Overcoming confounds and improving the interpretability of connectivity analyses

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GlaxoSmithKline - Neurophysics Workshop on Skeptical Neuroimaging

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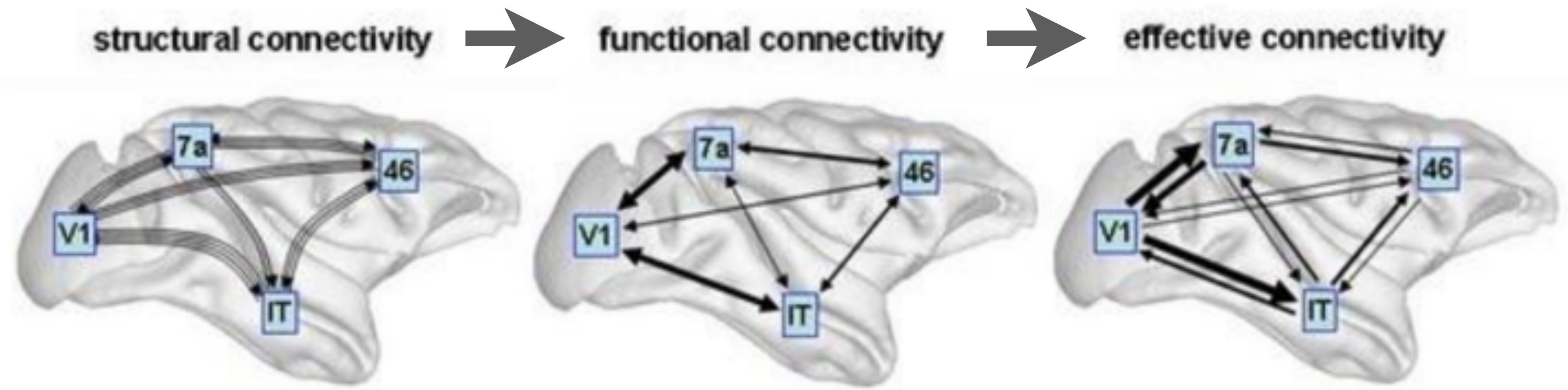
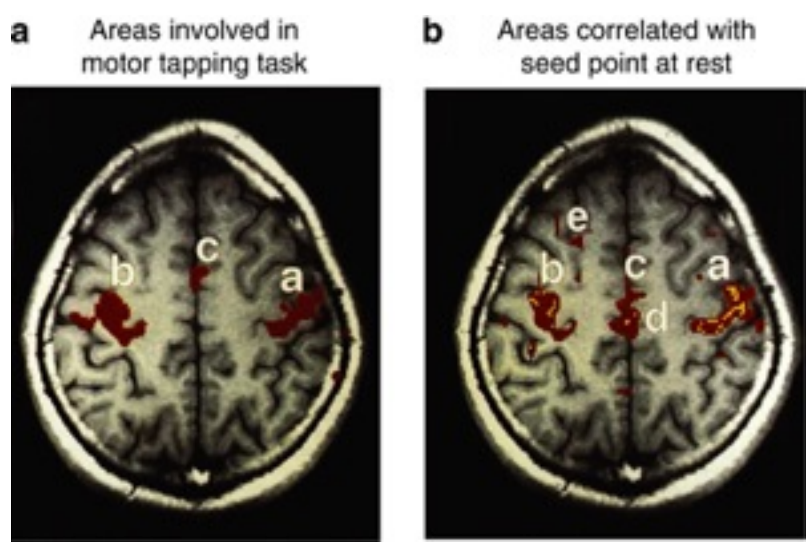
Oxford Centre for Functional MRI of the Brain

Brain connectivity in neuroimaging

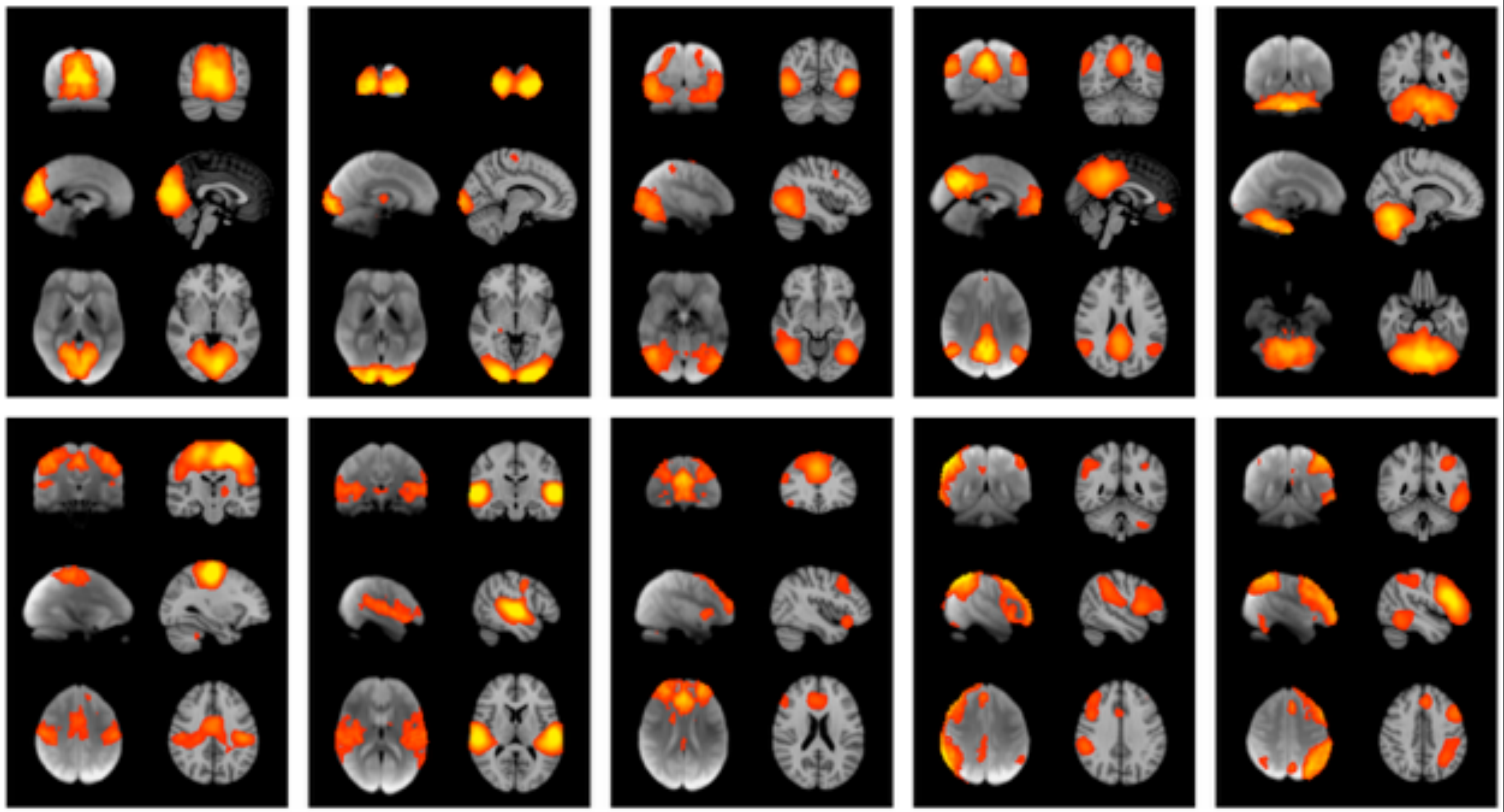


Sporns, 2007
Friston, 1995

Connectivity from uncontrolled fluctuations



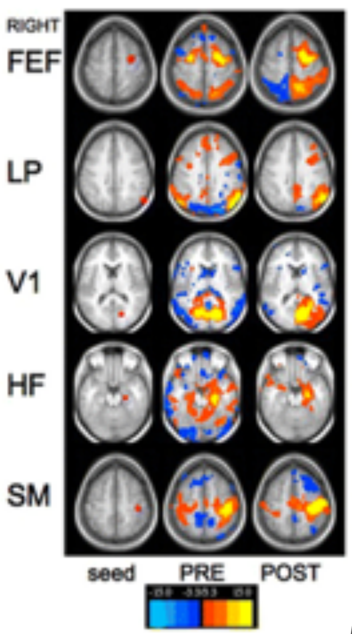
Biswal 1995



Smith 2009

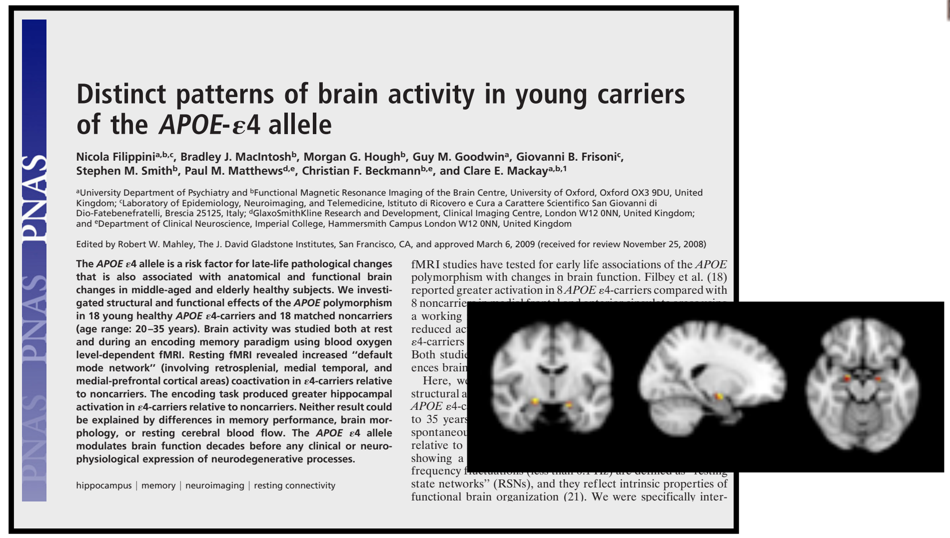
Brain Connectivity from uncontrolled fluctuations

