Spatiotemporal Mixed Modeling of task fMRI

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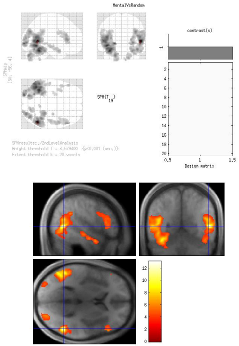
Scientific objective

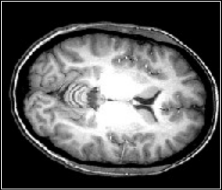
- A goal of neuroscience is to map the locations of brain activity that produce various thoughts and behaviors
- fMRI is used to localize patterns of activation in response to task stimuli
- Example: Theory of mind, or mentalizing, is the ability to infer another’s mental state



Overview of fMRI

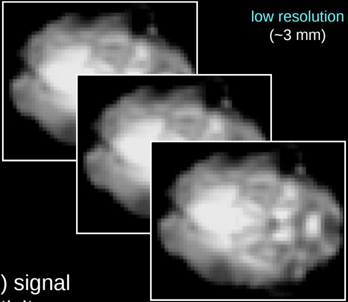
MRI

high resolution
(1 mm)



one image (no time)

fMRI



low resolution
(~3 mm)

many images
(e.g., every 2 sec for 5 mins)

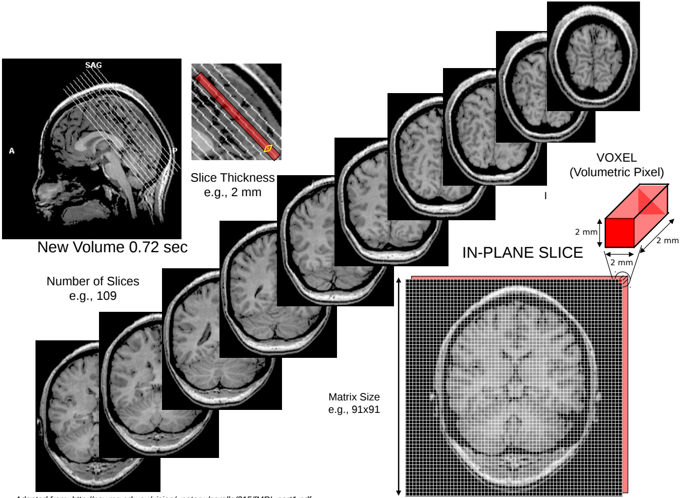
fMRI

Blood Oxygenation Level Dependent (BOLD) signal
-indirect, “sluggish” measure of neural activity

↑ neural activity ➔ ↑ blood oxygen ➔ ↑ fMRI signal

Adapted from: http://psy.mq.edu.au/vision/~peterw/corella/315/fMRI_part1.pdf

fMRI volumes



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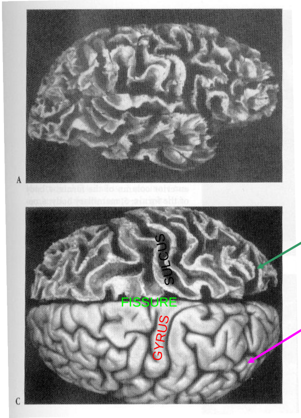
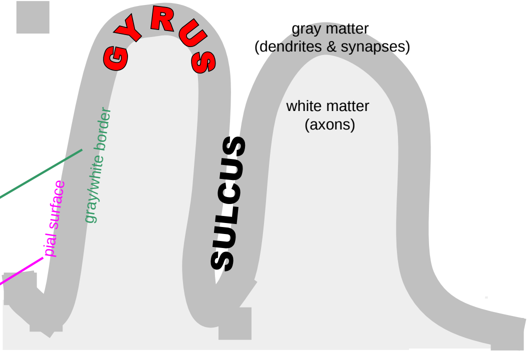
Topology of the brain





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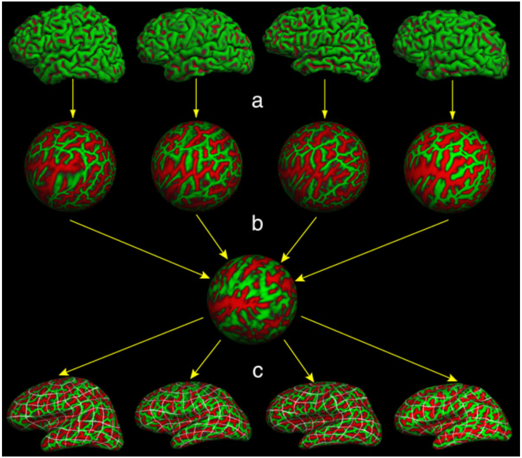
Surface registration: vertices



