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Supplementary Material: Dimension constraints improve hypothesis testing for large-scale, graph-associated, brain-image data

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Software versions

For statistical parametric (and nonparametric) mapping we used SPM12 and SnPM13. For visualizing and getting neuroscientific interpretation of the statistical findings, we used xjview8. For R packages, we used

- stats v 3.5.2 (for B-H adjust)
- locfdr v 1.1-8
- qvalue 2.12.0
- ashr v 2.2-7

lfdr$_2$ in toy problem

On the toy problem described in Section 1 of the main manuscript, we have observables X_1 and X_2 from the first condition and Y_1 and Y_2 from the second. Means are μ_{X_1}, μ_{X_2}, μ_{Y_1} and μ_{Y_2} respectively, conditional upon which, the observables are independent normals with those means and with constant variance $\sigma^2 > 0$. The four latent means fluctuate over the system by

Supplementary Table S1: mixture structure, toy problem; h encodes a Gaussian joint density of arguments, with mean zero in all components, marginal variance $1+\sigma^2$, and exchangeable covariance with all correlations equal to $1/(1+\sigma^2)$; fourth column indicates the number of free parameters integrated to give the last column.

Pair	Unit 1	Unit 2	mix prob	# free	predictive density
block	null	null	$p_{\text{block}} p_0$	1	$h(x_1, x_2, y_1, y_2)$
block	alt	alt	$p_{\text{block}}(1-p_0)$	2	$h(x_1, x_2)h(y_1, y_2)$
split	null	null	$(1-p_{\text{block}})p_0^2$	2	$h(x_1, y_1)h(x_2, y_2)$
split	null	alt	$(1-p_{\text{block}})p_0(1-p_0)$	3	$h(x_1, y_1)h(x_2)h(y_2)$
split	alt	null	$(1-p_{\text{block}})p_0(1-p_0)$	3	$h(x_2, y_2)h(x_1)h(y_1)$
split	alt	alt	$(1-p_{\text{block}})(1-p_0)^2$	4	$h(x_1)h(x_2)h(y_1)h(y_2)$

a discrete mixture that indicates strict equality constraints; the unconstrained common levels then fluctuate independently and according to the standard normal distribution. Discrete mixing is by two *coins*; the first has success probability p_{block}; in that event, called *block*, $\mu_{X_1} = \mu_{X_2}$ and $\mu_{Y_1} = \mu_{Y_2}$. Otherwise the units are *split*. A second coin has success probability p_0; this is tossed once if there is blocking and twice if not. Success on this second coin indicates $\mu_{X_1} = \mu_{Y_1}$ (which is the null hypothesis of interest). The following table shows the six discrete outcomes, their mixing probability, as well as the joint density of the observables conditional on that mixture component, but marginal to the latent mean values themselves.

From this table, the local FDR, is $\text{lfdr}_2 = P(\mu_{X_1} = \mu_{Y_1} | x_1, x_2, y_1, y_2)$

$$\text{lfdr}_2 \propto p_{\text{block}} p_0 h(x_1, x_2, y_1, y_2) + (1-p_{\text{block}})(p_0^2 h(x_1, y_1)h(x_2, y_2) + (1-p_0)p_0 h(x_1, y_1)h(x_2)h(y_2))$$

with proportionality resolved by summing over the six discrete possibilities.

Local approximation

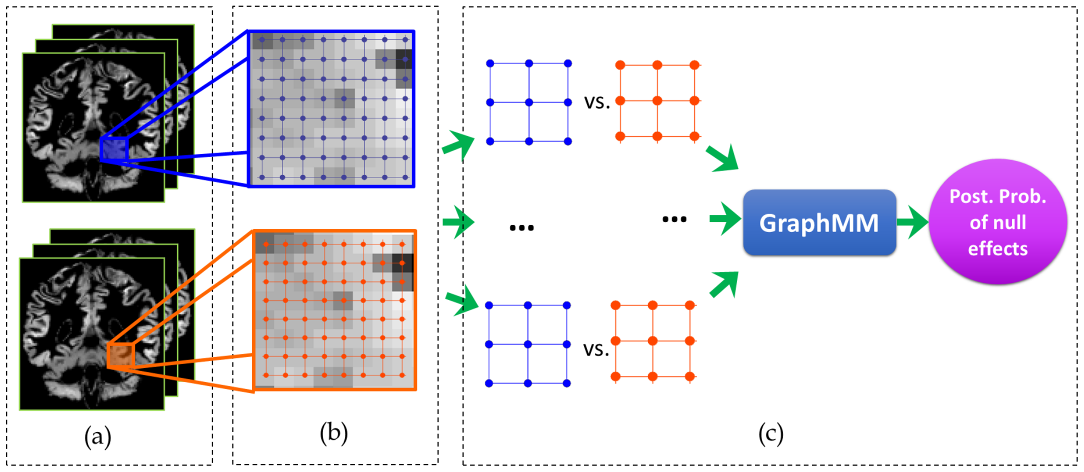
In many applications it is impractical to apply the model of Section 2 on the entire graph due to high dimensionality and general covariance structure. Since we expect most of the information relevant to inference about one node to come through nearby nodes, we deploy a local graph approximation which is amenable to parallel computing. For each node v, consider a neighborhood $\mathcal{N}_v$ of node v. $\mathcal{N}_v$ is chosen such that it is a connected component of graph G. `GraphMM`, then, is applied to model the data in this neighborhood

$$(\boldsymbol{X}_{\mathcal{N}_v}, \boldsymbol{Y}_{\mathcal{N}_v}) := \{(\boldsymbol{X}_u, \boldsymbol{Y}_u) : u \in \mathcal{N}_v\}$$

The node-specific posterior probabilities are approximated by

$$l_v := P(H_{0,v} | \boldsymbol{X}_{\mathcal{N}_v}, \boldsymbol{Y}_{\mathcal{N}_v}) = \sum_{\Psi, \boldsymbol{\Delta}} \mathbb{1}(\Delta_k = 0) 1(v \in b_k) P(\boldsymbol{\Delta}, \Psi | \boldsymbol{X}_{\mathcal{N}_v}, \boldsymbol{Y}_{\mathcal{N}_v}) \tag{0.1}$$

The local approximation procedure is illustrated by Fig. S1.