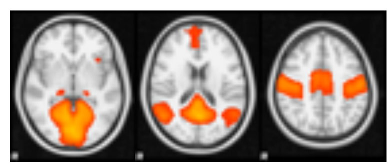
Functional connectivity analyses

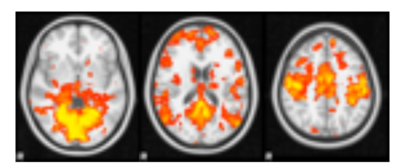


Johnstone JM 2008

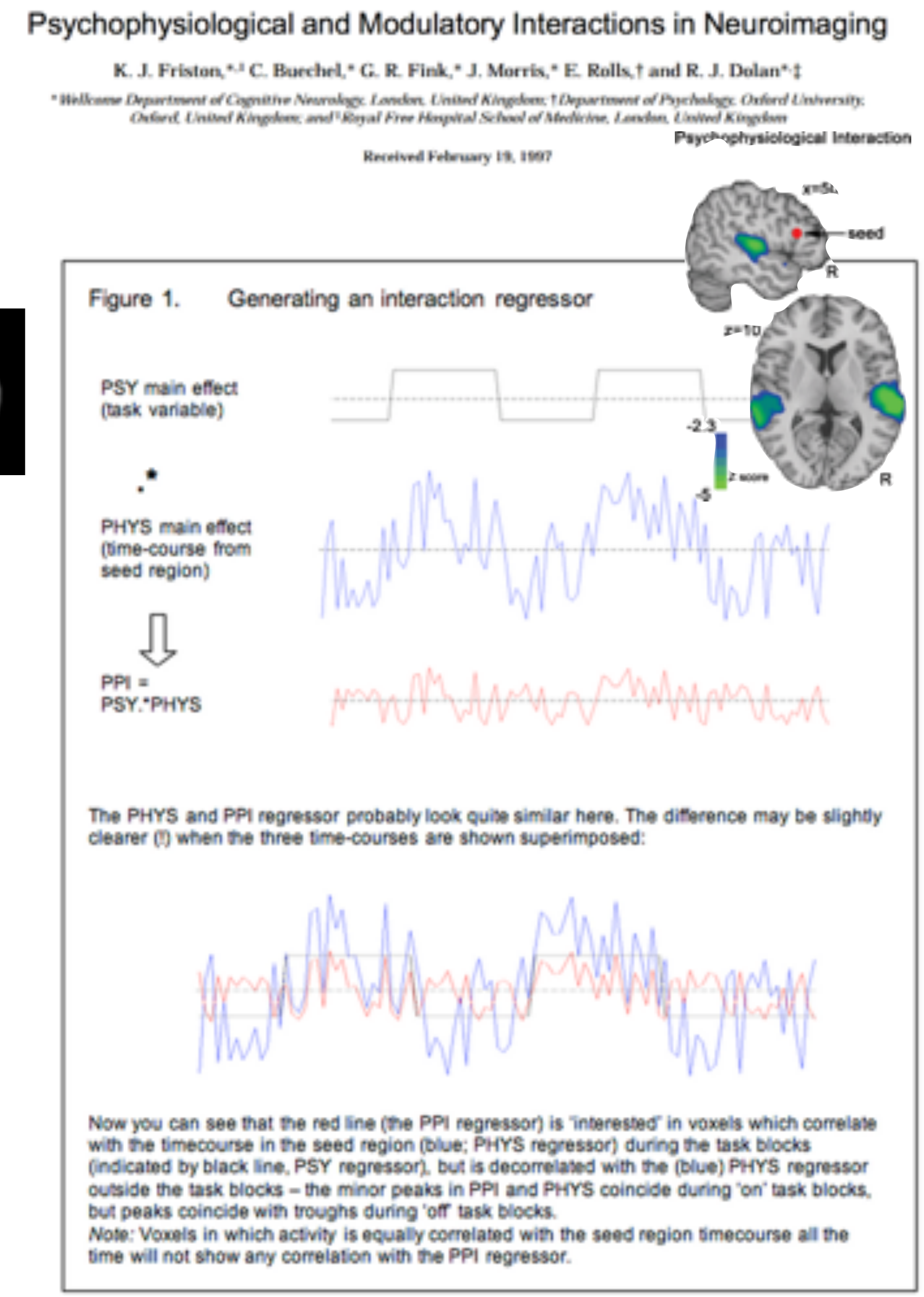
Seed region



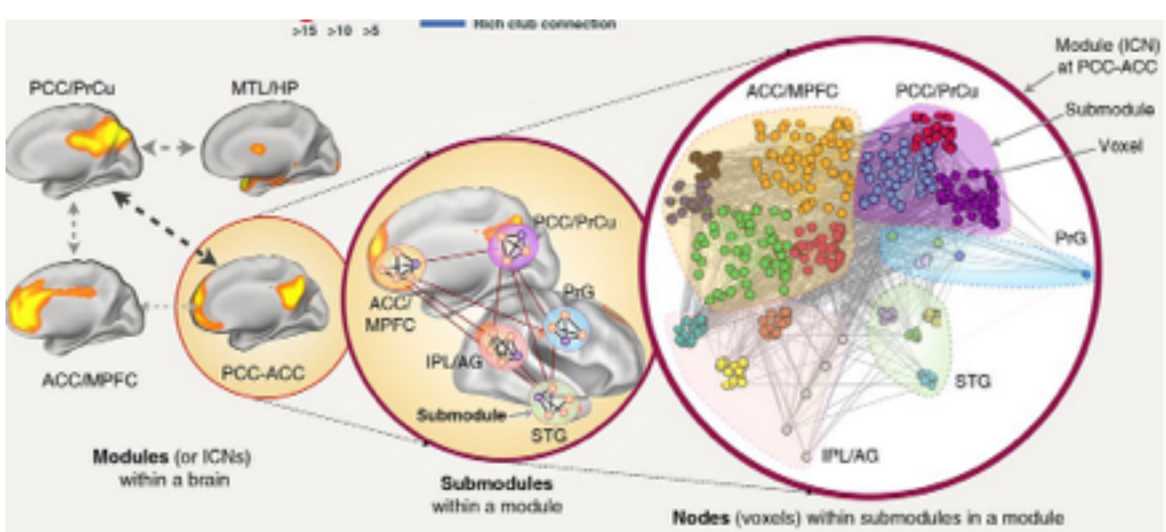




Dual Regression



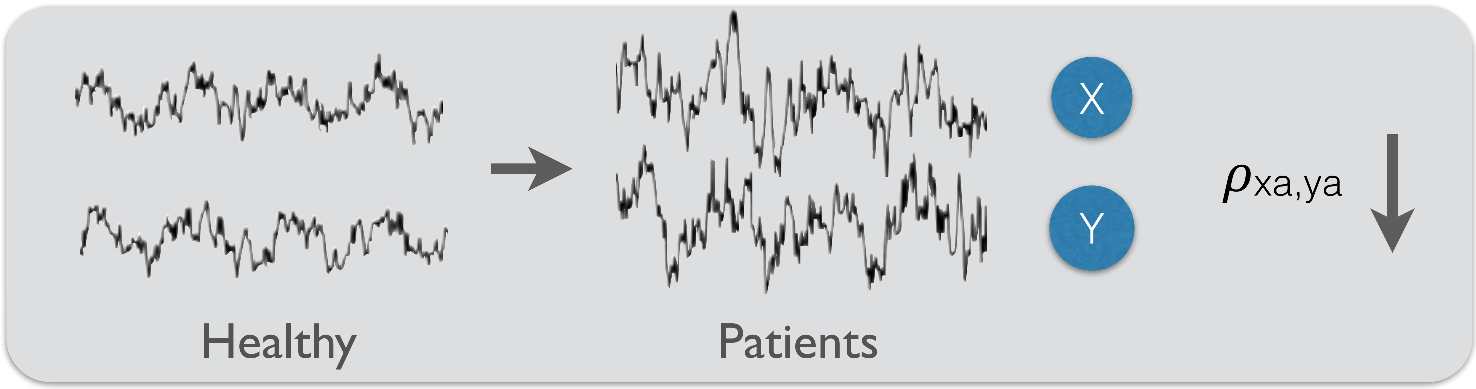
Psycho-physiological interactions



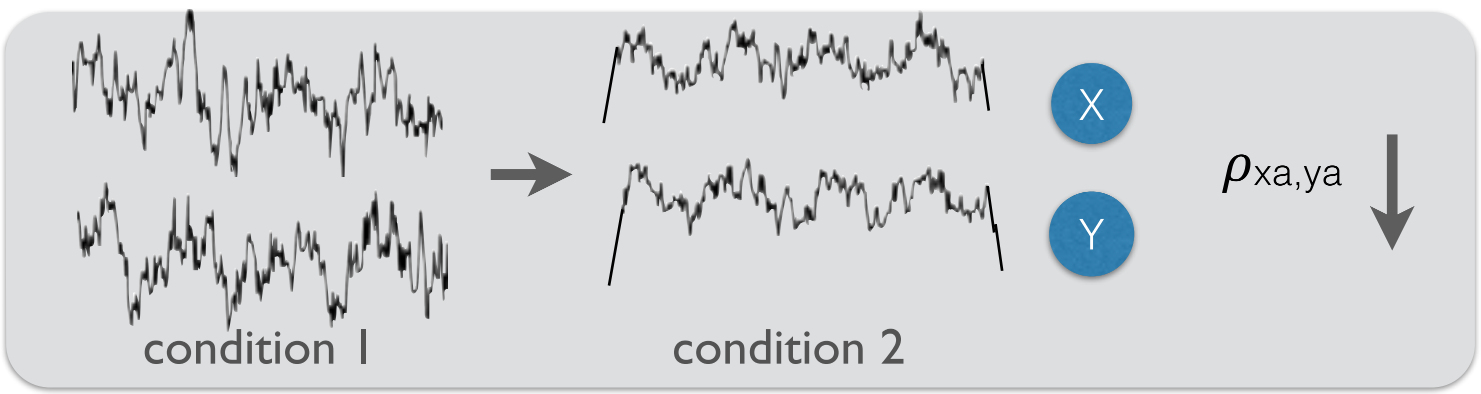
Analysis of graph theoretic measures

Reasons for skepticism..

With no model of signal, analyses will be extremely sensitive to variations in noise:



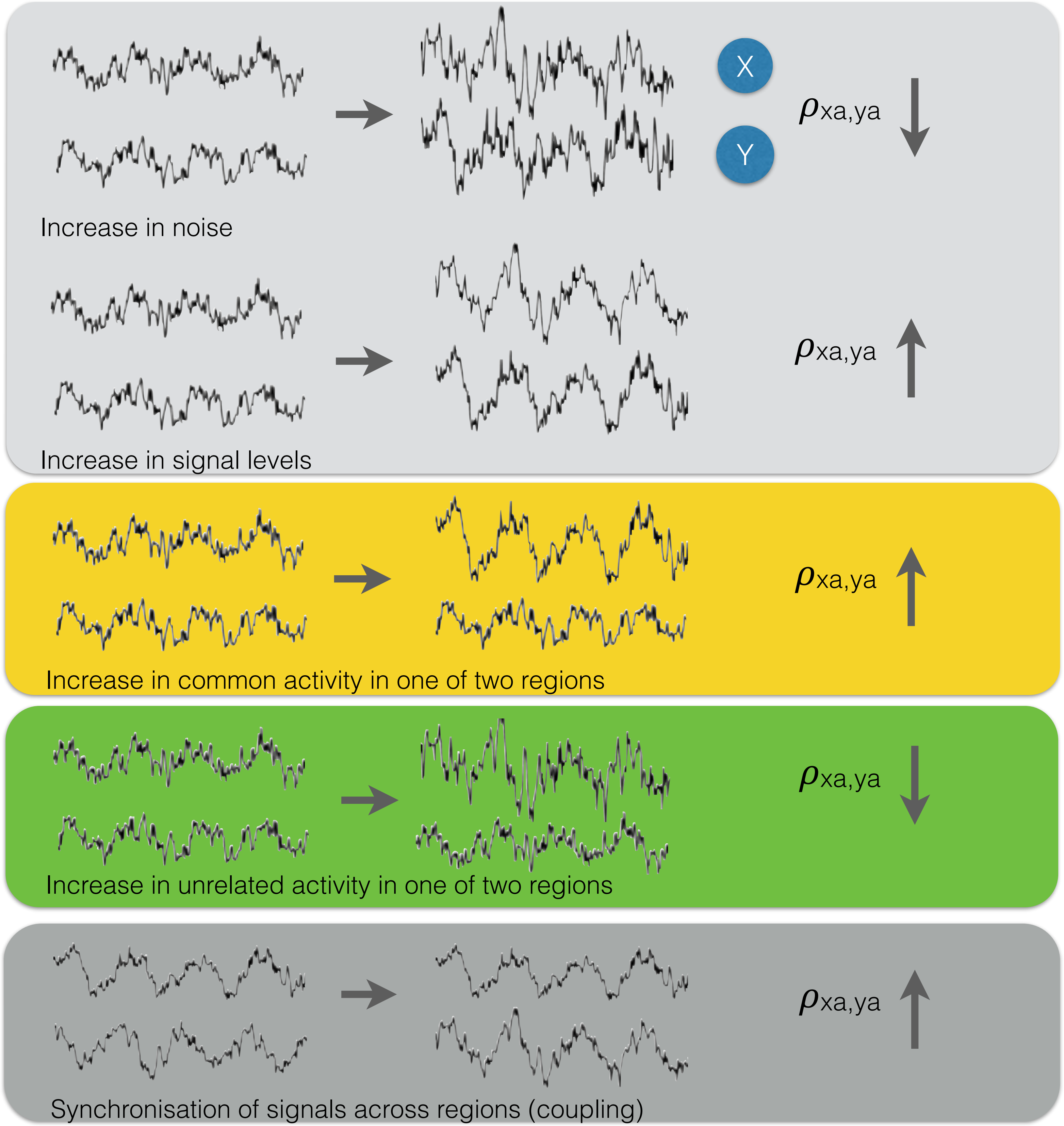
Differences in patient groups (e.g. vascular tone)