Challenges of fMRI

- Our example dataset:
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  - 9.9 billion data points
- After masking, we have
  $N = 20$, 2 sessions, $T = 274$, 230k voxels
  - 2.5 billion data points
- If we restrict ourselves to right cerebral cortex, $N = 20$, 2 session, $T = 274$, 30k vertices
  - 326 million data points

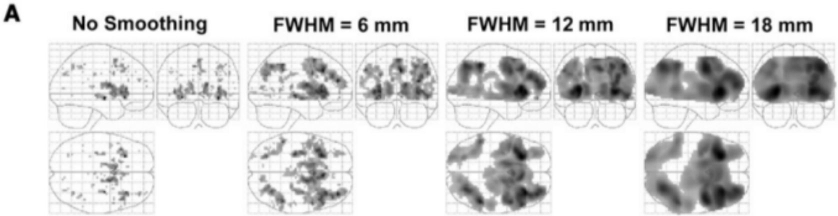
Motivation

Most popular approach: Massive Univariate Mixed Model (MUMM)

- Separate mixed model estimated for each voxel
- Spatial dependence can be accounted for post-estimation using random field theory
- Data are spatially smoothed with a Gaussian kernel during pre-processing to:
    1. Increase overlap of features between subjects
    2. Increase power and meet assumptions of random field theory
- Conflict: increase power but decrease precision of localization
- So how much smoothing? Not clear.

Smoothing affects inference

M. Mikl et al. / Magnetic Resonance Imaging 26 (2008) 490–503



Literature Review of Spatial Models

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4. [Kang et al., 2012] spatial modeling in spectral (time) domain allowing for correlated regions of interest (ROIs)
    - $N = 1$, 4 sessions, $V = 20$/ROI, 3 ROIs, $T = 480$

SPM and FSL: Massive univariate analysis

- $n \in \{1, \ldots, N\}$ denote subject
- $v \in \{1, \ldots, V\}$ denote location (voxel for volume data, vertex for surface data)
- $t \in \{1, \ldots, T\}$ index time
- $q \in \{1, \ldots, Q\}$ index the task
- Task onsets and duration: $I_{nq}(t)$; shape of the BOLD response to a stimulus: $h(t)$.

$$x_{ntq} = \int_0^{f_t} h(u) I_{nq}(f_t - u) du$$

where f_t is the time in seconds corresponding to the tth timepoint and we assume the same $h(t)$ for all voxels.

Hierarchical MUMM

$$(1-\phi_{nv1}B-\phi_{nv2}B^2-\phi_{nv3}B^3)\left\{y_{nvt}-\mathbf{x}'_{nt}\left(\beta_v+\boldsymbol{b}_{nv}\right)-\mathbf{z}'_{nt}\gamma_{nv}\right\} = \epsilon_{nvt}$$

with $\boldsymbol{b}_{nv} \overset{iid}{\sim} \mathcal{N}\{\mathbf{0}, \mathrm{diag}(\sigma^2_{b_1}, \ldots, \sigma^2_{b_Q})\}$ and $\epsilon_{nvt} \overset{iid}{\sim} \mathcal{N}(0, \tau^2_{nv})$. All b_{nvq} and ϵ_{nvt} are mutually independent.
Let $\mathbf{B} = \mathrm{diag}(\sigma^2_{b_1}, \ldots, \sigma^2_{b_Q})$. Then,

$$\mathrm{Cov}\,\mathbf{Y}_{nv} = \mathbf{X}_{nt}\mathbf{B}\mathbf{X}'_{nt} + \xi^2_{nv}\boldsymbol{\Psi}_{nv}. \tag{1}$$

MUMM estimators

To simplify the exposition, assume $\mathbf{z}_{nt} = 0$. Define

$$\hat{\mathbf{e}}_{nv} = (\mathbf{X}_n'\mathbf{X}_n)^{-1}\mathbf{X}_n'\mathbf{Y}_{nv}. \tag{2}$$