Supplementary Figure S1: Illustration for local approximation pipeline. (a) shows pre-processed MRI images of two conditions. (b) shows lattice graphs associated with the data. (c) shows local approximation procedure, in which neighborhood $\mathcal{N}_v$ of node v includes v and eight adjacent nodes. GraphMM model is applied to neighborhood data to get approximated posterior probability of null effects l_v as in (0.1).

Algorithm 1 Local approximation

Input: pre-processed MRI data $\boldsymbol{X}, \boldsymbol{Y}$.

Output: per voxel posterior probability of differential structure.

```
1:  procedure GraphMM($\boldsymbol{X}, \boldsymbol{Y}$)
2:      for $v$ in nodes do
3:          $G_{\text{local}} \leftarrow$ local graph around $v$
4:          $(\boldsymbol{X}_{\mathcal{N}_v}, \boldsymbol{Y}_{\mathcal{N}_v}) \leftarrow$ local data around $v$
5:          $hyp \leftarrow$ estimated hyperparameters($\boldsymbol{X}_{\mathcal{N}_v}, \boldsymbol{Y}_{\mathcal{N}_v}$)
6:          for $(\Psi, \boldsymbol{\Delta})$ in graph-respecting partitions of $G_{\text{local}}$ do
7:              $p(\boldsymbol{X}_{\mathcal{N}_v}, \boldsymbol{Y}_{\mathcal{N}_v} | \Psi, \boldsymbol{\Delta}) \leftarrow$ marginal density of data local to $v$
8:              $p(\Psi, \boldsymbol{\Delta}) \leftarrow$ prior mass of local state.
9:          end for
10:         Scale to get $p(\Psi, \boldsymbol{\Delta} | \boldsymbol{X}_{\mathcal{N}_v}, \boldsymbol{Y}_{\mathcal{N}_v})$ for all graph-respecting partitons $(\Psi, \boldsymbol{\Delta})$
11:         $l_v \leftarrow P(H_{0,v} | \boldsymbol{X}_{\mathcal{N}_v}, \boldsymbol{Y}_{\mathcal{N}_v}))$                # Using formula 0.1
12:     end for
13: end procedure
```

For results in Sections 3.1 and 3.2, we did local approximation on a 3×3 neighborhood of each node, as illustrated in Fig. S1. In this case we can enumerate all the graph-respecting partitions (we devised a data-augmentation sampling scheme that makes use of spanning trees within the input graph; see last section of supplement). Then, we are able to enumerate all the pairs $(\Psi, \boldsymbol{\Delta})$ and compute the exact posterior distribution.

Algorithm 2 General framework for all the simulation scenarios

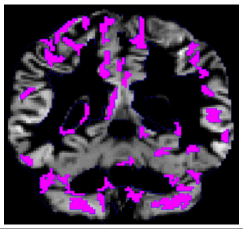
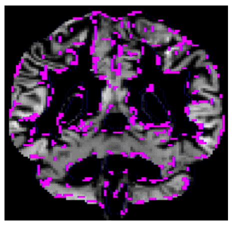
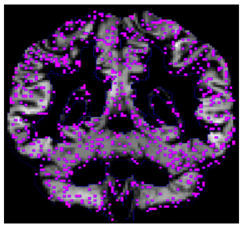
```
Input: MRI dataset for condition 1, G1, a $N \times M_X$ matrix; real dataset for condition 2, G2, a $N \times M_Y$ matrix.
Output: synthetic dataset 1 $\boldsymbol{X}$; synthetic dataset 2 $\boldsymbol{Y}$.

Step 1: $S_1 \leftarrow$ sample-covariance(G1).
Step 2: $S_2 \leftarrow$ sample-covariance(G2).
Step 3: $\mathbf{V} \leftarrow S_1 + 0.5\mathbf{I}$                    # $\mathbf{I}$ is identity matrix.
Step 4: $\mathbf{W} \leftarrow S_2 + 0.5\mathbf{I}$                    # Add a small value to the diagonal of
                                                    $S_1, S_2$ to get positive definite matrices.
Step 5: $Avg \leftarrow$ average-over-replicate(G1, G2)       # $Avg$ is a vector of length $N$

        ##### Implement for step 6 to 9 depends on specific scenario #####
Step 6: $\Psi \leftarrow$ cluster($Avg$)                       # $\Psi = \{b_1, \dots, b_K\}$ is a graph-
                                                    respecting partition on $Avg$
Step 7: $\Delta \leftarrow$ changed-block indicator            # $\Delta = \{\Delta_1, ..., \Delta_K\}$ is a binary vector,
                                                    $\Delta_k = 1$ iff $b_k$ is a changed-block.
Step 8 & 9:
    $\varphi \leftarrow$ simulated block means for condition 1
    $\delta \leftarrow$ simulated changed effects              # $\delta_k = 0$ iff $\Delta_k = 0$; when $\Delta_k \neq 0$, $\delta_k$ is
                                                    simulated from some distribution (e.g
                                                    beta, uniform)
    $\nu \leftarrow \phi + \delta$                                 # $\nu$ is simulated block means for condi-
                                                    tion 2.
    $\mu_X \leftarrow$ simulated node means for condition 1
    $\mu_Y \leftarrow$ simulated node means for condition 2    # $\mu_X, \mu_Y$ satisfy clustering constraints
                                                    on the means w.r.t $\Psi$ as in (??).
        ##########
Step 10: $\boldsymbol{X} \leftarrow$ Multivariate Normal $(\mu_X, \mathbf{V})$
Step 11: $\boldsymbol{Y} \leftarrow$ Multivariate Normal $(\mu_Y, \mathbf{W})$
```

Simulation study details

The graph associated with data is a lattice graph representing spatial dependence, in which the vertices are the pixels and the edges connect neighboring voxels. The analysis of `GraphMM` involves estimating hyper parameters: prior null probability p_0, prior mean μ_0 and standard deviation τ^2 of block mean of group 1, prior mean δ_0 and standard deviation σ^2 of difference in block mean between 2 groups, prior covariance matrix A for group 1 and matrix B for group 2. Different strategies for estimating hyperparameters have been considered,