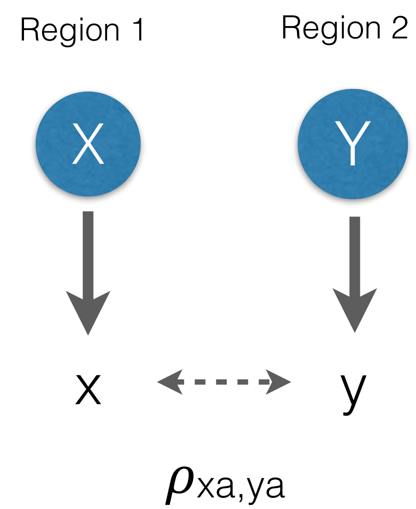


Differences across activation states (e.g. BOLD ceiling)

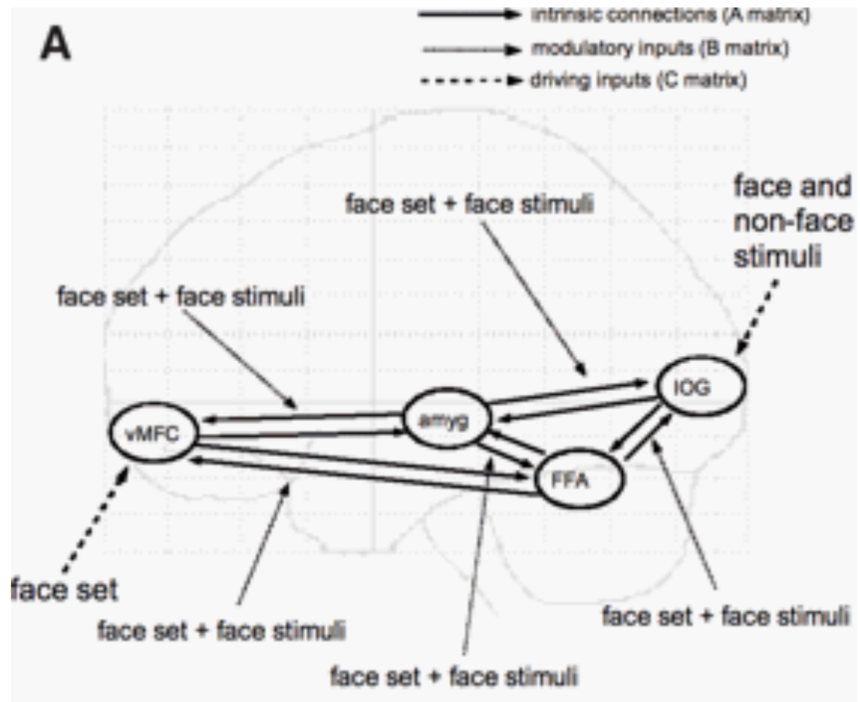
Reasons for skepticism..

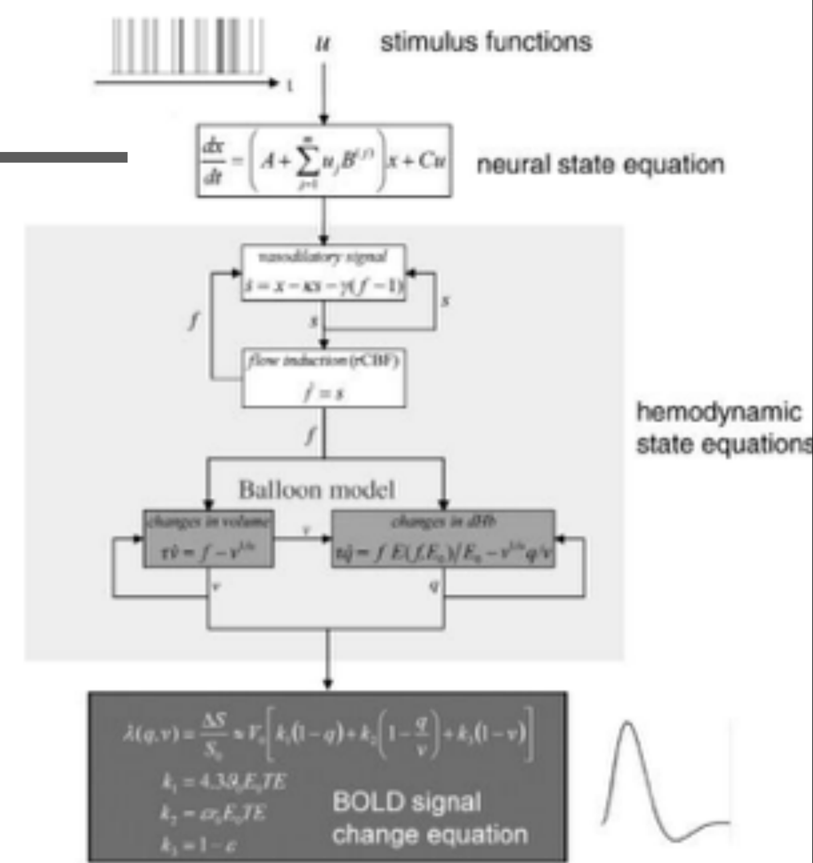
Correlation on its own in general provides little insight the changes/differences in signal

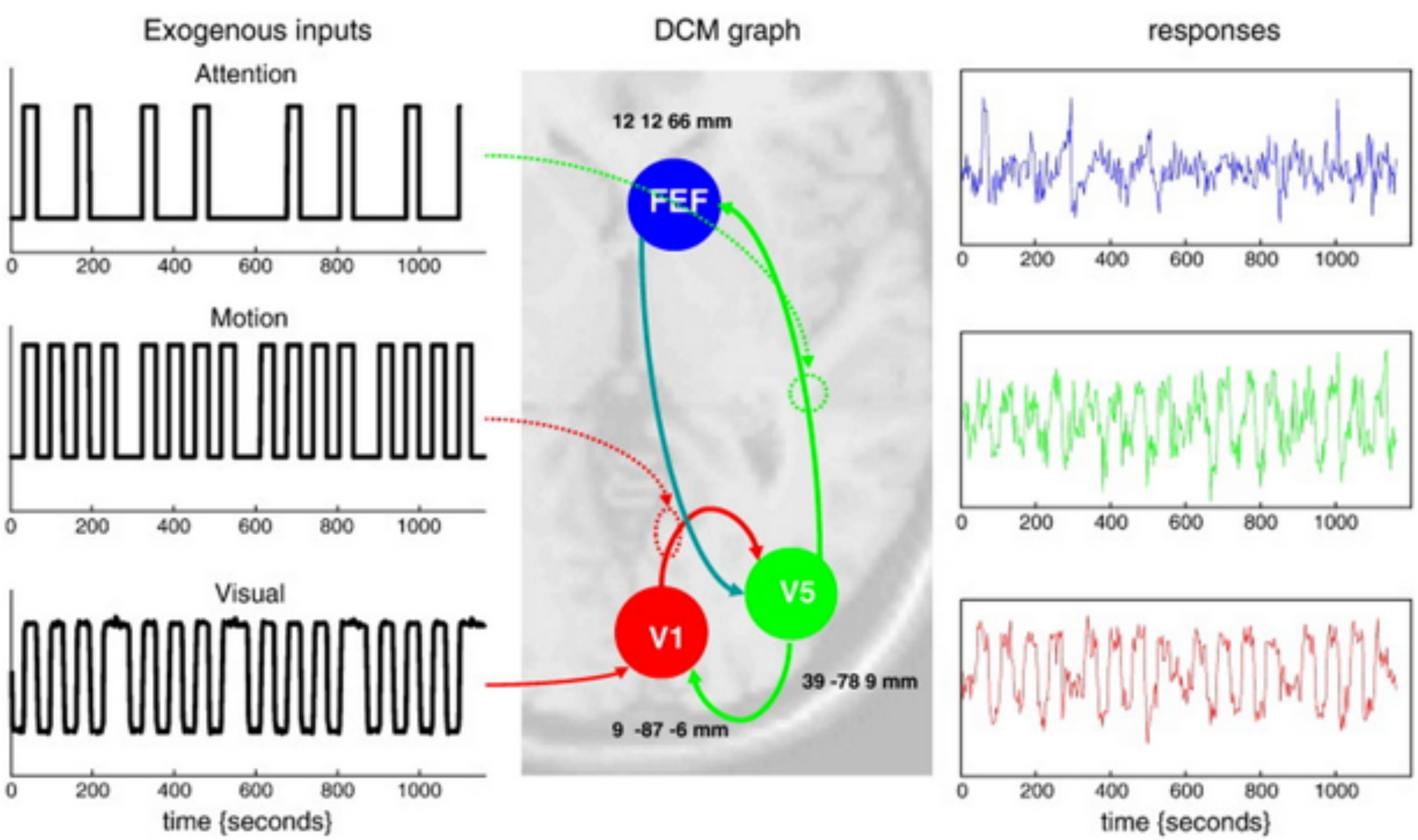




Dynamic Causal Modelling







DCM of random fluctuations

Stochastic DCM: models endogenous stochastic fluctuations

- Variational Bayesian generalised filtering estimation
- Communicated dynamics are modelled to have low frequency dynamics