Define the estimate of the population coefficients:

$$\hat{\beta}_v = \frac{1}{N}\sum_{n=1}^{N}\hat{\mathbf{e}}_{nv}. \tag{3}$$

Define the estimate of the variance of the fixed effect estimator:

$$\widehat{\mathrm{Cov}}\,\hat{\beta}_v = \frac{1}{N(N-1)}\sum_{n=1}^{N}\left(\hat{\mathbf{e}}_{nv} - \hat{\beta}_v\right)\left(\hat{\mathbf{e}}_{nv} - \hat{\beta}_v\right)'. \tag{4}$$

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4. Leverage improvements in registration using geodesic distances and improvements in parcellation using the Gordon parcels.
5. Fast estimators of spatial dependence that can be used for whole-brain multi-subject studies.

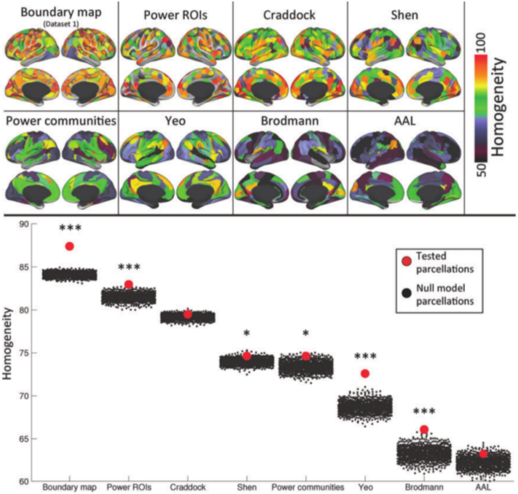
STMM

Define a separate model for each parcel.
To simplify the notation, let us consider a single region and ignore the index for region.
Let

$$\mathbf{Y}_n = [y_{n11}, \ldots, y_{n1T}, y_{n21}, \ldots, y_{n2T}, \ldots, y_{nVT}]'$$

denote the BOLD signal for the nth subject at the vertices in our region, where V is the number of vertices in the region.
Let $\mathbf{Y} = [\mathbf{Y}_1', \ldots, \mathbf{Y}_N']'$.

[Gordon et al., 2014]



STMM

$$y_{nvt} = \mathbf{x}'_{nt}(\beta + \boldsymbol{u}_v + \boldsymbol{s}_n + \boldsymbol{b}_{nv}) + \mathbf{z}'_{nt}\gamma_{nv} + a_{nvt}, \tag{5}$$

where

$$\boldsymbol{u}^q \sim \mathcal{N}(\mathbf{0}, \sigma^2_{u_q}\boldsymbol{\Gamma}_q);$$

$$\boldsymbol{s}_n \overset{iid}{\sim} \mathcal{N}(\mathbf{0}, \mathbf{S})$$

with $\mathbf{S} = \mathrm{diag}(\sigma^2_{s_1}, \ldots, \sigma^2_{s_Q})$;

$$\boldsymbol{b}^q_n \overset{iid}{\sim} \mathcal{N}(\mathbf{0}, \sigma^2_{b_q}\Omega_q);$$

and

$$\boldsymbol{a} \sim \mathcal{N}(\mathbf{0}, \oplus_{n=1}^{N} \oplus_{v=1}^{V} \xi^2_{nv}\boldsymbol{\Psi}_{nv}).$$

Spatial Correlation

We assume the spatial correlation structure defined by exponential covariogram:

$$\boldsymbol{\Gamma}_{q;vv'} = e^{-\theta_{bq}||v-v'||}$$

and

$$\Omega_{q;vv'} = e^{-\theta_{bq}||v-v'||}.$$

Covariance Model

$$\operatorname{Cov} y_{nvt}, y_{n'v't'} =$$

$$\begin{cases} \mathbf{x}'_{nt}(\mathbf{U}+\mathbf{S}+\mathbf{B})\mathbf{x}_{nt'} + \xi^2_{nv}\psi^{(nv)}_{tt'} & n = n';\, v = v';\ \text{any } t, t' \\ \mathbf{x}'_{nt}(\mathbf{U}\Gamma_{vv'} + \mathbf{S} + \mathbf{B}\Omega_{vv'})\mathbf{x}_{nt'} & n = n';\, v \neq v';\ \text{any } t, t' \\ \mathbf{x}'_{nt}\mathbf{U}\Gamma_{vv'}\mathbf{x}_{n't'} & n \neq n';\ \text{any } v, v';\ \text{any } t, t' \end{cases}$$

No independence anywhere.

