Multiple hypotheses testing in functional neuroimaging applications

Time-resolved electromagnetic brain mapping

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Functional neuroimaging

- Human brain mapping
  - Study normal and pathological brain functions
- Multiple modalities
  - Positon Emission Tomography (PET)
  - functional Magnetic Resonance Imaging (fMRI)
  - Electrophysiology: electro (EEG) & magneto encephalography (MEG)

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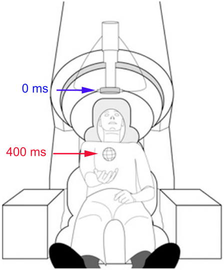
MEG/EEG imaging
Chronography of brain activations



P. Senot, S. Baillet, B. Renault & A. Berthoz, in revision

Properties

- Synoptic detection of brain activations
- Reasonable spatial resolution at the regional scale ($\sim$ 1cm)
- Excellent time resolution ($\sim$ 1ms)

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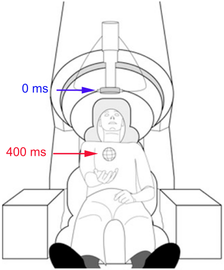

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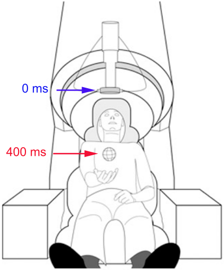

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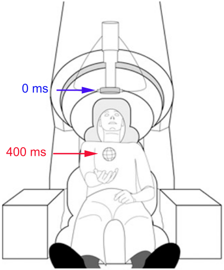

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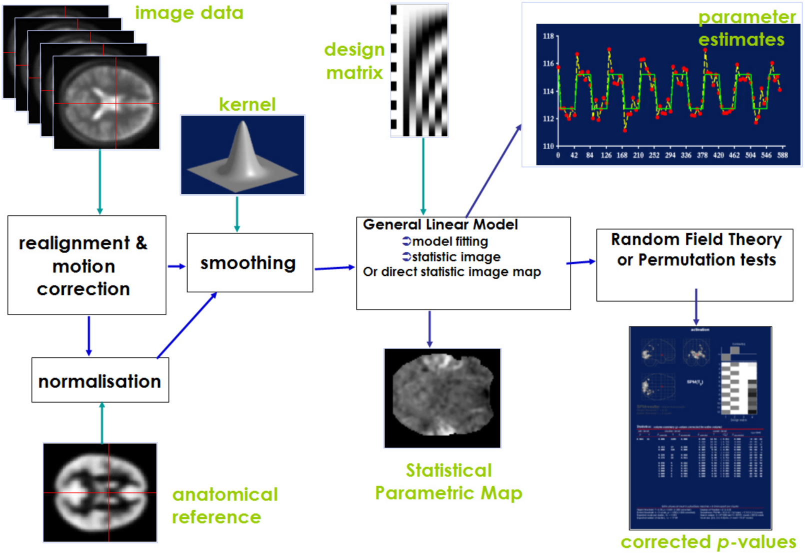
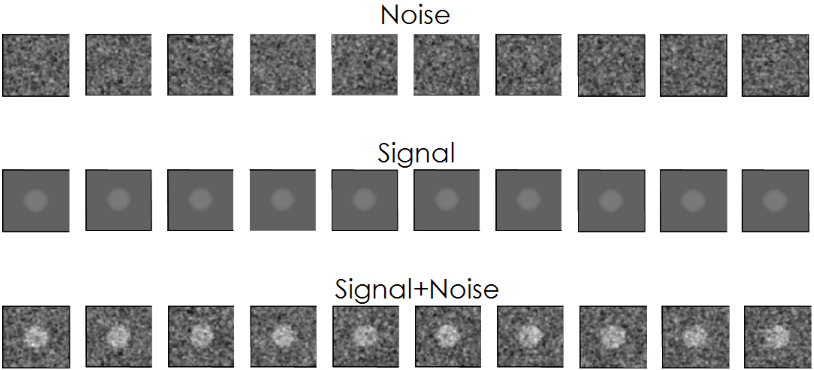
A pipeline of processes



adapted from Will Penny, University College London

Inference for images



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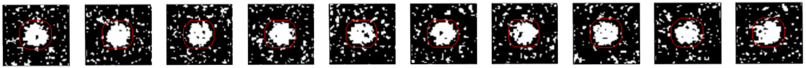
Uncorrected *p*-value, $\alpha = 0.1$