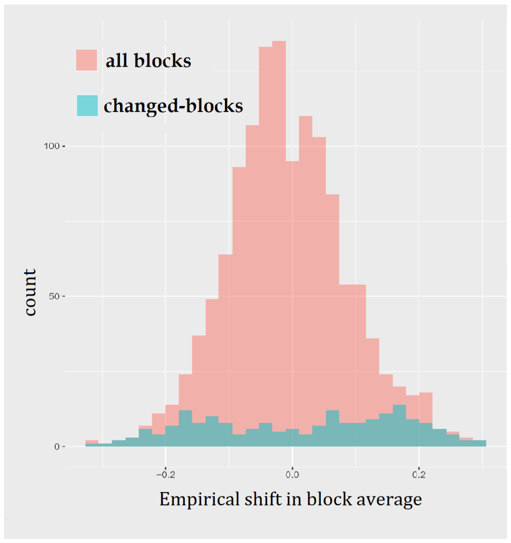
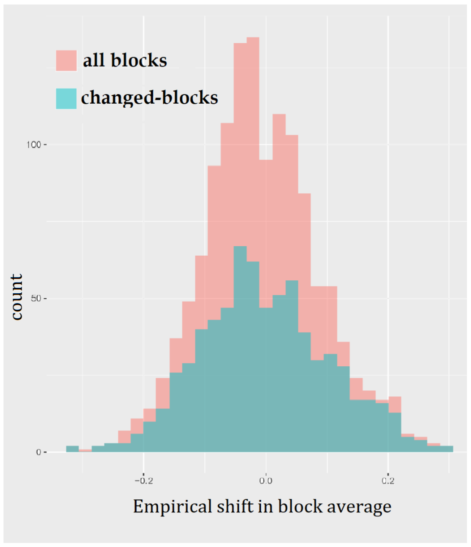
- *Estimating prior null probability p_0:* We experimented with both `qvalue` or `ahsr` to get the estimated value of p_0. Package `qvalue` produces conservative estimate of p_0 without any assumption on the distribution of effects. Hence it is a safe and conservative choice under general settings. Package `ashr`, on the other hand, provides conservative estimate

Supplementary Table S2: Description for simulation 1, 2 and 3. Text with blue color and figures emphasizes that these simulations differ in the average size of latent blocks. In the figures, area with magenta color shows changed-blocks. We can see that the size of changed-blocks decreases in simulation 1, 2 and 3. Especially simulation 3 has no clustering effect, i.e the block size is 1 for all blocks.

	Scenario 1	Scenario 2	Scenario 3
Step 6	* Use greedy clustering method [?] * Partition is adjusted to respect lattice graph. * There are 1313 blocks, average block size is 3.9	Same as scenario 1	* Each node itself is a block. * There are 5236 blocks, block size is 1
Step 7	* 50 blocks with size from 12 to 14 are chosen to be changed-block * Average size of changed-block is 13.6 * Percentage of changed-nodes: 14.3%	* 300 blocks with size from 2 to 5 are chosen to be changed-block * Average size of changed-block is 2.6 * Percentage of changed-nodes: 14.9%	* 15% of the nodes are chosen to be changed-nodes
Step 8, 9	$m_x \leftarrow$ block average of MRI data group 1 $m_y \leftarrow$ block average of MRI data group 2 $max.d \leftarrow \max(m_y - m_x)$ $min.d \leftarrow \min(m_y - m_x)$ $\varphi \leftarrow m_x$ For changed-blocks: $\delta \sim$ Uniform$(min.d, max.d)$	Same as scenario 1	$m_x \leftarrow$ block average of MRI data group 1 $sd_x \leftarrow$ sample block standard deviation group 1 $mar.m \leftarrow$ mean(m_x) $mar.sd \leftarrow$ mean(sd_x) $\varphi \sim$ Normal$(mar.m, mar.sd)$ $m_y \leftarrow$ block average of MRI data group 2 $max.d \leftarrow \max(m_y - m_x)$ $min.d \leftarrow \min(m_y - m_x)$ For changed-blocks: $\delta \sim$ Beta(2, 2) $\delta \leftarrow \delta * (max.d - min.d) + min.d$
Figure			

under the assumption that the distribution of effects is unimodal. Furthermore, in our graph-based mixture model, the distribution of effects δ_k was assumed to be a mixture of probability mass at 0 and normal distribution, which satisfies unimodal assumption. Therefore, using package `ashr` to estimate for p_0 meshes with our `GraphMM`. The estimation of p_0 is based on the whole dataset, computing prior to the local approximation

Supplementary Table S3: Description for simulation 4 and 5. Text with blue color and figures emphasizes that these simulations differ in the percentage of changed-nodes. The figures show histogram of block avergage shifts across 2 groups for all blocks (red area) and for changed-blocks (green area).

	Simulation 4	Simulation 5
Step 6	* Use greedy clustering method [?] * Partition is adjusted to respect lattice graph. * There are 1313 blocks, average block size is 3.9	Same as Simulation 4
Step 7	$m_x \leftarrow$ block average of MRI data group 1 $m_y \leftarrow$ block average of MRI data group 2 $diff \leftarrow m_y - m_x$ $prob \leftarrow$ increasing function of $\|diff\|$ and belongs in (0,1) $\Delta \sim$ Bernoulli($prob$) * Percentage of changed-nodes: 16.4%	* Similar to simulation 4, except that * Percentage of changed-nodes: 50.3%
Step 8 & 9	* If block k is a changed-block: $\varphi[k] \leftarrow m_x[k]$ $\delta[k] \leftarrow diff[k]$ * If block k is not a changed-block: $\varphi[k] \leftarrow (m_x[k] + m_y[k])/2$ $\delta[k] \leftarrow 0$	Same as Simulation 4
Figure		

procedure. In reported computations we used `ashr` package for p_0.

