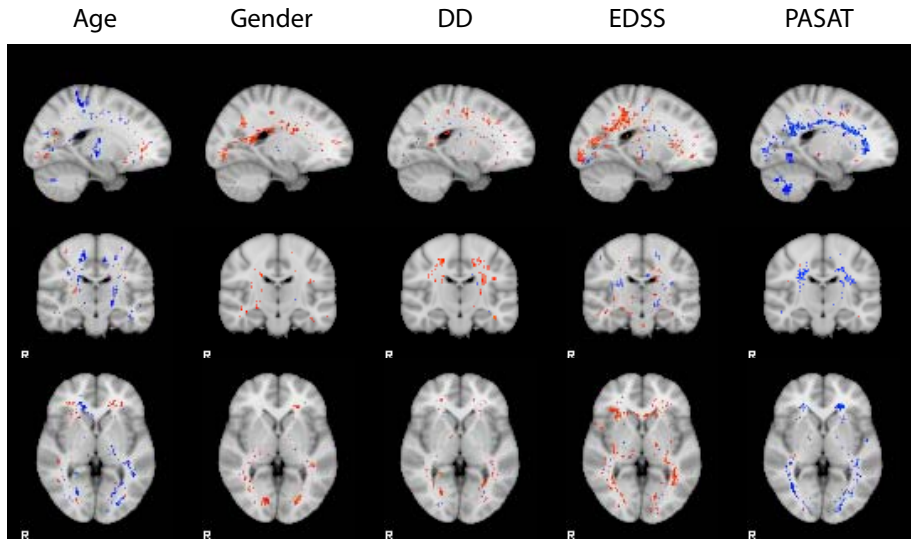
DD

EDSS

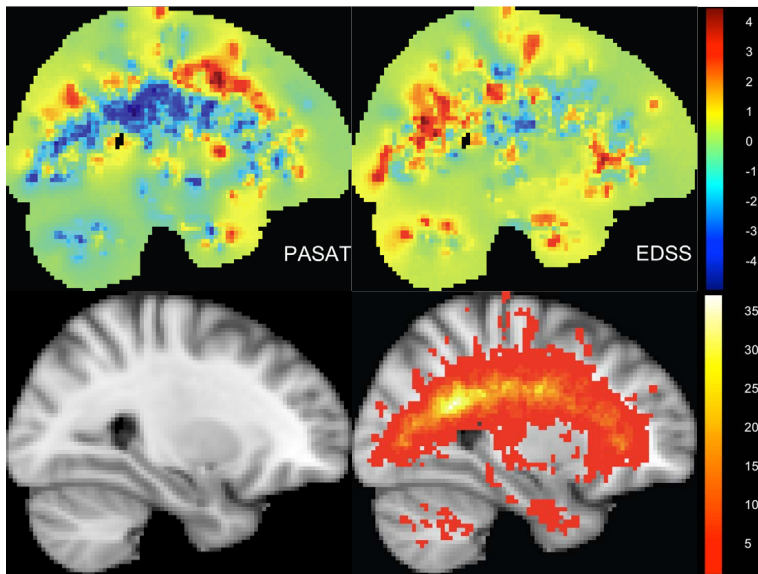
PASAT



Voxel-wise Firth Regression Coefficients



Spatially Varying Coefficients: EDSS & PASAT



Leave-one-out Classification Results

Bayesian Spatial Model					
(Average classification rate: 82.8%)					
	CIS	RLRM	PRP	SCP	PRL
CIS	1.000	0.000	0.000	0.000	0.000
RLRM	0.243	0.734	0.000	0.023	0.000
PRP	0.154	0.000	0.846	0.000	0.000
SCP	0.140	0.000	0.00	0.860	0.000
PRL	0.100	0.000	0.100	0.100	0.700

Firth Logistic Regression					
(Average classification rate: 30.0%)					
	CIS	RLRM	PRP	SCP	PRL
CIS	0.000	1.000	0.000	0.000	0.000
RLRM	0.052	0.821	0.006	0.087	0.034
PRP	0.000	0.538	0.000	0.385	0.077
SCP	0.000	0.302	0.023	0.582	0.093
PRL	0.000	0.400	0.000	0.500	0.100

- CIS - 11 subjects; RLRM - 173 subjects; PRP - 13 subjects; SCP - 43 subjects; PRL - 10 subjects.

Leave-one-out Classification Results

Bayesian Spatial Model						Naïve Bayesian Classifier					
(Average classification rate: 82.8%)						(Average classification rate: 24.5%)					
	CIS	RLRM	PRP	SCP	PRL		CIS	RLRM	PRP	SCP	PRL
CIS	1.000	0.000	0.000	0.000	0.000	CIS	0.000	1.000	0.000	0.000	0.000
RLRM	0.243	0.734	0.000	0.023	0.000	RLRM	0.046	0.757	0.017	0.093	0.087
PRP	0.154	0.000	0.846	0.000	0.000	PRP	0.077	0.769	0.000	0.077	0.077
SCP	0.140	0.000	0.00	0.860	0.000	SCP	0.023	0.744	0.023	0.070	0.140
PRL	0.100	0.000	0.100	0.100	0.700	PRL	0.000	0.600	0.000	0.000	0.400

- CIS - 11 subjects; RLRM - 173 subjects; PRP - 13 subjects; SCP - 43 subjects; PRL - 10 subjects.

- A Bayesian spatial generalized linear mixed model with spatially varying coefficients
- Respects binary nature of the data
- Exploits the spatial structure and produces regularized estimates of lesion maps without a fixed smoothing parameter
- Explicitly models covariates and allows for spatially varying coefficients
- Detects spatial dependence between lesion location and covariates
- Suitable to model any patterns of lesion data
- Can be easily extended to include other covariates of interest
- Potentials in classification of different subtypes of MS

- Albert, J. H. and Chib, S. (1993). Bayesian analysis of binary and polychotomous response data. *JASA* 88: 669-679.
- Bates, E. et al. (2003). Voxel-based lesion-symptom mapping. *Nature Neurosci.* 6: 448-449.
- Besag, J. (1993). Towards Bayesian image analysis. *Journal of Applied Statistics* 20: 107-119.
- Charil, A. et al. (2003). Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis: application to 452 patient data sets. *NeuroImage* 19: 532-544.
- Charil, A. et al. (2007). Focal cortical atrophy in multiple sclerosis: relation to lesion load and disability. *NeuroImage* 34: 509-517.
- Filli, L. et al. (2012). Spatiotemporal distribution of white matter lesions in relapsing-remitting and secondary progressive multiple sclerosis. *Multiple Sclerosis Journal* 18: 1577-1584.
- Firth, D. (1993). Bias reduction of maximum likelihood estimates. *Biometrika* 80: 27-38.
- Gelfand, A. E. et al. (2003). Spatial modeling with spatially varying coefficient processes. *JASA* 98: 387-396.
- Holland, C. M. et al. (2012). The relationship between normal cerebral perfusion patterns and white matter lesion distribution in 1,249 patients with multiple sclerosis. *Journal of Neuroimaging* 22: 129-136.
- Kincses, Z. T. et al. (2011). Lesion probability mapping to explain clinical deficits and cognitive performance in multiple sclerosis. *Multiple Sclerosis Journal* 17: 681-689.
- Mardia, K. V. (1988). Multi-dimensional multivariate Gaussian Markov random fields with application to image processing. *Journal of Multivariate Analysis* 24: 265-284.

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Thanks for Your Attention!