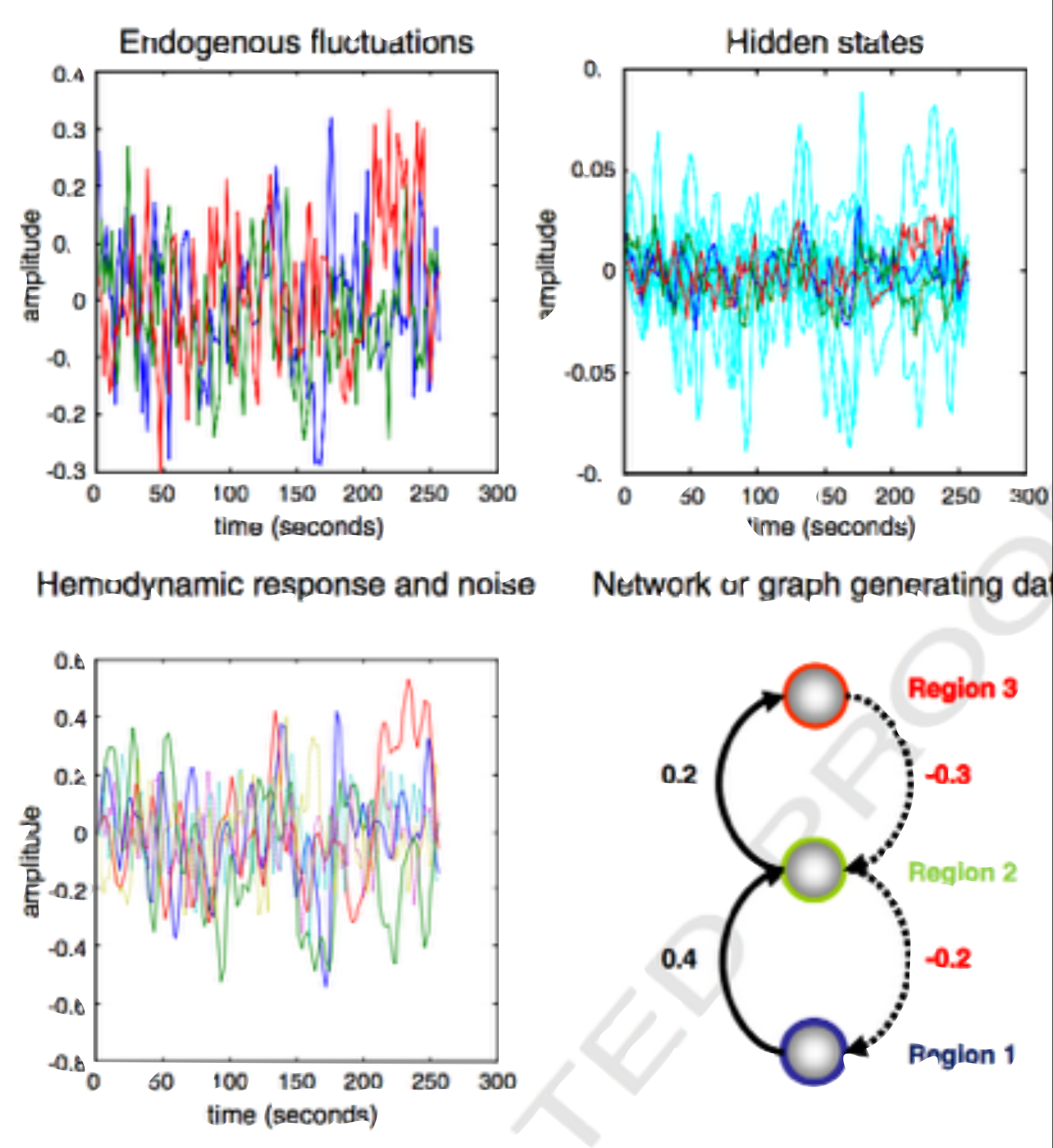
Recent alternate approach uses deterministic model using on cross-spectra of time series.

Strengths:

Models can distinguish SNR changes, different types of inter-regional connectivity topologies

Generative model:

- estimates physiological variables (pharma)
- can be used to generate expected observable statistics such as correlation, graph-theoretic measures, etc.



Friston et al, Math Prob Eng 2010;Friston et al Neuroimage 2011; Friston et al Neuroimage 2014

DCM of random fluctuations

Stochastic DCM: models endogenous stochastic fluctuations

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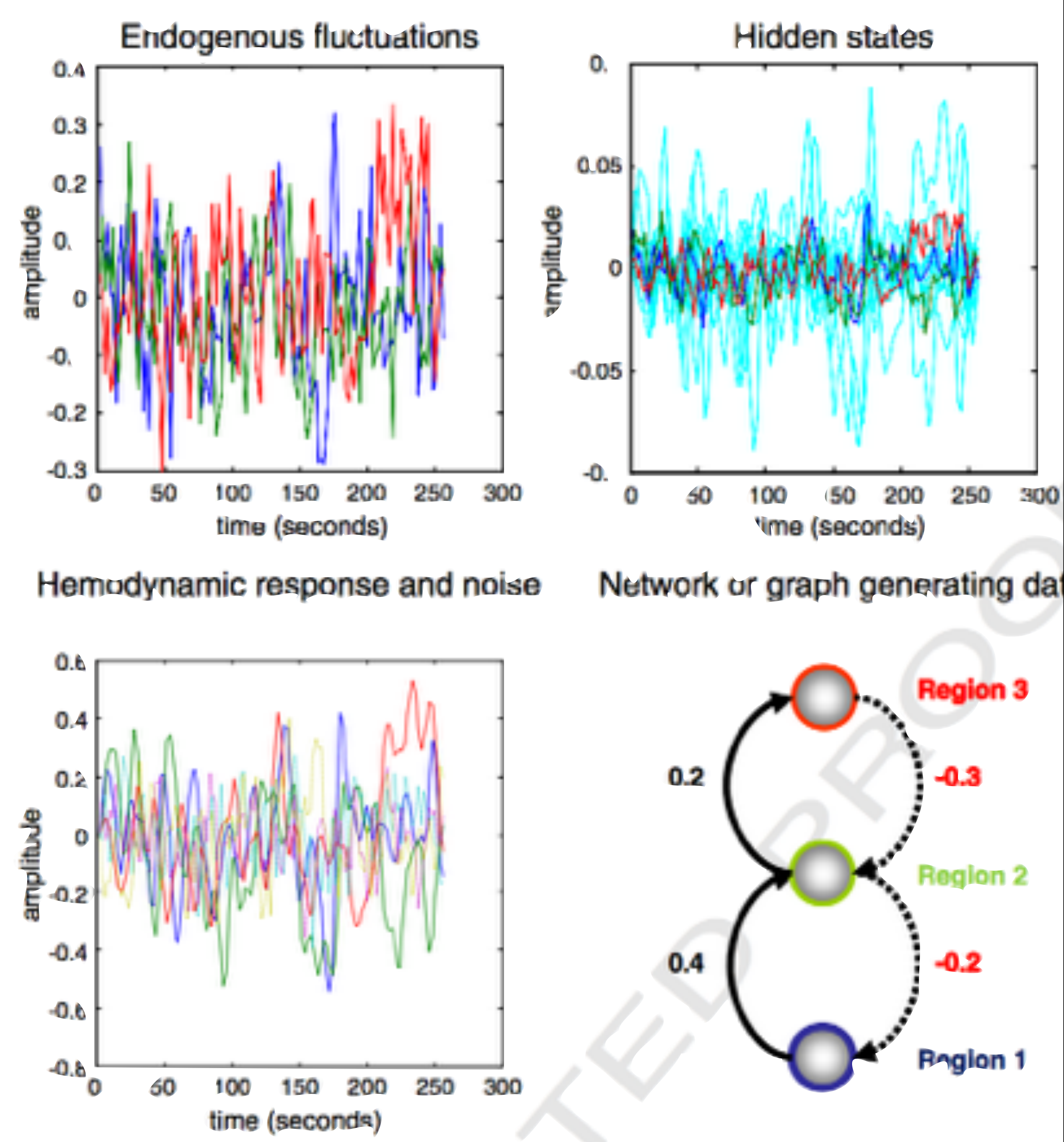
Recent alternate approach uses deterministic model using on cross-spectra of time series.



Limitations:

Models are complex, computationally challenging:

- require ROI definition - not mapping
- test limited numbers of model topologies
- may not account for/identify large-scale dynamics
- high-dimensional models - may difficult to interpret

Friston et al, Math Prob Eng 2010;Friston et al Neuroimage 2011; Friston et al Neuroimage 2014

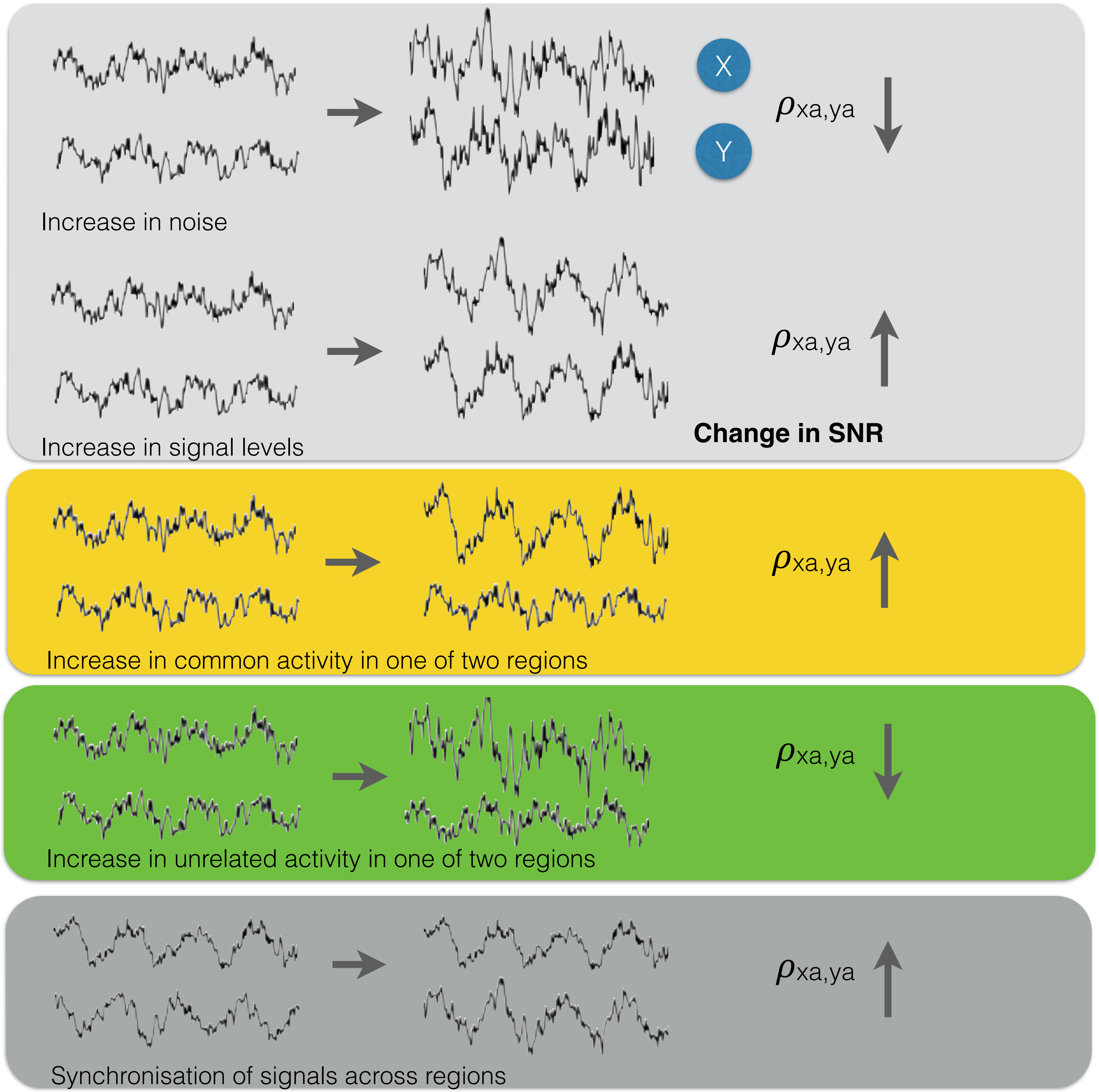
Goal

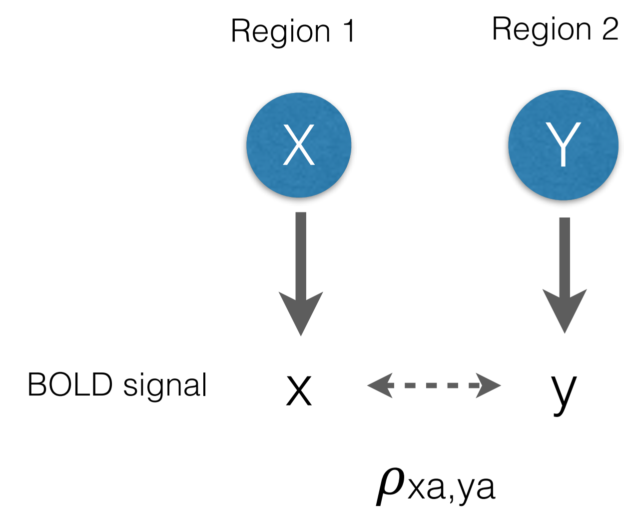
Identify a simple approach to characterising connectivity that can provide some of the insight provided by DCM, while still enabling mapping.