- *Estimating other hyperparameters:* We consider 3 approaches: global, local and mixed estimation. With global estimation, the hyperparameters are estimated using the whole dataset and computed prior to the local approximation procedure. With local estimation, hyperparameters are estimated for each neighborhood, during the local approximation procedure. With mixed estimation, all hyperparameters are estimated locally except for matrices A and B, which are estimated globally. These approaches, local, mixed and global provides increasingly conservative estimates in that order. In following simulation and application, we present results using mixed estimation.

Computing marginal likelihood

We derive the marginal likelihood using Laplace approximation. Consider the notations as in Section 2 of main paper. Let K_Ψ be the number of blocks corresponding to partition $\mathbf{\Psi}$ and K_{diff} be the number of changed blocks, which means

$$K_{\text{diff}} = \sum_{k=1}^{K_\Psi} \mathbb{1}(\Delta_k = 1)$$

Denote the ordered indices of changed blocks as $(j_1, j_2, \dots, j_{K_{\text{diff}}})$. We re-parametrize the model in order to remove the clustering constraints on the means

$$\boldsymbol{\epsilon} := (\delta_{j_1}, \delta_{j_2}, \dots, \delta_{j_{K_{\text{diff}}}})$$

Then, the free parameters are $(\boldsymbol{\varphi}, \boldsymbol{\epsilon})$ and the marginal likelihood function can be written as

$$\begin{aligned} f(\boldsymbol{X}, \boldsymbol{Y} | \mathbf{\Psi}, \mathbf{\Delta}) &= \int f(\boldsymbol{X}, \boldsymbol{Y}, \boldsymbol{\varphi}, \boldsymbol{\epsilon} | \mathbf{\Psi}, \mathbf{\Delta}) \mathrm{dP}(\boldsymbol{\varphi}) \mathrm{dP}(\boldsymbol{\epsilon}) \\ &= C_1 C_2 \int_{\mathbb{R}^{K_\Psi + K_{\text{diff}}}} \exp\left[(\text{df} + M_X) F(\boldsymbol{\varphi}, \boldsymbol{\epsilon})\right] \mathrm{d}\boldsymbol{\varphi}\, \mathrm{d}\boldsymbol{\epsilon} \end{aligned}$$

where

$$C_1 = C_1(N, M_X, M_Y, \text{df}) = \frac{(|A||B|)^{\frac{d}{2}} \Gamma_N\left(\frac{\text{df}+M_X}{2}\right) \Gamma_N\left(\frac{\text{df}+M_Y}{2}\right)}{\left[\Gamma_N\left(\frac{\text{df}}{2}\right)\right]^2}$$

$$C_2 = C_2(\boldsymbol{\Psi}, \boldsymbol{\Delta}, \tau, \sigma) = \exp\left[-K_\Psi \log(\tau\sqrt{2\pi}) - K_{\text{diff}} \log(\sigma\sqrt{2\pi})\right]$$

$$F(\boldsymbol{\varphi}, \boldsymbol{\delta}) = -\frac{1}{2}\log|\widetilde{A}| - \frac{\text{df} + M_Y}{2(\text{df} + M_X)}\log|\widetilde{B}| - \frac{1}{2\tau^2(\text{df} + M_X)}\sum_{k=1}^{K_\Psi}(\varphi_k - \mu_0)^2$$
$$-\frac{1}{2\sigma^2(\text{df} + M_X)}\sum_{l=1}^{K_{\text{diff}}}(\epsilon_l - \delta_0)^2$$

$$\widetilde{A} = A + (M_X - 1)S_1 + M_X S_2$$

$$S_1 = \frac{1}{M_X - 1}\sum_{m=1}^{M_X}(\boldsymbol{X_m} - \overline{\boldsymbol{X}})(\boldsymbol{X_m} - \overline{\boldsymbol{X}})^\tau$$

$$S_2 = (\overline{\boldsymbol{X}} - \boldsymbol{\mu_X})(\overline{\boldsymbol{X}} - \boldsymbol{\mu_X})^\tau$$

$$\widetilde{B} = B + (M_Y - 1)T_1 + M_Y T_2$$

$$T_1 = \frac{1}{M_Y - 1}\sum_{r=1}^{M_Y}(\boldsymbol{Y_r} - \overline{\boldsymbol{Y}})(\boldsymbol{Y_r} - \overline{\boldsymbol{Y}})^\tau$$

$$T_2 = (\overline{\boldsymbol{Y}} - \boldsymbol{\mu_Y})(\overline{\boldsymbol{Y}} - \boldsymbol{\mu_Y})^\tau$$

Apply Laplace's approximation, we get

$$\log f(\boldsymbol{X}, \boldsymbol{Y}|\boldsymbol{\Psi}, \boldsymbol{\Delta}) \approx \log C_1 + \log C_2 + \frac{K_\Psi + K_{\text{diff}}}{2}\log\frac{2\pi}{\text{df} + M_X}$$
$$+(\text{df} + M_X)F(\widehat{\boldsymbol{\varphi}}, \widehat{\boldsymbol{\epsilon}}) - \frac{1}{2}\log|-H(F)(\widehat{\boldsymbol{\varphi}}, \widehat{\boldsymbol{\epsilon}})| \quad (0.2)$$

In the next step, we derive the explicit formula for the gradient and Hessian matrix of F. Let L be the allocation matrix with size $N \times K_\Psi$ where $c_{vk} = 1$ if and only iff node v belong to block k. Let R be a $K_\Psi \times K_{\text{diff}}$ matrix such that column lth of R has value 1 at position j_l and has value 0 at other postions. Then we can relate the mean vectors with the new parameters $(\boldsymbol{\varphi}, \boldsymbol{\epsilon})$ as follows

$$\boldsymbol{\delta} = R\boldsymbol{\epsilon}$$

$$\boldsymbol{\mu_X} = L\boldsymbol{\varphi} \qquad \boldsymbol{\mu_Y} = L(\boldsymbol{\varphi} + \boldsymbol{\delta})$$

We consider following notations.