11.3% 11.3% 12.5% 10.8% 11.5% 10.0% 10.7% 11.2% 10.2% 9.5%

Percentage of null pixels that are false positives

Consequences

- False conclusion: on average, 10% of *unactive* voxels are declared as *active*
- Need to define a null hypothesis for images of statistics

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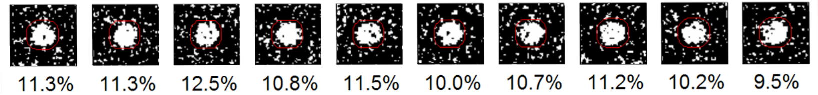

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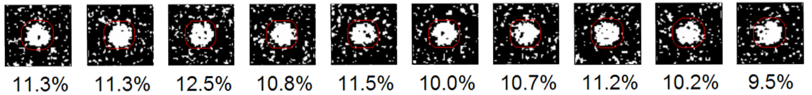

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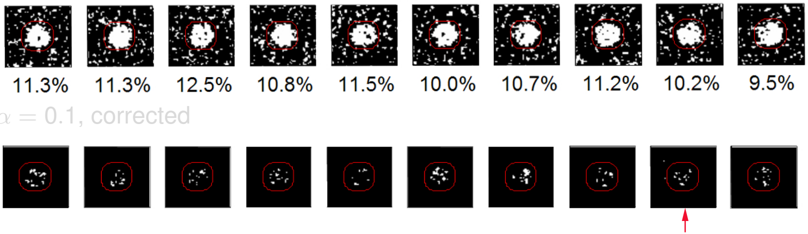
Controlling the error rate

Family-wise null hypothesis

- *Activation is zero everywhere*
- If we reject a voxel null hypothesis *at any voxel*, we reject the family-wise null hypothesis
- Any false positive (FP) in the image yields a Family Wise Error (FWE)
- Family-Wise Error Rate (FWER) = corrected *p*-value

$\alpha = 0.1$, uncorrected



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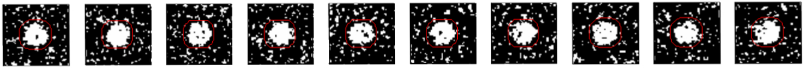

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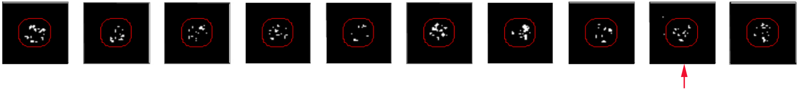

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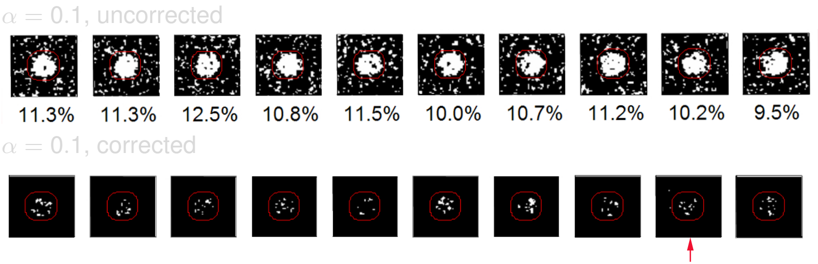

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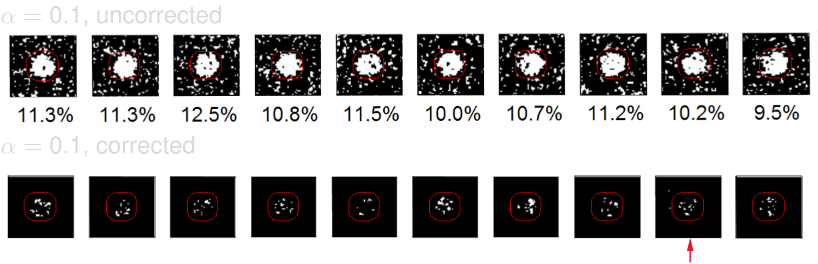