Strategy:

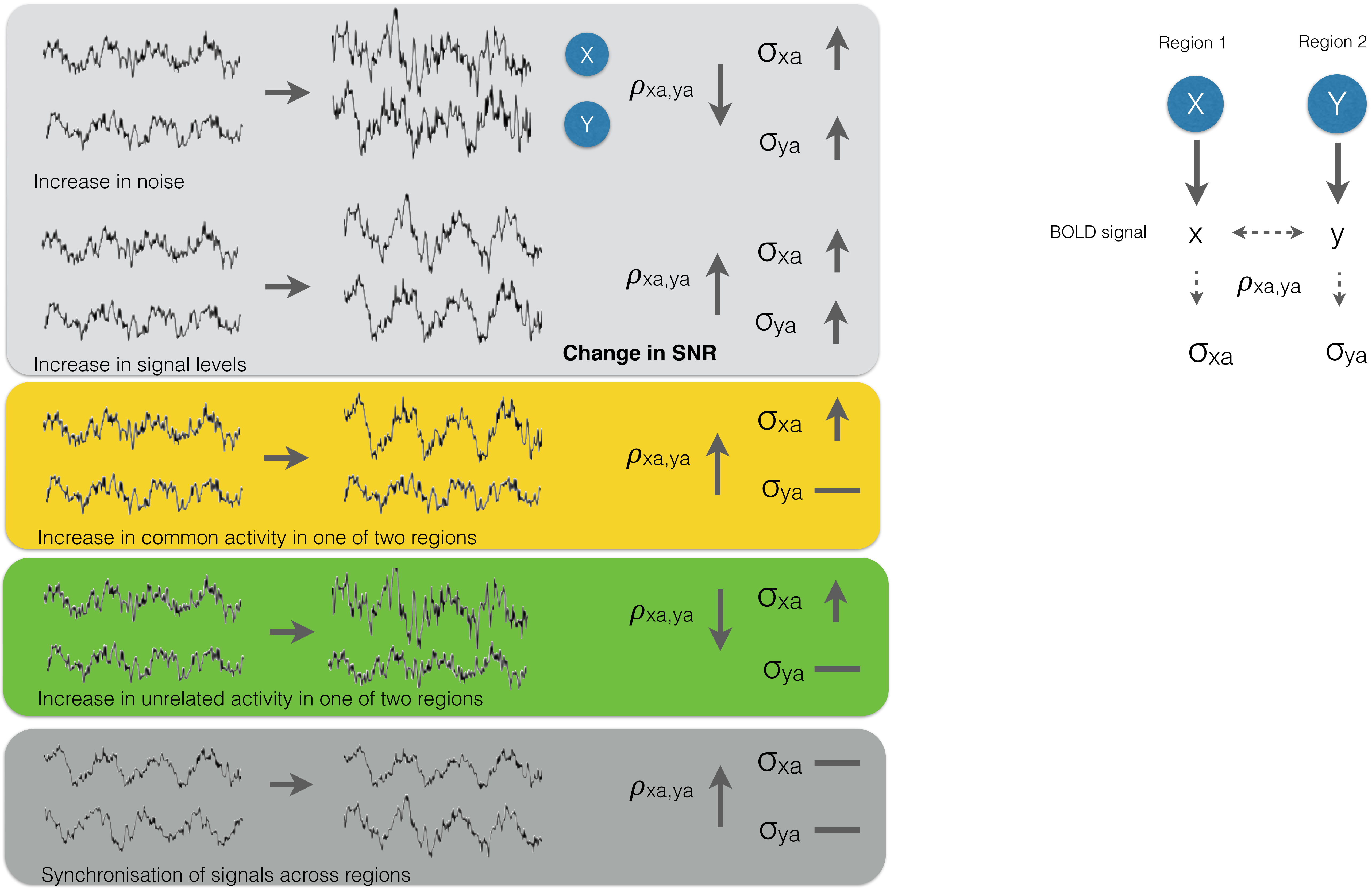
Focus on identification of types of pairwise changes in relationship

Basic features of dynamics affecting connectivity



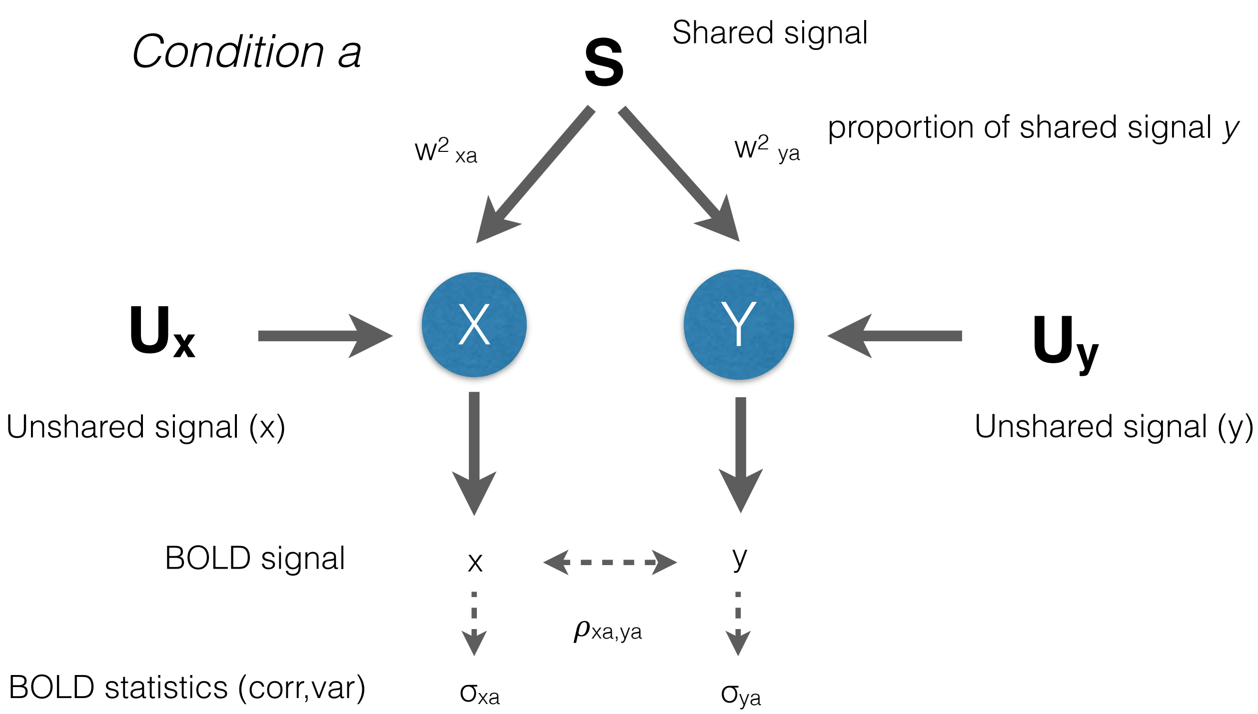


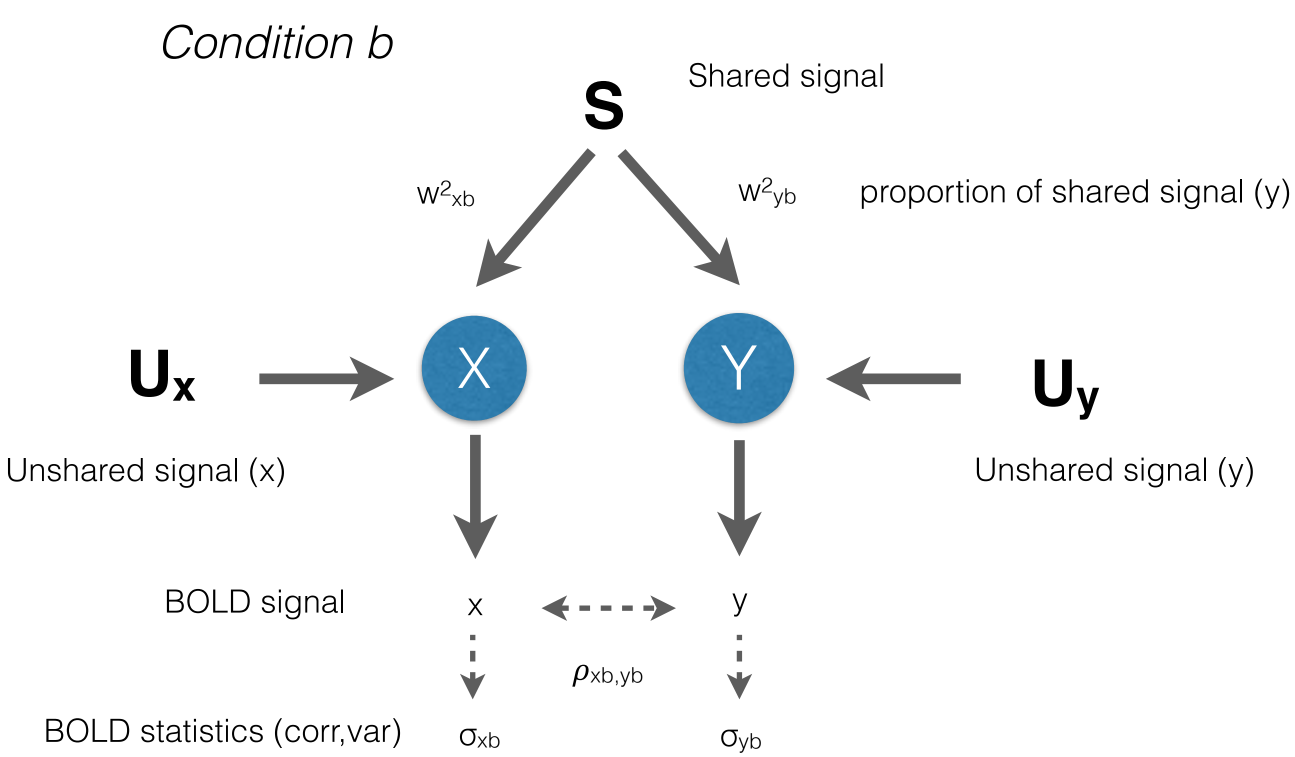
Basic features of dynamics affecting connectivity



Shared/Unshared Signal Model

Pairwise model linking regions X and Y.