ML and REML impossible

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- We can not use maximum likelihood or restricted maximum likelihood methods to fit this model due to the enormous size of the covariance matrix, which is non-sparse for each parcel.
- In our application, the largest parcel's covariance matrix is 11 million by 11 million.
- The method we will propose involves a 39,440 $\times$ 39,440 covariance matrix, which is about as much as we can handle with 32GB of RAM and computational shortcuts such as Sherman-Morrison-Woodbury.

Second-level model

Transform the time dimension from T to the number of covariates Q:

$$\boldsymbol{d}_{nv} = \mathbf{K}_n{}'\mathbf{Y}_{nv}. \tag{6}$$

Define the second-level model

$$\begin{aligned}\boldsymbol{d} &= (\mathbf{1}_N \otimes \mathbf{1}_V \otimes \mathbf{I}_Q)\boldsymbol{\beta} + (\mathbf{1}_N \otimes \mathbf{I}_V \otimes \mathbf{I}_Q)\boldsymbol{u} + (\mathbf{I}_N \otimes \mathbf{1}_V \otimes \mathbf{I}_Q)\boldsymbol{s} \\ &+ (\mathbf{I}_N \otimes \mathbf{I}_V \otimes \mathbf{I}_Q)\boldsymbol{b} + \{_c\ \{_c\ \mathbf{K}_n'\boldsymbol{a}_{nv}\}_{v=1}^{V}\}_{n=1}^{N}.\end{aligned}$$

Estimation highlights

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3. Define a novel covariogram to allow vertex-specific temporal correlation

$$\delta_q(d_{nvq}, d_{nv'q}) = \begin{cases} \sigma^2_{u_q} + \sigma^2_{s_q} + \sigma^2_{b_q} + \beta^2_q & v = v', \\ (\sigma^2_{s_q} + \beta^2_q) + (\sigma^2_{u_q} + \sigma^2_{b_q})e^{-\theta_q ||v-v'||} & v \neq v'. \end{cases}$$

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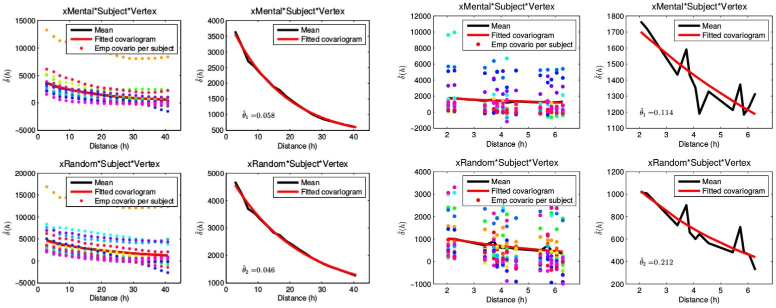
4. Define novel empirical covariogram for tolerance ν:

$$\hat{\delta}_n(h) = \frac{1}{N_h} \sum_{\{v,v'\}:\ \|v-v'\| \in (h-\nu, h+\nu]} d_{nvq} d_{nv'q} \quad (7)$$

We can estimate θ_q without knowing the other parameters!

Estimating the spatial correlation parameter

Figure : Empirical covariogram and fitted exponential covariogram for the spatial random effects for a large (777 vertices) and very small (29 vertices) parcel.



ANOVA estimators of variance components

Decompose the variance of the transformed data, $\boldsymbol{d}_{nv} = \mathbf{K}_n{}'\mathbf{Y}_{nv}$.