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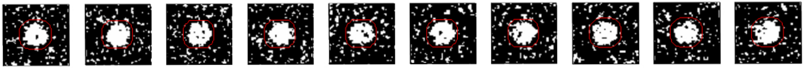

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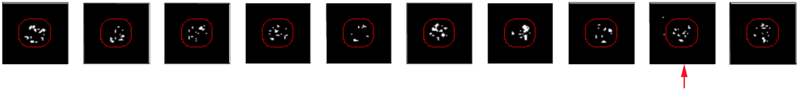

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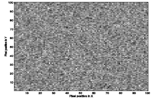
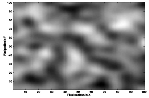
Bonferroni correction





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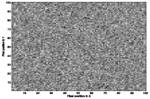

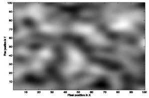

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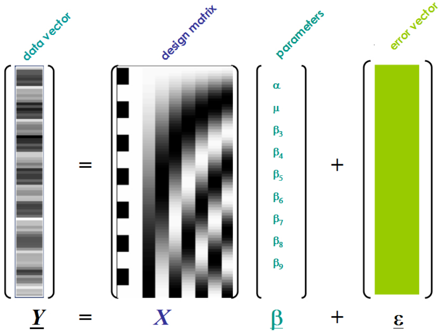
The General(ized) Linear Model
Random-field theory



adapted from S. Kiebel & A. Holmes, SPM short course, 2002

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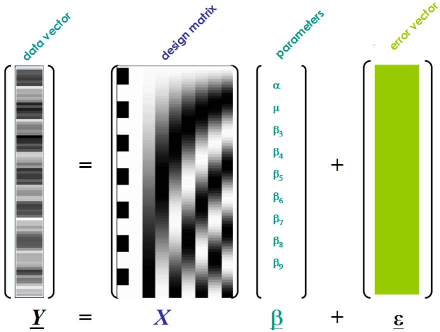

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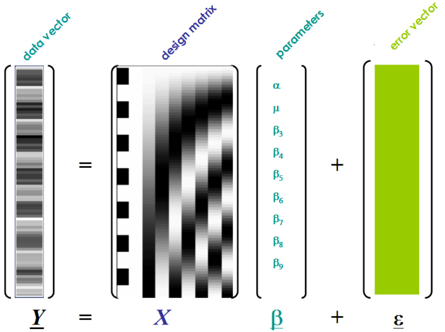

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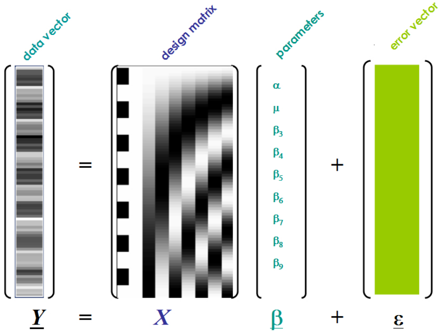

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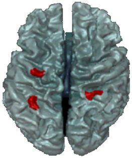
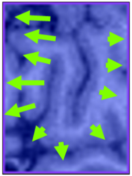
When the image support is a surface

Back to MEG/EEG imaging





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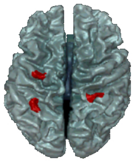

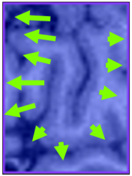

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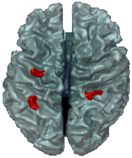

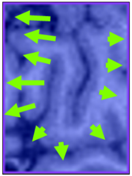

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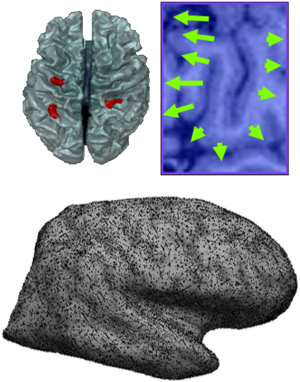