Model Formulation

BOLD signal for condition a as a function of S and Ux Uy.

$$x_a = \sigma_{x_a}(w_{x_a}\boldsymbol{S} + \sqrt{1 - w_{x_a}^2}\,\boldsymbol{U_x}) \tag{1}$$

$$y_a = \sigma_{y_a}(w_{y_a}\boldsymbol{S} + \sqrt{1 - w_{y_a}^2}\,\boldsymbol{U_y}) \tag{2}$$

Proportion of shared signal in each region is bounded by correlation

$$\rho_{x_a,y_a} = \frac{cov\,(x_a, y_a)}{\sigma_{x_a}\sigma_{y_a}} \tag{3}$$

$$\rho_{x_a,y_a} = \frac{w_{x_a}\sigma_{x_a}w_{y_a}\sigma_{y_a}}{\sigma_{x_a}\sigma_{y_a}} \tag{4}$$

$$\rho_{x_a,y_a} = w_{x_a}w_{y_a} \qquad \longrightarrow \qquad \rho_a < w_{x_a} < 1 \tag{5}$$

Condition b produces some change in levels of shared and unshared signals - $w_{xb} = c_x w_{xa}$, $w_{yb} = c_y w_{ya}$. , matching the total change in variance:

$$\begin{aligned} x_b &= \sigma_{x_a}\left(c_x w_{x_a}\boldsymbol{S} + u_x\sqrt{1 - w_{x_a}^2}\cdot\boldsymbol{U_x}\right) \\ &= \sigma_{x_b}\left(\frac{\sigma_{x_a}}{\sigma_{x_b}}c_x w_{x_a}\boldsymbol{S} + \frac{\sigma_{x_a}}{\sigma_{x_b}}u_x\sqrt{1 - w_{x_a}^2}\cdot\boldsymbol{U_x}\right) \end{aligned} \tag{6}$$

New observed variance can be expressed:

$$\sigma_{x_b}^2 = \sigma_{x_a}^2\left(c_x^2 w_{x_a}^2 + u_c^2\left(1 - w_{x_a}^2\right)\right) \tag{7}$$

$\rho_{xb,yb}$ can be expressed in terms of σ_{xa},σ_{xb} σ_{ya}, σ_{yb}, w_{ay}, and u_x

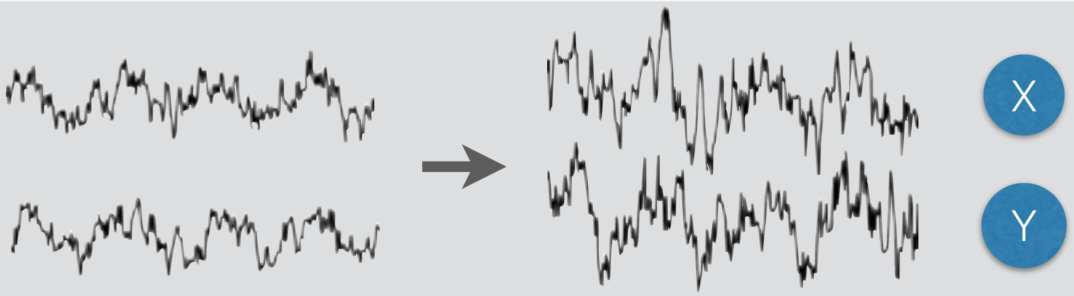
$$\begin{aligned} \rho_b &= \rho_a\frac{\sigma_{x_a}}{\sigma_{x_b}}\frac{\sigma_{y_a}}{\sigma_{y_b}}c_x c_y && (8) \\ &= \rho_a\frac{\sigma_{x_a}}{\sigma_{x_b}}\frac{\sigma_{y_a}}{\sigma_{y_b}}\sqrt{\frac{\sigma_{x_b}^2}{\sigma_{x_a}^2} - u_x^2\left(1 - w_{x_a}^2\right)}\cdot\frac{1}{w_{x_a}}\sqrt{\frac{\sigma_{y_b}^2}{\sigma_{y_a}^2} - u_y^2\left(1 - w_{y_a}^2\right)}\cdot\left|\frac{w_{x_a}}{\rho_a}\right| && (9) \\ &= \text{sign}\,(\rho_a)\sqrt{1 - \frac{\sigma_{x_a}^2}{\sigma_{x_b}^2}\left(u_x^2 - w_{x_a}^2\right)}\sqrt{1 - \frac{\sigma_{y_a}^2}{\sigma_{y_b}^2}\left(u_y^2 - \frac{\rho_a^2}{w_{x_a}^2}\right)} && (10) \end{aligned}$$

Given the limits on w_{ay}, maximum effects of particular changes in signal and noise on $\rho_{xb,yb}$ can be determined based on variance changes. E.g. if there was no change in signal levels:

$$\rho_b = \rho_a\frac{\sigma_{x_a}}{\sigma_{x_b}}\frac{\sigma_{y_a}}{\sigma_{y_b}}$$

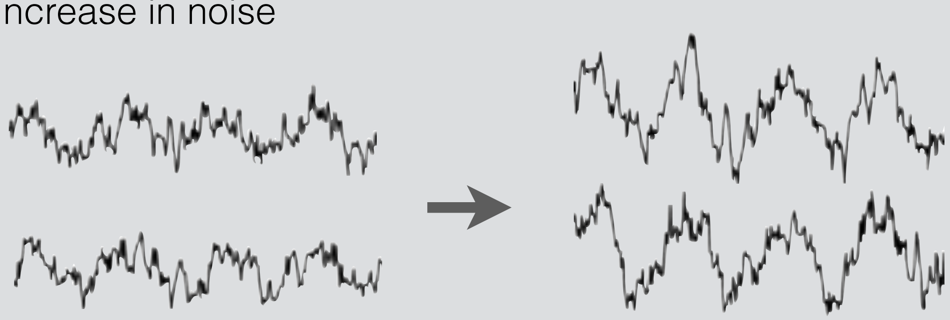
Determining possibility of different changes

$\rho_{xa,ya}$ σ_{xa}, σ_{xb} σ_{ya}, σ_{yb}, $\longrightarrow$ $\rho_{xb,yb}$



Increase in noise

$\rho_{x,y}$ $\downarrow$ | σ_{xa} $\uparrow$ $c_x=1$ $(u_x>1)$ | σ_{ya} $\uparrow$ $c_y=1$ $(u_y>1)$



Increase in signal levels

$\rho_{x,y}$ $\uparrow$ | σ_{xa} $\uparrow$ $c_x>1$ $(u_x=1)$ | σ_{ya} $\uparrow$ $c_y>1$ $(u_y=1)$

Change in SNR

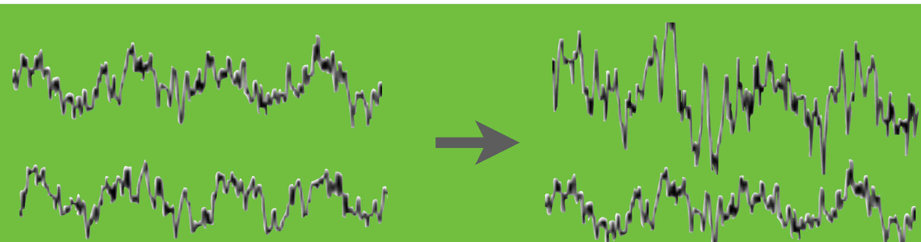
$$\rho_b = \rho_a \frac{\sigma_{x_a}}{\sigma_{x_b}} \frac{\sigma_{y_a}}{\sigma_{y_b}}$$

Increase in common activity in one of two regions

$\rho_{x,y}$ $\uparrow$ | σ_{xa} $\uparrow$ $c_x>1$ $(u_x=1)$ | σ_{ya} — $c_y=1$ $(u_y=1)$

$$\max(\rho_b) = \mathrm{sign}(\rho_a)\sqrt{1 - m\,(1-\rho_a^2)}$$

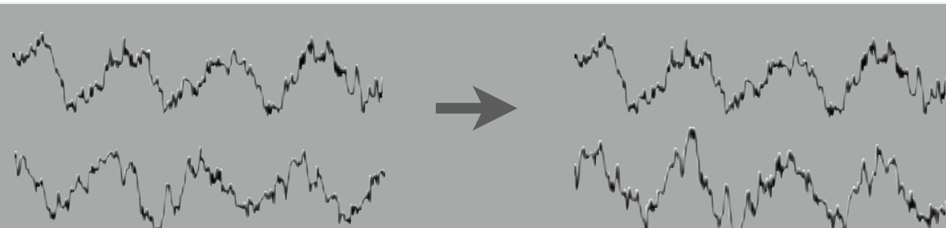
where $m = \min\left(\frac{\sigma_y^2}{\sigma_x^2}, \frac{\sigma_x^2}{\sigma_y^2}\right)$



Increase in unrelated activity in one of two regions

$\rho_{x,y}$ $\downarrow$ | σ_{xa} $\uparrow$ $c_x=1$ $(u_x>1)$ | σ_{ya} — $c_y=1$ $(u_y=1)$

$$\rho_b = \rho_a \frac{\sigma_{x_a}}{\sigma_{x_b}} \frac{\sigma_{y_a}}{\sigma_{y_b}}$$

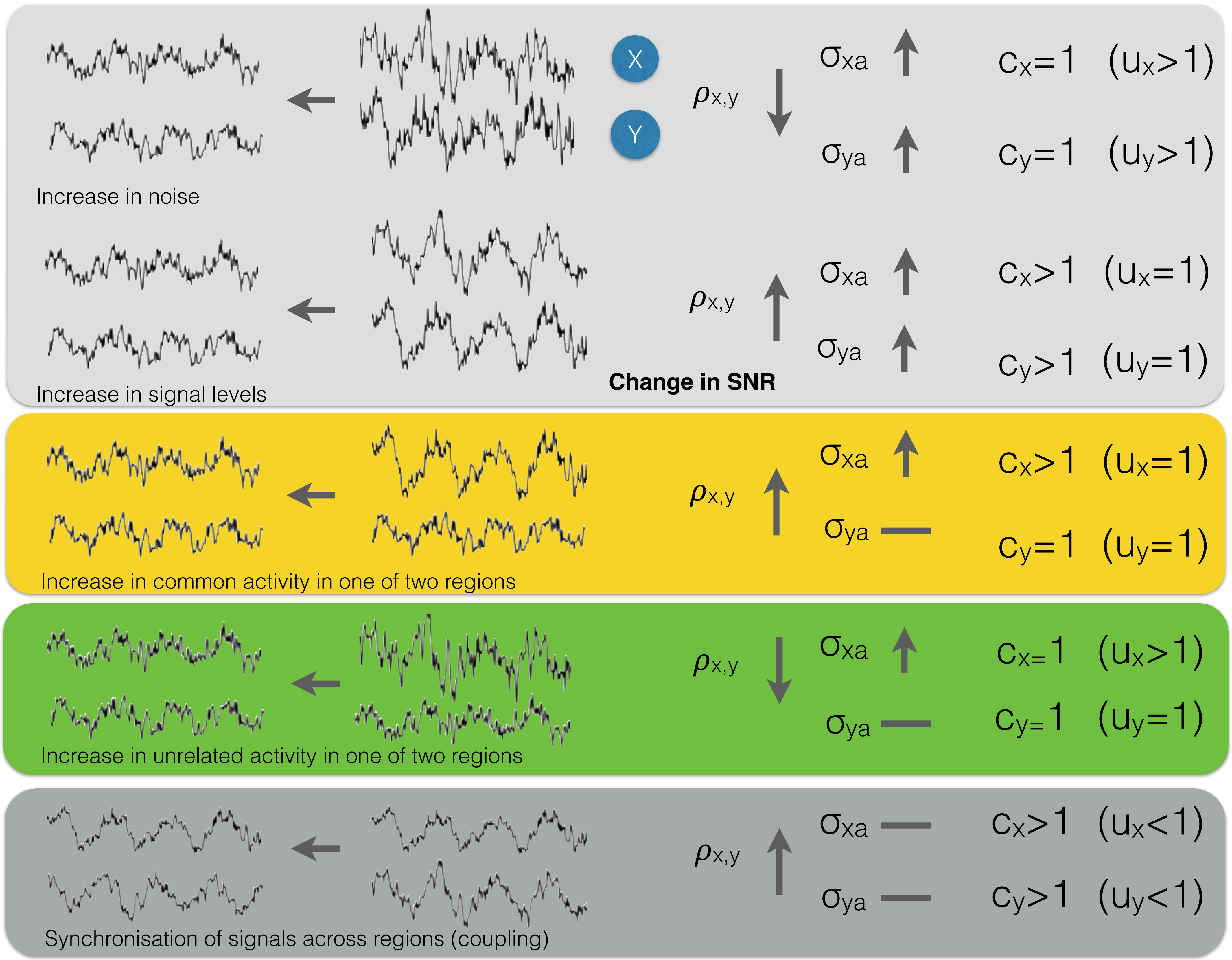


Synchronisation of signals across regions (coupling)