Source	DF	Sum of Squares
Vertex	V-1	$\sum_{n=1}^{N}\sum_{v=1}^{V}(\bar{\boldsymbol{d}}_{\cdot v} - \bar{\boldsymbol{d}}_{\cdot\cdot})(\bar{\boldsymbol{d}}_{\cdot v} - \bar{\boldsymbol{d}}_{\cdot\cdot})'$
Subject	N-1	$\sum_{n=1}^{N}\sum_{v=1}^{V}(\bar{\boldsymbol{d}}_{n\cdot} - \bar{\boldsymbol{d}}_{\cdot\cdot})(\bar{\boldsymbol{d}}_{n\cdot} - \bar{\boldsymbol{d}}_{\cdot\cdot})'$
Subject-Vertex	(N-1)(V-1)	$\sum_{n=1}^{N}\sum_{v=1}^{V}(\boldsymbol{d}_{nv} - \bar{\boldsymbol{d}}_{n\cdot} - \bar{\boldsymbol{d}}_{\cdot v} + \bar{\boldsymbol{d}}_{\cdot\cdot})(\boldsymbol{d}_{nv} - \bar{\boldsymbol{d}}_{n\cdot} - \bar{\boldsymbol{d}}_{\cdot v} + \bar{\boldsymbol{d}}_{\cdot\cdot})'$

ANOVA estimators of variance components

Let $g_q = \sum_{v=1}^{V} \sum_{v'=1}^{V} \mathbf{\Gamma}_{q;v,v'}$ and $\mathbf{G} = \mathrm{diag}(g_1, \ldots, g_Q)$.
Let $w_q = \sum_{v=1}^{V} \sum_{v'=1}^{V} \Omega_{q;v,v'}$ and $\mathbf{W} = \mathrm{diag}(w_1, \ldots, w_Q)$.

Source	EMS
Vertex	$\left(\frac{NV}{V-1}\mathbf{I}_Q - \frac{N}{V(V-1)}\mathbf{G}\right)\mathbf{U} + \left(\frac{V}{V-1}\mathbf{I}_Q - \frac{1}{V(V-1)}\mathbf{W}\right)\mathbf{B} + \frac{1}{NV}\sum_{n=1}^{N}\sum_{v'=1}^{V}\mathbf{K}_n\mathbf{\Psi}_{nv'}\mathbf{K}_n'$
Subject	$V\mathbf{S} + \frac{1}{V}\mathbf{W}\mathbf{B} + \frac{1}{NV}\sum_{n=1}^{N}\sum_{v=1}^{V}\xi_{nv}^2\mathbf{K}_n'\mathbf{\Psi}_{nv}\mathbf{K}_n$
Subject-Vertex	$\left(\frac{V}{V-1}\mathbf{I}_Q - \frac{1}{V(V-1)}\mathbf{W}\right)\mathbf{B} + \frac{1}{NV}\sum_{n=1}^{N}\sum_{v=1}^{V}\xi_{nv}^2\mathbf{K}_n'\mathbf{\Psi}_{nv}\mathbf{K}_n$

BLUEs, BLUPs, and eBLUPs

Define the BLUE for regional activation:

$$\hat{\beta} = \left\{(\mathbf{1}'_N \otimes \mathbf{1}'_V \otimes \mathbf{I}_Q)\boldsymbol{\Sigma}^{-1}(\mathbf{1}_N \otimes \mathbf{1}_V \otimes \mathbf{I}_Q)\right\}^{-1}(\mathbf{1}'_N \otimes \mathbf{1}'_V \otimes \mathbf{I}_Q)\boldsymbol{\Sigma}^{-1}\boldsymbol{d} \tag{8}$$

$$\mathrm{Cov}\,\hat{\beta} = \left\{(\mathbf{1}'_N \otimes \mathbf{1}'_V \otimes \mathbf{I}_Q)\boldsymbol{\Sigma}^{-1}(\mathbf{1}_N \otimes \mathbf{1}_V \otimes \mathbf{I}_Q)\right\}^{-1}.$$

Define the BLUP for vertex activation:

$$\hat{\boldsymbol{u}} = \Gamma(\mathbf{1}'_N \otimes \mathbf{I}_V \otimes \mathbf{I}_Q)\boldsymbol{\Sigma}^{-1}\left(\boldsymbol{d} - \mathbf{1}_N \otimes \mathbf{1}_V \otimes \hat{\beta}\right). \tag{9}$$

We can also estimate $\mathrm{Cov}\,\hat{\boldsymbol{u}}$.