$$S_3 = \frac{1}{M_X - 1} A + S_1 \qquad T_3 = \frac{1}{M_Y - 1} B + T_1$$

$$v_X = S_3^{-1} \overline{\boldsymbol{X}} \qquad v_Y = T_3^{-1} \overline{\boldsymbol{Y}}$$

$$s_0 = \frac{M_X - 1}{M_X} + \overline{\boldsymbol{X}}^\tau v_X \qquad t_0 = \frac{M_Y - 1}{M_Y} + \overline{\boldsymbol{Y}}^\tau v_Y$$

$$Q_X = L^\tau S_3^{-1} L \qquad Q_Y = L^\tau T_3^{-1} L$$

$$w_X = S_3^{-1} \boldsymbol{\mu_X} \qquad w_Y = T_3^{-1} \boldsymbol{\mu_Y}$$

$$u_X = L^\tau (w_X - v_X) \qquad u_Y = L^\tau (w_Y - v_Y)$$

$$b_X = \frac{1}{s_0 - 2{v_X}^\tau \boldsymbol{\mu_X} + \boldsymbol{\mu_X}^\tau w_X}$$

$$b_Y = \frac{1}{t_0 - 2{v_Y}^\tau \boldsymbol{\mu_Y} + \boldsymbol{\mu_Y}^\tau w_Y}$$

The formula for the gradient of F is.

$$\frac{\partial F}{\partial \boldsymbol{\varphi}} = \left[-b_X u_X - \frac{\mathrm{df} + M_Y}{\mathrm{df} + M_X} b_Y u_Y - \frac{1}{\tau^2 (\mathrm{df} + M_X)} (\varphi_k - \mu_0 \boldsymbol{J}_{K_\Psi}) \right]^\tau$$

$$\frac{\partial F}{\partial \boldsymbol{\epsilon}} = \left[- \frac{\mathrm{df} + M_Y}{\mathrm{df} + M_X} b_Y u_Y - \frac{1}{\sigma^2 (\mathrm{df} + M_X)} (\delta_k - \delta_0 \boldsymbol{J}_{K_\Psi}) \right]^\tau R$$

$$\frac{\partial F}{\partial (\boldsymbol{\varphi}, \boldsymbol{\epsilon})} = \begin{bmatrix} \frac{\partial F}{\partial \boldsymbol{\varphi}} & \frac{\partial F}{\partial \boldsymbol{\epsilon}} \end{bmatrix}$$

where $\boldsymbol{J}_{K_\Psi}$ is a vector of ones with size K_Ψ.

Next, the formula for Hessian matrix of F is

$$\frac{\partial^2 F}{\partial \boldsymbol{\varphi}\, \partial \boldsymbol{\varphi}^\tau} = -b_X (Q_X - 2 b_X u_X {u_X}^\tau) - \frac{\mathrm{df} + M_Y}{\mathrm{df} + M_X} b_Y (Q_Y - 2 b_Y u_Y {u_Y}^\tau) - \frac{1}{\tau^2 (\mathrm{df} + M_X)} \mathbb{1}_{K_\Psi \times K_\Psi}$$

$$\frac{\partial^2 F}{\partial \boldsymbol{\epsilon}\, \partial \boldsymbol{\epsilon}^\tau} = R^\tau \left[- \frac{\mathrm{df} + M_Y}{\mathrm{df} + M_X} b_Y (Q_Y - 2 b_Y u_Y {u_Y}^\tau) \right] R - \frac{1}{\sigma^2 (\mathrm{df} + M_X)} \mathbb{1}_{K_{\mathrm{diff}} \times K_{\mathrm{diff}}}$$

where $\mathbb{1}_{K \times K}$ is the identity matrix of size $K \times K$.

$$\frac{\partial^2 F}{\partial \boldsymbol{\varphi}\, \partial \boldsymbol{\epsilon}^\tau} = \left[- \frac{\mathrm{df} + M_Y}{\mathrm{df} + M_X} b_Y (Q_Y - 2 b_Y u_Y {u_Y}^\tau) \right] R$$

$$H(F) = \begin{bmatrix} \dfrac{\partial^2 F}{\partial \boldsymbol{\varphi}\, \partial \boldsymbol{\varphi}^\tau} & \dfrac{\partial^2 F}{\partial \boldsymbol{\varphi}\, \partial \boldsymbol{\epsilon}^\tau} \\ \\ \dfrac{\partial^2 F}{\partial \boldsymbol{\epsilon}\, \partial \boldsymbol{\varphi}^\tau} & \dfrac{\partial^2 F}{\partial \boldsymbol{\epsilon}\, \partial \boldsymbol{\epsilon}^\tau} \end{bmatrix}$$

Finally, the maximizer $((\widehat{\boldsymbol{\varphi}}, \widehat{\boldsymbol{\epsilon}}))$ can be found using Broyden–Fletcher–Goldfarb–Shanno algorithm.

Importance of the graph-respecting constraint

We do a sanity check to confirm that statistical efficiency gains may arise by regularizing the expected values through the graph-respecting assumption. In a predictive simulation of the 3×3 lattice, we generate synthetic Gaussian data D as follows: expected values are guided by some generative graph-respecting partition Ψ^* (drawn from a prior); block-specific means are realized as i.i.d. Gaussian$(0, \sigma^2 = 1/4)$ variables; the 9 data elements in D deviate from these means by realizations of i.i.d. Gaussian$(0, \sigma^2 = 1)$ variables. Each simulated data set is one instance of data when the generative setting is graph-respecting. We take each such simulated data set and work out what two different analysts would surmise about the generative partition. Analyst A knows that the expected values follow some partition structure. Analyst B knows also that the expected values follow a graph-respecting partition. Each analyst computes a posterior distribution, say $P_{\text{analyst}}(\Psi|D)$, over the set of partitions; indeed each posterior distribution is concentrated at some level around the generative partition Ψ^*. A simple measure of the concentration is through the induced distribution on the Adjusted Rand Index, which measures a similarity $S(\Psi, \Psi^*)$ between two partitions. For any level of similarity, s, each analyst has a posterior probability $p_{\text{analyst}}(s, D) = P\left[S(\Psi, \Psi^*) \leqslant s | D\right]$. Figure S3 compares analysts by the average of these posterior similarity distributions $p_{\text{analyst}}(s, D)$ over data sets D. It reveals that by enforcing regularity on the prior distribution over partitions (i.e., by enforcing the graph-respecting property), we tend to place greater posterior probability mass near the generative partition. In applications where the graph conveys structure of expected values, the graph-respecting assumption may usefully regularize the local FDR computations to benefit sensitivity.