$\rho_{x,y}$ $\uparrow$ | σ_{xa} — $c_x>1$ $(u_x<1)$ | σ_{ya} — $c_y>1$ $(u_y<1)$

Determining possibility of different changes

$\rho_{xb,yb}$ σ_{xa}, σ_{xb} σ_{ya}, σ_{yb}, $\longrightarrow$ $\rho_{xa,ya}$

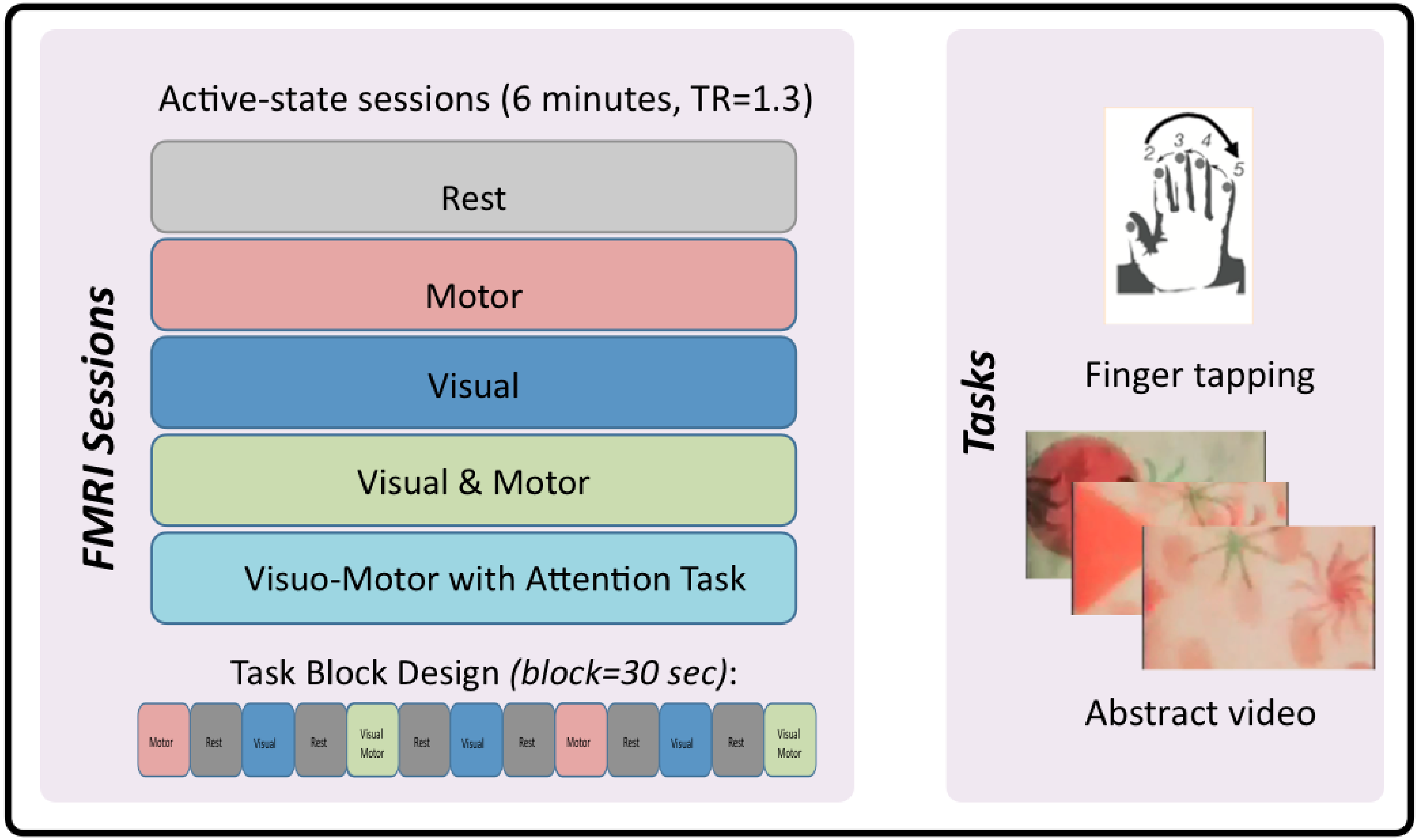


$$\rho_a \frac{\sigma_{y_a}}{\sigma_{y_b}} < w_{x_a} < \min\left(\frac{\sigma_{x_b}}{\sigma_{x_a}}, 1\right)$$

$$\max\left(\rho_a, \sqrt{1 - \frac{\sigma_{x_b}^2}{\sigma_{x_a}^2}}\right) < w_{x_a} < \rho_a \frac{1}{\sqrt{1 - \frac{\sigma_{y_b}^2}{\sigma_{y_a}^2}}}$$

$$\rho_a \frac{\sigma_{y_a}}{\sigma_{y_b}} < w_{x_a} < \min\left(\frac{\sigma_{x_b}}{\sigma_{x_a}}, 1\right)$$

Experiment

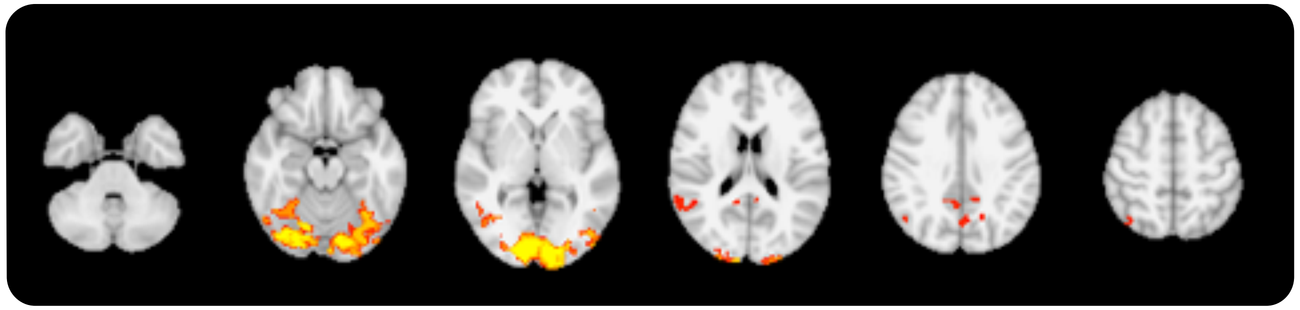


Are changes in connectivity across associated with variance changes?

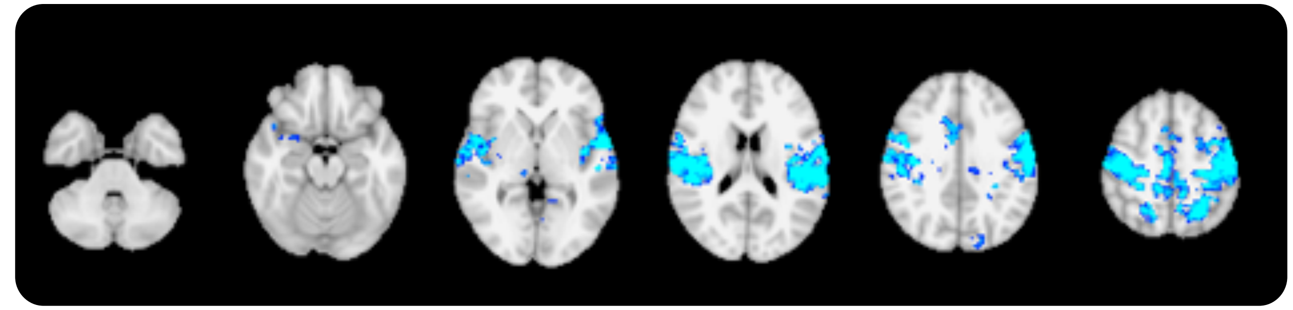
Do these changes correspond to particular types of changes in connectivity - are they predicted by model?

How about activation levels?