Approximate inference

$$[\boldsymbol{u}|\boldsymbol{d}, \widehat{\Sigma}, \hat{\beta}] \sim \mathcal{N}\left(\widehat{\Gamma}\left\{\mathbf{1}_N' \otimes \mathbf{I}_V \otimes \mathbf{I}_Q\right\}\widehat{\Sigma}^{-1}\left(\boldsymbol{d} - \mathbf{1}_N \otimes \mathbf{1}_V \otimes \hat{\beta}\right),\right.$$
$$\left.\widehat{\Gamma} - \widehat{\Gamma}\left\{\mathbf{1}_N' \otimes \mathbf{I}_V \otimes \mathbf{I}_Q\right\}\widehat{\Sigma}^{-1}\left\{\mathbf{1}_N \otimes \mathbf{I}_V \otimes \mathbf{I}_Q\right\}\widehat{\Gamma}\right).$$

For an arbitrary contrast vector $\mathbf{c}$,

$$H_0 : \mathbf{c}'[\beta', \mathrm{E}(\boldsymbol{u}|\boldsymbol{d})']' = 0$$
$$H_A : \mathbf{c}'[\beta', \mathrm{E}(\boldsymbol{u}|\boldsymbol{d})']' \neq 0.$$

We use $\hat{\boldsymbol{u}}$ as our estimate of $\mathrm{E}(\boldsymbol{u}|\boldsymbol{d})$. Approximate t-statistic:

$$t = \frac{\mathbf{c}'[\hat{\beta}', \hat{\boldsymbol{u}}']'}{\left\{\mathbf{c}'(\widehat{\mathrm{Cov}}\,\hat{\beta} \oplus \widehat{\mathrm{Cov}}\,\hat{\boldsymbol{u}})\mathbf{c}\right\}^{1/2}}.$$

Estimators are approximately unbiased

	Truth	df	Mean STMM	Var STMM	Bias^2 STMM	MSE STMM
τ^2_{nv}	30000	-	29811	3434698	35882	3470580
ϕ_{nv1}	0.2000	-	0.1988	0.0020	0.0000	0.0020
ϕ_{nv2}	0.1000	-	0.0969	0.0020	0.0000	0.0021
ϕ_{nv3}	0.0000	-	-0.0008	0.0020	0.0000	0.0020
β_1	20.0	-	19.9	16.2	0.0	16.2
$\sigma^2_{u_1}$	75.0	214	77.0	776.0	4.1	780.2
$\sigma^2_{s_1}$	250	29	241	8521	84	8605
$\sigma^2_{b_1}$	750	6206	750	3517	0	3517
θ_{b_1}	0.200	-	0.201	0.002	0.000	0.002
β_2	-20.0	-	-20.0	17.5	0.0	17.5
$\sigma^2_{u_2}$	75.0	214	75.9	808.2	0.9	809.0
$\sigma^2_{s_2}$	250	29	244	7947	38	7985
$\sigma^2_{b_2}$	750	6206	749	3747	2	3749
θ_{b_2}	0.200	-	0.203	0.002	0.000	0.002

Table : Accuracy of estimators for 1000 simulations with 30 subjects each in which 215 vertices were located according to a Gordon Parcel (ID 82).

STMM: more power with no **U**; less power with **U**

		Region			Vertex		
Scenario	Model	$\beta_1 = 20$ (Power)	$\beta_2 = 0$ (Type 1)	Contrast (Power)	$\beta_1 + u_{v1}$ (Power)	$\beta_2 + u_{v2}$ (Type 1*)	Contrast (Power)
$\theta_1 = \theta_2 = 5$ $\sigma^2_{u_1} = \sigma^2_{u_2} = 0$	MUMM	1.00	0.72	1.00	0.61	0.05	0.38
	ROIMM	1.00	0.05	0.99	-	-	-
	STMM	1.00	0.06	0.99	1.00	0.02	0.99
$\theta_1 = \theta_2 = 5$ $\sigma^2_{u_1} = \sigma^2_{u_2} = 100$	MUMM	1.00	0.70	1.00	0.57	0.19	0.41
	ROIMM	1.00	0.05	1.00	-	-	-
	STMM	1.00	0.06	1.00	0.63	0.02	0.35
$\theta_1 = \theta_2 = 0.2$ $\sigma^2_{u_1} = \sigma^2_{u_2} = 0$	MUMM	1.00	0.72	1.00	0.61	0.05	0.39
	ROIMM	1.00	0.05	0.99	-	-	-
	STMM	1.00	0.04	0.99	1.00	0.02	0.98
$\theta_1 = \theta_2 = 0.2$ $\sigma^2_{u_1} = \sigma^2_{u_2} = 100$	MUMM	1.00	0.79	1.00	0.56	0.19	0.42
	ROIMM	1.00	0.14	0.95	-	-	-
	STMM	0.99	0.03	0.86	0.57	0.02	0.31

Table : Power and type 1 error rates based on 300 simulations for each scenario.