Numerical example on control vs late MCI

The Alzheimer's Disease Neuroimaging (ADNI) project was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. The overarching goal of ADNI study comprises of detecting Alzheimer's Disease (AD) at the earliest possible stage, identifying ways to track the disease progression with biomarkers and support advances in AD intervention, prevention and treatments. ADNI is the result of the efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada.

Number of significant voxels at various thresholds and cluster sizes

Figure S4 presents the number of significant voxels at various FDR thresholds; Figure S5 shows sizes of clusters of significant voxels. In both cases we consider the 3D brain lattice.

Graph respecting partitions

Let $G = (V, E)$ denote a simple undirected graph. Over the n nodes in V we are interested in partitions $\pi = \{b\}$, corresponding to disjoint subsets of V, (i.e., blocks), whose union equals the whole vertex set V. We say that π respects G if each block b induces a connected subgraph G_b, and we are interested in probability distributions over this restricted class of partitions as an avenue to improved statistical inference. Observe first that a graph-respecting partition π may be encoded with a vector of binary edge variables: $Z = \{Z_e : e \in E\}$ such that any two neighboring nodes in the same block have $Z_e = 1$, and any two neighboring nodes in different blocks have $Z_e = 0$. In general, these requirements – that within-block edges are on $(Z_e = 1)$ and between-block edges are off $(Z_e = 0)$ – are such that some binary vectors Z are not allowed. One exception is when G is a tree:

Lemma 1: There is a 1-1 correspondence between graph-respecting partitions of a tree on n nodes and the set of length $n - 1$ binary vectors.

Notice that we can recover the blocks of the encoded partition by creating a new graph G' from the original G through the removal of edges where $Z_e = 0$. Then the connected components of what we call the decimated graph G' are the blocks of π. In this special case where G is a tree, we could develop MCMC proposals by randomizing the representation vector Z. But how could we take advantage of this scheme if G is not a tree?

Suppose that G is connected. (If not, we need to consider the following computation performed separately on the different connected components.) Let $\mathcal{S}$ denote the set of spanning trees of G and $Z_S = \{Z_e : e \in \text{edges}(S)\}$ be a binary edge labeling of spanning tree $S \in \mathcal{S}$. Together, the tree S and its edge labeling Z_S provide a data augmentation of the partition π. Clearly a partition can be derived from $\phi = (S, Z_S)$ by decimating the edges of G that are either not in S or are in S but with edge-label 0, and then associating blocks with the connected components of the decimated graph. In general, there will be multiple ϕ's corresponding to a given partition π, each one associated with a different spanning tree of G; we call $\Phi_\pi = \{\phi = (S, Z_S) : \pi(\phi) = \pi\}$, where we've allowed notation $\pi(\phi)$ to denote the partition induced by the input. We find a formula for the cardinality of Φ_π, which may be useful in deriving MCMC samplers against a particular target distribution over partitions.

For each block b of a graph-respecting partition π, the induced subgraph

$$G_b = (V_b = b, E_b = \{e = \{i, j\} : i, j \in b, e \in E\})$$

is connected and has at least one spanning tree; the total number of such trees for G_b is $N_b = \det(L_b)$, where L_b is any $n_b - 1 \times n_b - 1$ principal sub matrix of the graph Laplacian $D_b - A_b$, where D_b is a diagonal matrix holding the node degrees in G_b, and A_b is the incidence matrix describing this same subgraph. This is an application of Kirchhoff's matrix-tree theorem. Of importance in relating the different subgraphs G_b is the hyper-graph H in which nodes are blocks of π and multi-edges between nodes correspond to all the between-block edges in G:

$$H = \left(V_H = \pi, E_H = E \cap [\cup_b E_b]^c\right).$$

By another application of the matrix-tree theorem, the number N_H of spanning trees of H is $\det(L_H)$, where L_H is an $n_H - 1 \times n_H - 1$ principal sub matrix of $D_H - A_H$.

Lemma 2: The cardinality of Φ_π, denoted $N(\pi)$, satisfies $N(\pi) = N_H \prod_{b \in \pi} N_b$.

We augment the partition π of G to the pair $\phi = (S, Z_S)$ holding both a spanning tree S and a vector of binary labels Z_S which encodes the partition of S. For any target distribution $p(\pi)$ we develop a Markov chain sampler by running a chain over the space of ϕ's, which by construction is a union of sets Φ_π. The idea is that the target distribution of a Markov chain in the augmented space is

$$p(\phi) = p(\pi(\phi)) \times \frac{1}{N[\pi(\phi)]}. \tag{0.3}$$

Generatively, this is equivalent to realizing π from $p(\pi)$ and then selecting one of its $N(\pi)$ representations $\phi \in \Phi_\pi$ uniformly at random. Of course we cannot easily generate from $p(\pi)$; the point is that the data augmentation offers a variety of proposal mechanisms that might drive a Metropolis-Hastings sampler. We envision two coupled proposals:

1. Update Z_S for a fixed spanning tree (and thus change the partition).

2. Update spanning tree S but keep the same partition $\pi(\phi)$ (and thus update Z_S).

Partition update: Suppose the chain is at state $\phi = (S, Z_S)$ and we propose a new state $\phi^* =$

(S, Z_S^*) by randomizing the representation vector Z_S but keeping the spanning tree fixed. For example, we could generate entries Z_e^* as independent Bernoulli trials with some edge-specific success probability. Data dependent probabilities might improve mixing, and we might randomize only a fraction of the entries in order to simplify the update and improve its acceptance rate. Call $q_S(Z_S^*|Z_S)$ the probability mass associated with this proposal; then the Metropolis-Hastings ratio for this case is

$$\begin{aligned}\mathrm{MH} &= \frac{p(\phi^*)}{p(\phi)} \times \frac{q_S(Z_S|Z_S^*)}{q_S(Z_S^*|Z_S)} \\ &= \frac{p[\pi(\phi^*)]}{p[\pi(\phi)]} \times \frac{N[\pi(\phi)]}{N[\pi(\phi^*)]} \times \frac{q_S(Z_S|Z_S^*)}{q_S(Z_S^*|Z_S)}.\end{aligned}$$