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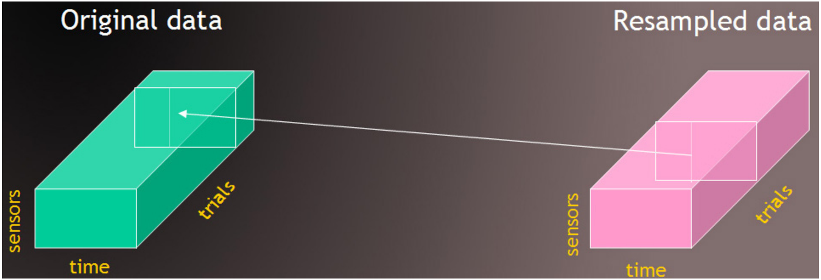
First approach: *the bootstrap*

Take advantage of repeated measurements (*trials*) in M/EEG

- non-parametric bootstrap generates surrogate data sets
- computer-intensive data resampling



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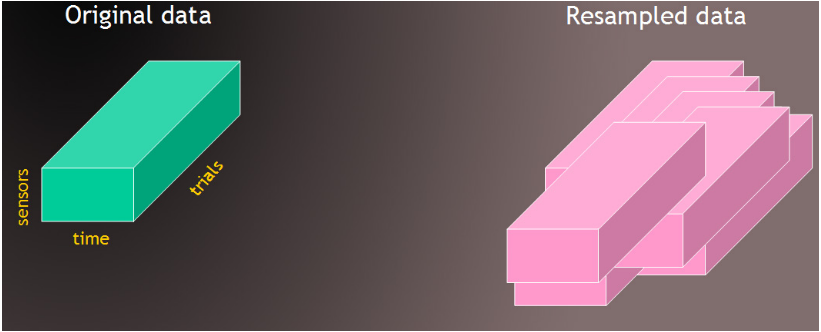
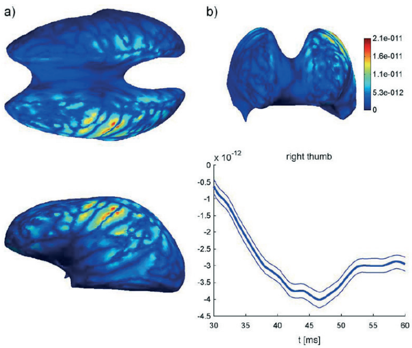
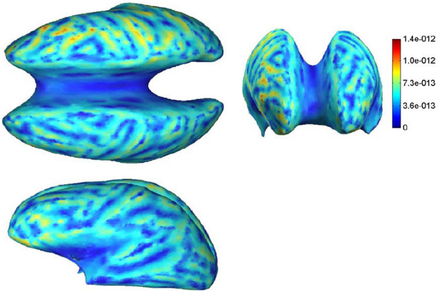


Bootstrapping current density maps

- from [Meunier et al. 2001] & [Darvas et al. 2005]





Bootstrap sample standard deviations

Bootstrap sample average amplitudes

Bootstrap samples of source amplitudes are not independent

- Control the FWER using permutation techniques

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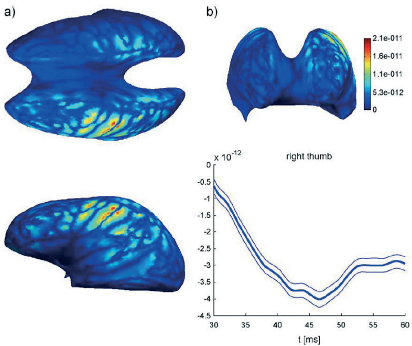

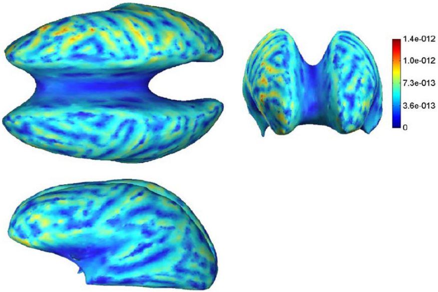

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Controlling the FWER using permutations

Design thresholds with control on the FWER by estimating the maximum (summarizing) statistic under H_0