(xMental - xRandom) from HCP ToM

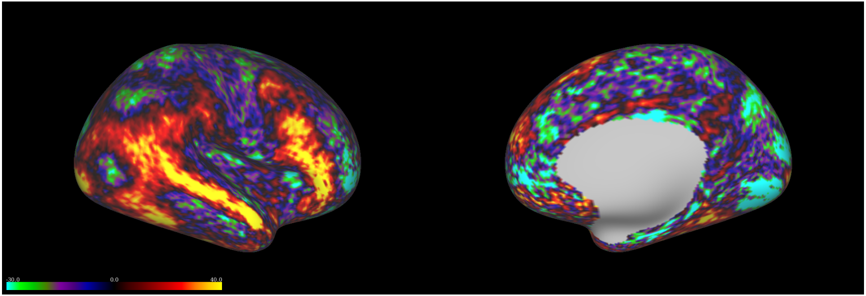


Figure : Contrast in activation from the mentalizing versus random tasks from the MUMM.

(xMental - xRandom) from HCP ToM

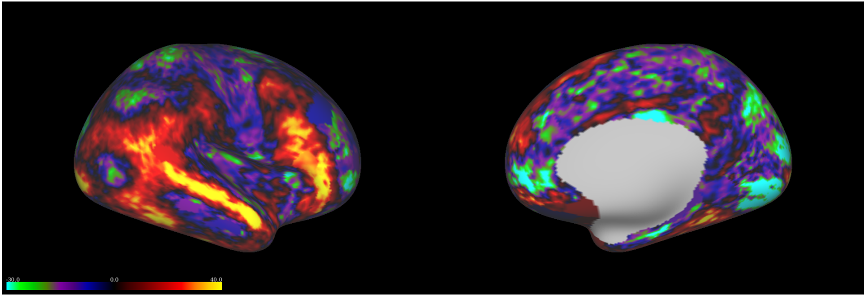


Figure : Contrast in activation from the mentalizing versus random tasks from the STMM.

t-statistic (xMental-xRandom) from HCP ToM

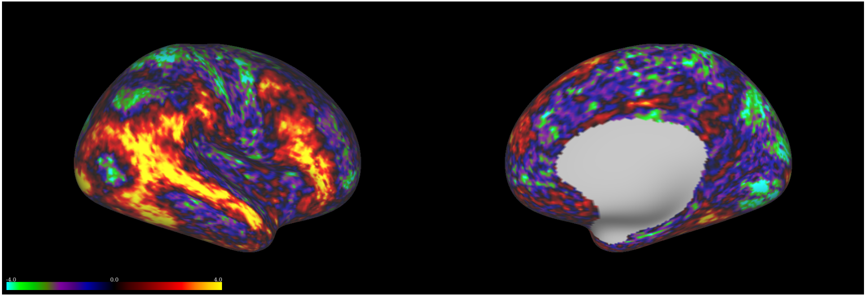


Figure : The contrast t-statistic from the MUMM

t-statistic (xMental-xRandom) from HCP ToM

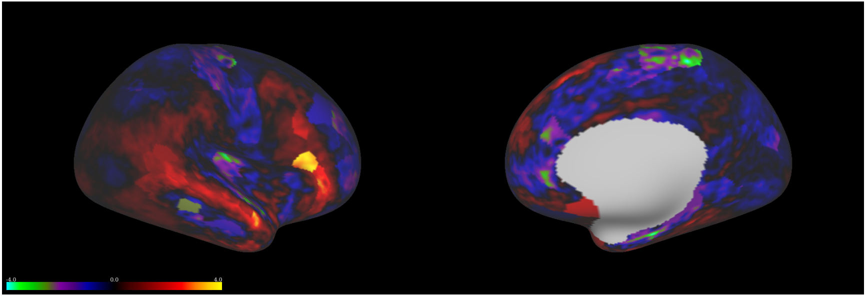


Figure : The contrast t-statistic from the STMM

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5. Fast estimators of spatial dependence.

Discussion and the future

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