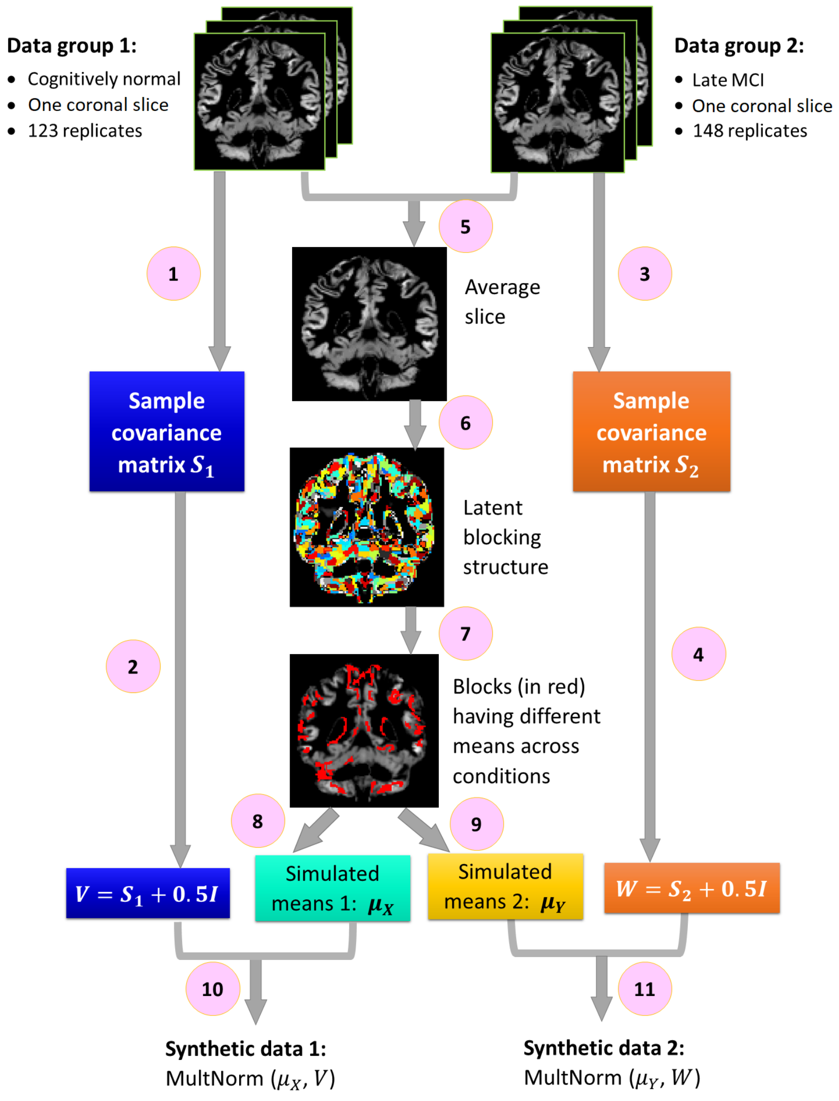
The first ratio on the right may be relatively simple, especially for product-partition models, since only the blocks incurring some change are retained. The third ratio, of q's, may also be simple if we use independent Bernoulli's to randomize the entries. What is critical then is the middle ratio, whose value is available according to Lemma 2.

Tree update: Suppose the chain is at state $\phi = (S, Z_S)$ and we propose a new spanning tree S^* uniformly over the set of possibilities $\mathcal{S}$, for example via Wilson's loop-erased random walk. Relative to the current partition $\pi = \pi(\phi)$, there is exactly one binary encoding vector $Z_{S^*}^*$ corresponding to S^*, by Lemma 1, and so we have proposed the state $\phi^* = \left(S^*, Z_{S^*}^*\right)$ that induces the same partition, and thus is an element of Φ_π. The Metropolis-Hastings ratio for target (0.3) is

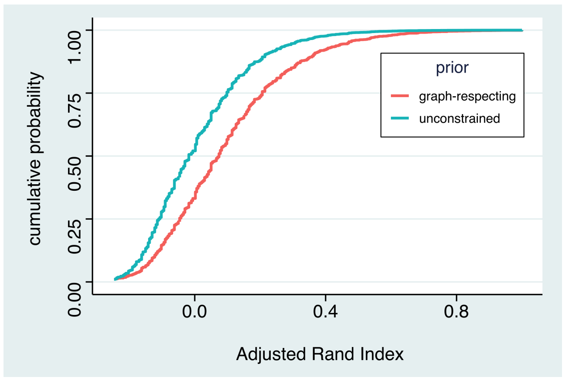
$$\mathrm{MH} = \frac{p(\phi^*)}{p(\phi)} \times \frac{p(\phi^* \longrightarrow \phi)}{p(\phi \longrightarrow \phi^*)} = 1 \times 1.$$

Thus, any proposal obtained by randomizing the spanning tree while keeping partition fixed is surely accepted.