- Solution 1: use random field theory
  - Approximate analytical solutions (assume same parametric distribution at each spatial location, smooth PSF, smooth patterns, etc.)
- Solution 2: use data resampling
  - Empirical distributions (assume no parametric distributions & adaptive to underlying correlation patterns)

$$P(FWER) = P(\cup_i T_i > u \mid H_0) = P(\max_i T_i > u \mid H_0)$$

$$= 1 - F_{\max T \mid H_0}(u) = 1 - (1 - \alpha) = \alpha$$

from [Pantazis et al. 2005]

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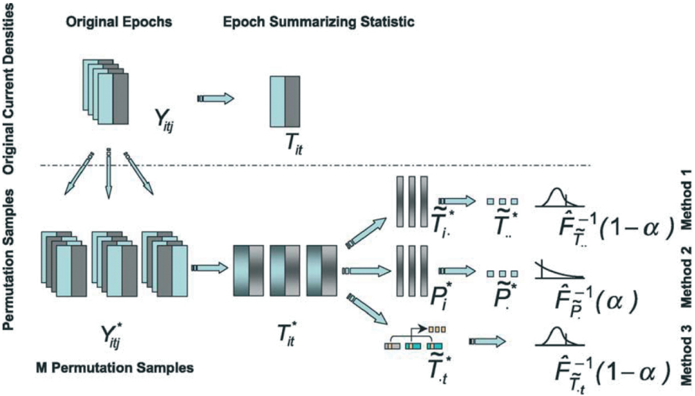
$$T_{it} = \frac{\hat{\mu}_{it}}{\hat{\sigma}_i / \sqrt{J}}$$



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3 summarizing approaches are available:

- space-time summary: epochwise thresholds
- space-time summary with intermediate conversion to *P*-values: uniform-specificity epochwise thresholds
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Summary statistics for three permutation methods

	Time-summarizing	Space-summarizing
Method 1	$\tilde{T}_{i\cdot}^{*} = \max_{t>0} \lvert T_{it}^{*} \rvert$	$\tilde{T}_{\cdot\cdot}^{*} = \max_i \tilde{T}_{i\cdot}^{*}$
Method 2	$P_i^{*} = p_i(\tilde{T}_{i\cdot}^{*})$	$\tilde{P}^{*} = \min_i \tilde{P}_i^{*}$
Method 3		$\tilde{T}_{\cdot t}^{*} = \max_i \lvert T_{it}^{*} \rvert$

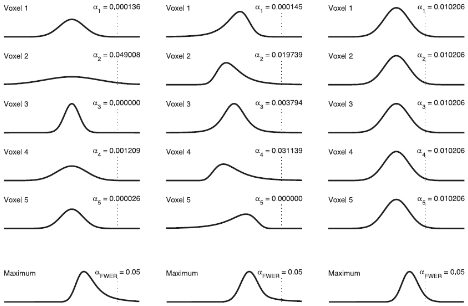
The permutation samples are T_{it}^{*}, with i the spatial index, and t the time index. The tilde indicates the maximum over the dotted subscript; $p_i(\cdot)$ is the permutation *P*-value function using only data from spatial location i.

from [Pantazis et al. 2005]

Controlling the FWER using permutations

Heterogeneous voxel null distribution ($\alpha = 0.05$)

1. Using sample average, instead of T statistics
2. Non-Gaussian, variance-normalized voxel null distribution
3. Homogeneous voxel null distribution



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Results
Simulations

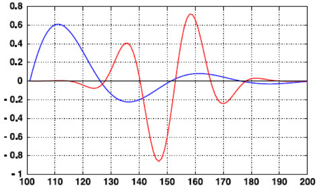


Fig. 4. Time-courses of simulated sources, blue for source 1 and red for source 2. The pattern of activation mimics a typical neuroimaging study where an early response to a stimulus propagates to another brain region giving a delayed component.

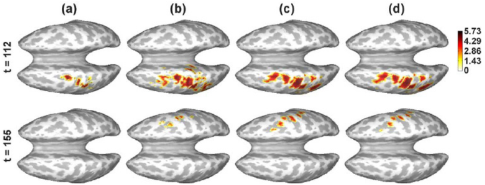


Fig. 5. Examples of significant activation maps for permutation and random field methods for two time instances, (a) permutation method 1 using unsmoothed CDMs, (b) permutation method 3 using unsmoothed CDMs, (c) permutation method 3 using smoothed CDMs, (d) random field using smoothed CDMs. The first method controls FWER over space and time, while the last three methods control FWER over space for one time point only.