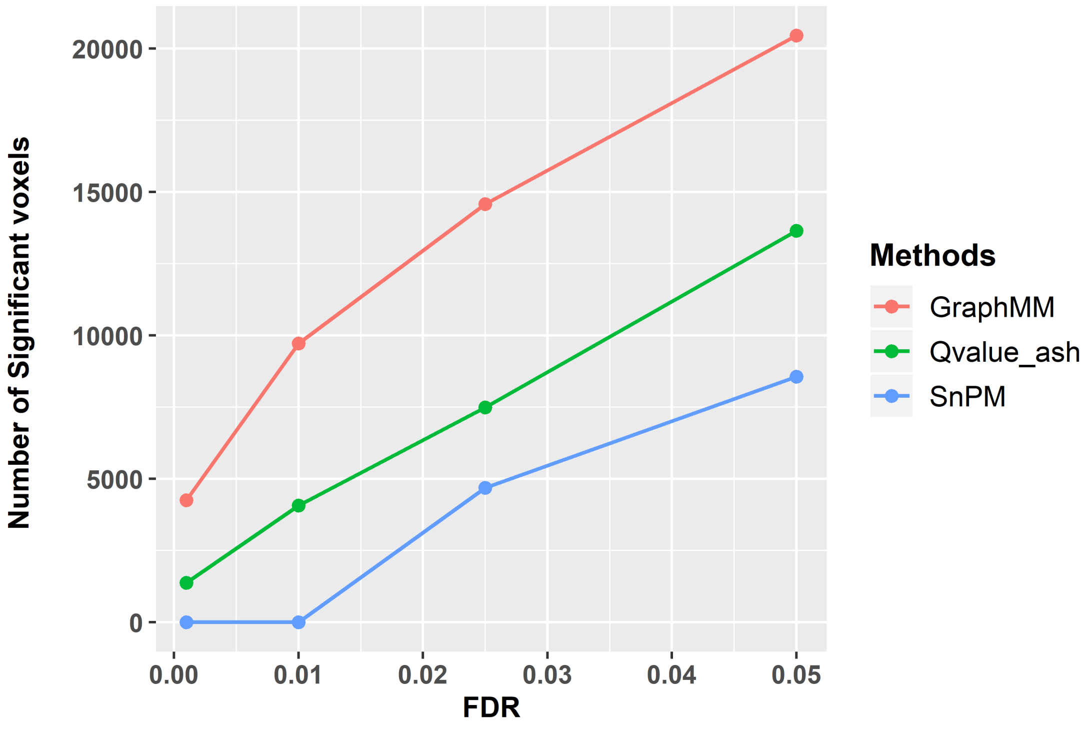
The spanning tree representation above could be used to construct a posterior MCMC sampler. We experimented with such a sampler, but the main paper reports local computations based on explicit sumations over the discrete states; ordinary MCMC was not required. However, we did use a prior-sampler version of the spanning-tree sampler as a simple way to enumerate all graph respecting partitions on a given local graph.


Data group 1:
Cognitively normal
One coronal slice
123 replicates
Data group 2:
Late MCI
One coronal slice
148 replicates
5
1
3
Average slice
Sample covariance matrix S_1
Sample covariance matrix S_2
6
Latent blocking structure
2
7
4
Blocks (in red) having different means across conditions
8
9
$V = S_1 + 0.5I$
Simulated means 1: μ_X
Simulated means 2: μ_Y
$W = S_2 + 0.5I$
10
11
Synthetic data 1: MultNorm (μ_X, V)
Synthetic data 2: MultNorm (μ_Y, W)

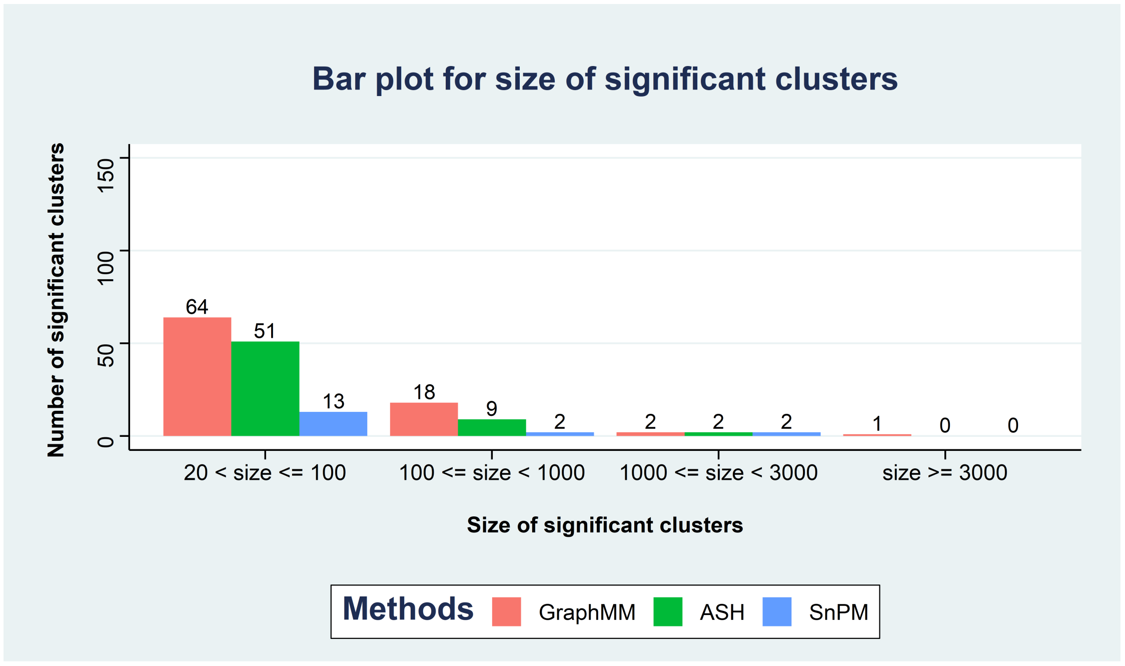
Supplementary Figure S2: Structure of data-driven simulation (Scenarios 1-5): Steps 1-4 make the correlation structure of synthetic data similar to that of MRI data. Steps 5-7 aim to mimic the mean structure and clustering pattern of MRI data. Steps 8-11 simulate data following multivariate normal distribution with specified correlation and mean structure.



Supplementary Figure S3: Shown are predictive averages of posterior similarity distributions between the generative mean partition and the posterior distribution over partitions for two analysts. For each similarity value s (Adjusted Rand Index), each curve records the predictive average $E\left[P(S(\Psi, \Psi^*) \leqslant s|D)|\text{OK}\right]$, where OK is the event that the true partition Ψ^* is graph-respecting. One analyst uses a prior that ignores the graph; the other uses a graph-respecting prior. The analyst who has regularized posterior computations tends to place more posterior probability near the generative partition.



Supplementary Figure S4: Plot of Controlled FDR vs. Number of significant voxels on the whole brain data. The figure confirms the high yield of GraphMM.



Supplementary Figure S5: Bar plot for summary on the size of significant clusters. By definition, a significant region is a collection of significant voxels that is spatially connected.