Results
Monte-Carlo simulations

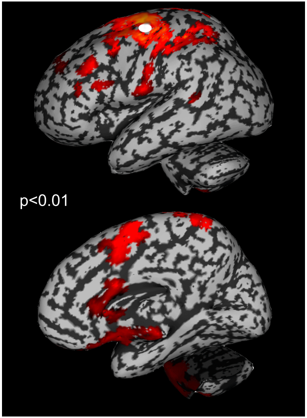
Noise-only simulation results for control of spatial and spatiotemporal FWER at nominal level $\alpha = 5\%$

	Unsmoothed CDMs		Smoothed CDMs	
	Threshold	Observed FWER	Threshold	Observed FWER
Spatiotemporal FWER methods				
Permutation method 1	5.350	0.0600	5.245	–
Spatial FWER methods				
Permutation method 3	4.059	0.0480	3.980	–
Random field method	4.453	0.0139	4.081	0.0340

The Monte Carlo standard error for the spatiotemporal FWER is 0.0218; for the spatial FWER, it is 0.0022.

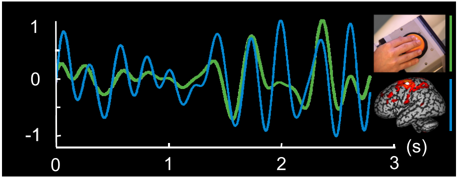
- Permutation is an exact approach.

Imaging stationary brain processes
Visuomotor coordination



Imaging in the Fourier domain

- Group study: 14 subjects
  → inference at the group level, anatomical co-registration
- Oscillatory neural activity
- Identify interactions between time series



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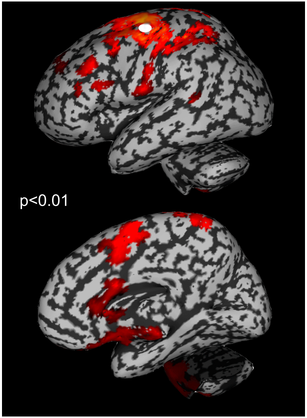
Visuomotor coordination



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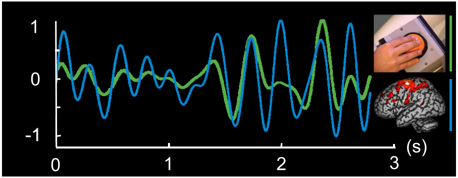

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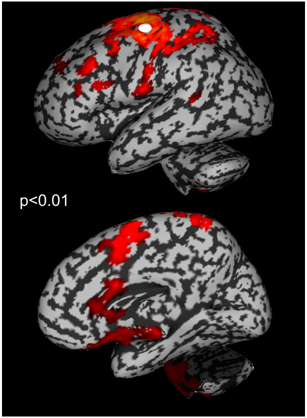

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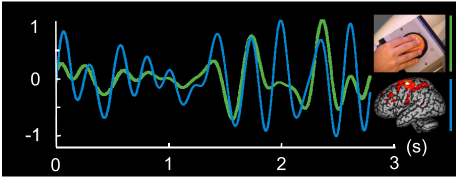

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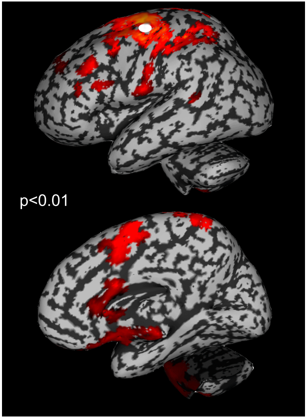

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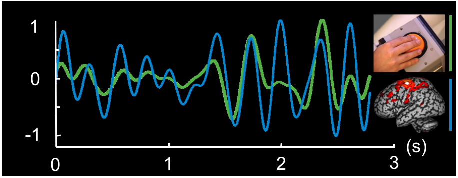

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