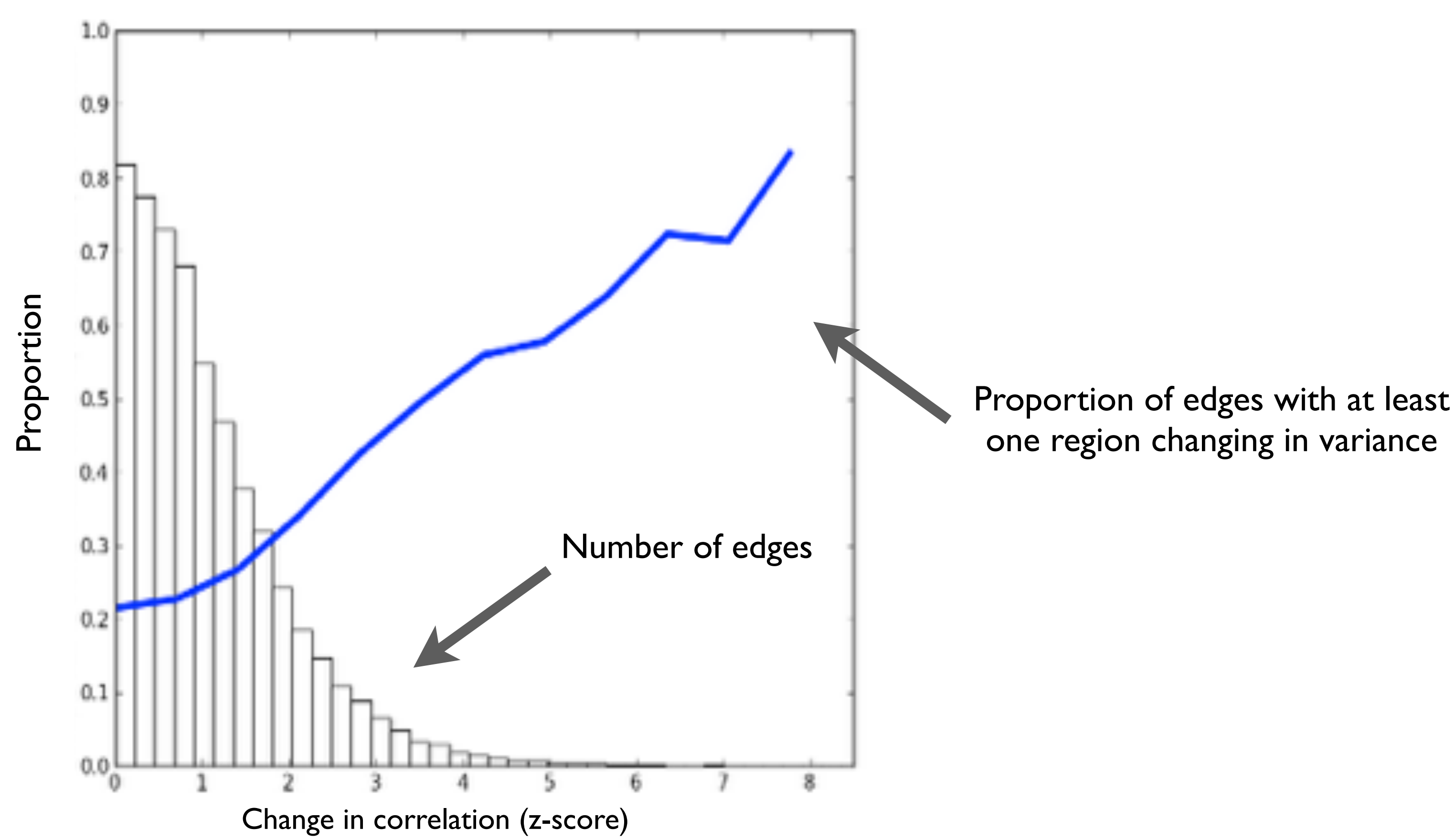
Results

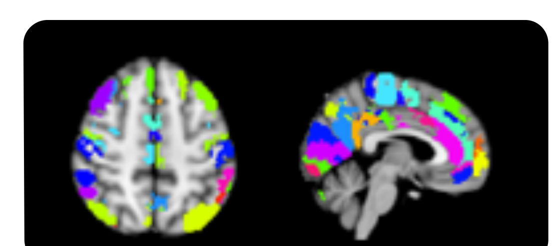


Variance changes from rest for visual



Variance changes from rest for motor





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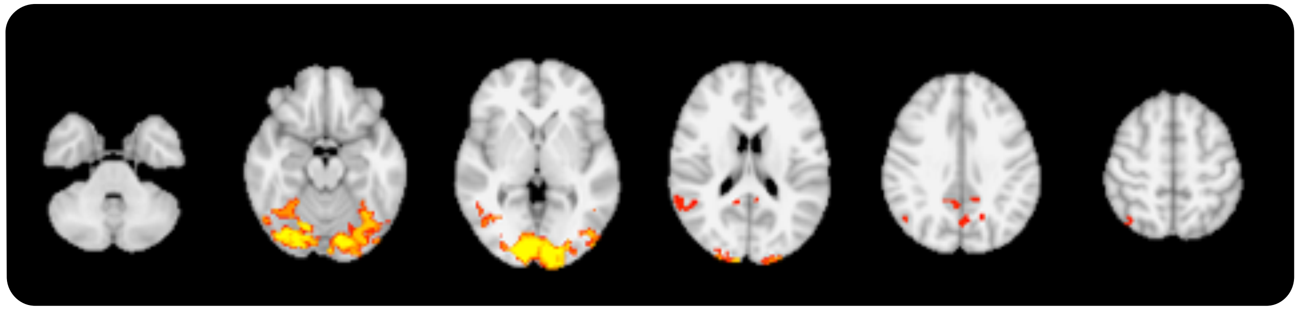

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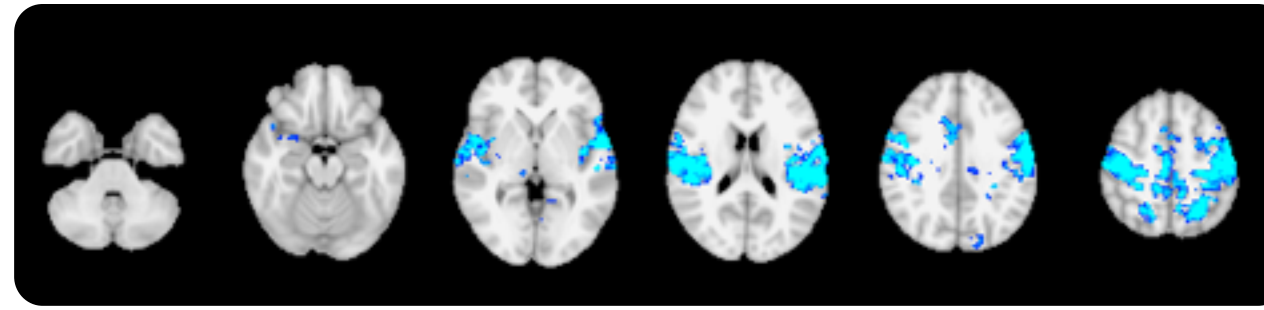
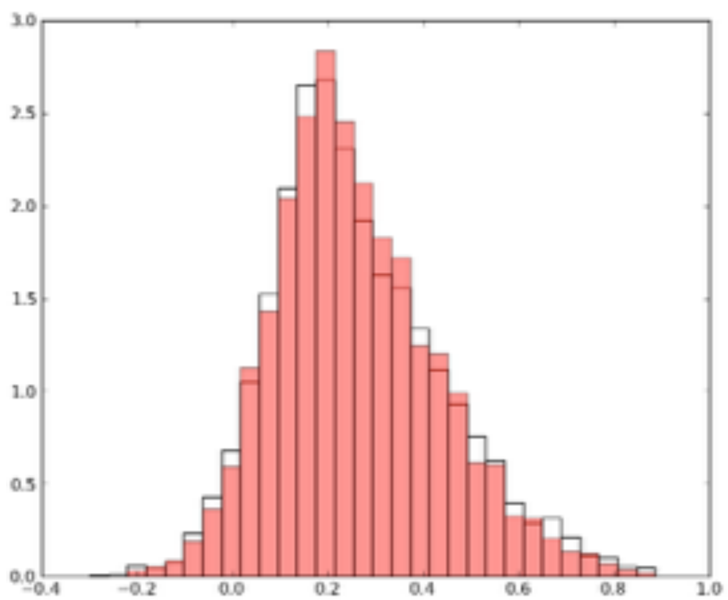
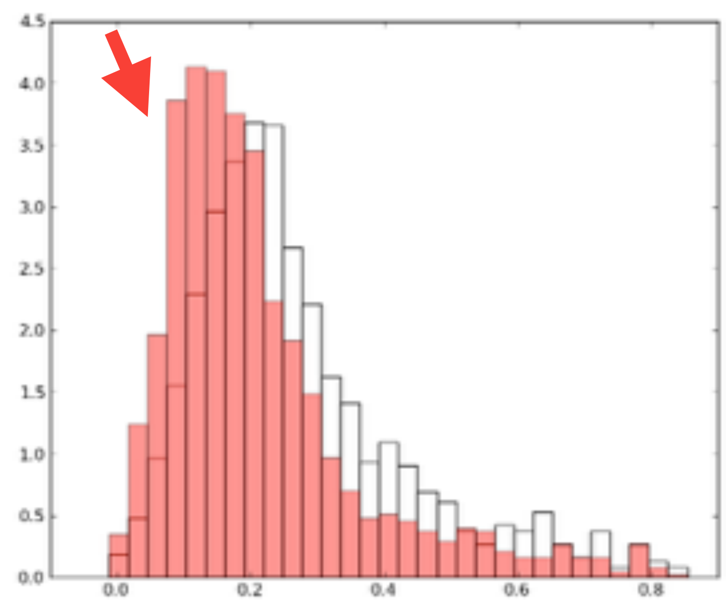


Variance changes from rest for motor

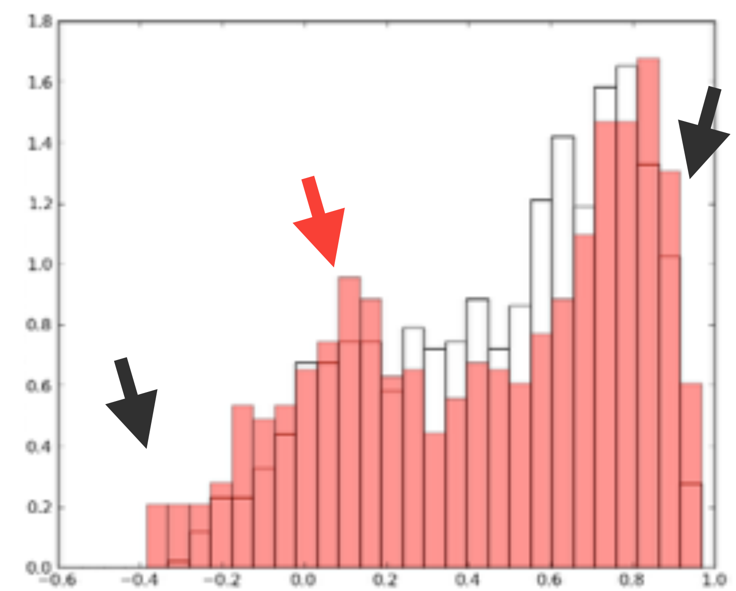
No change in variance.



One region increases in variance

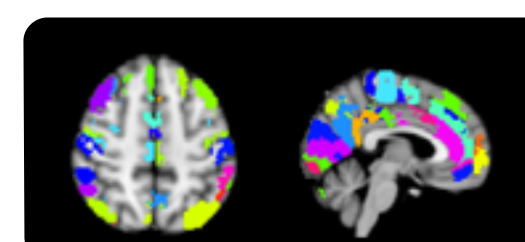


Both regions increase in variance

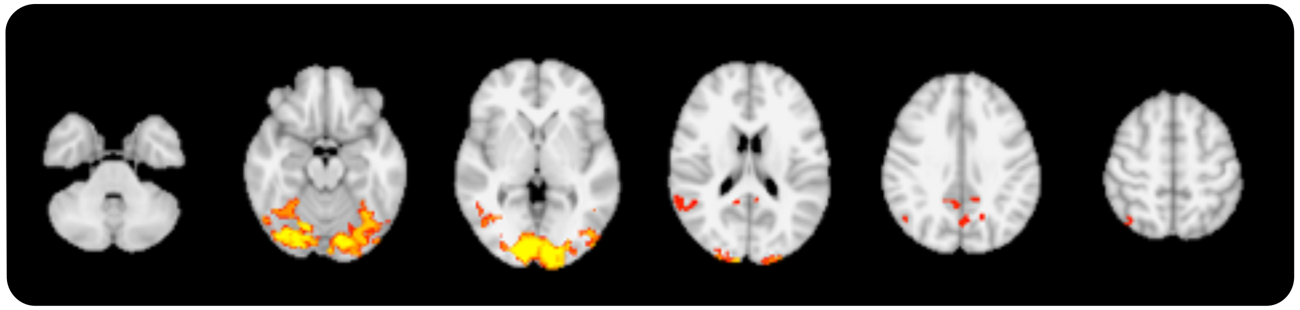


Rest

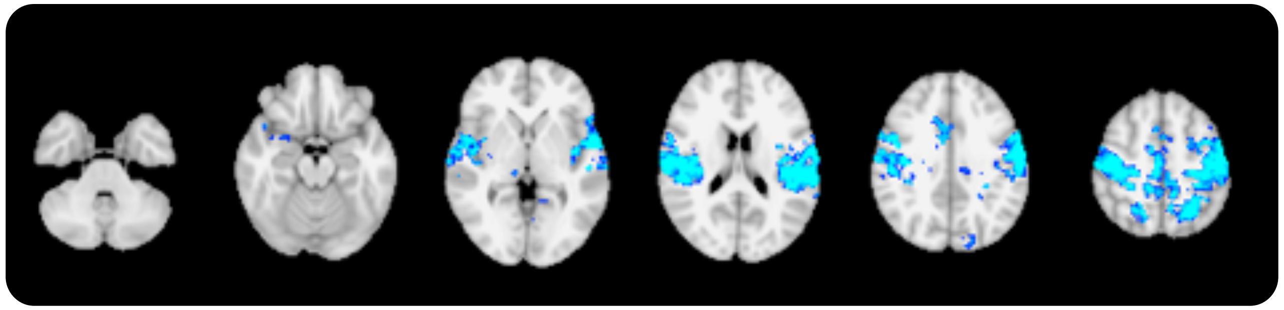
Visual movie



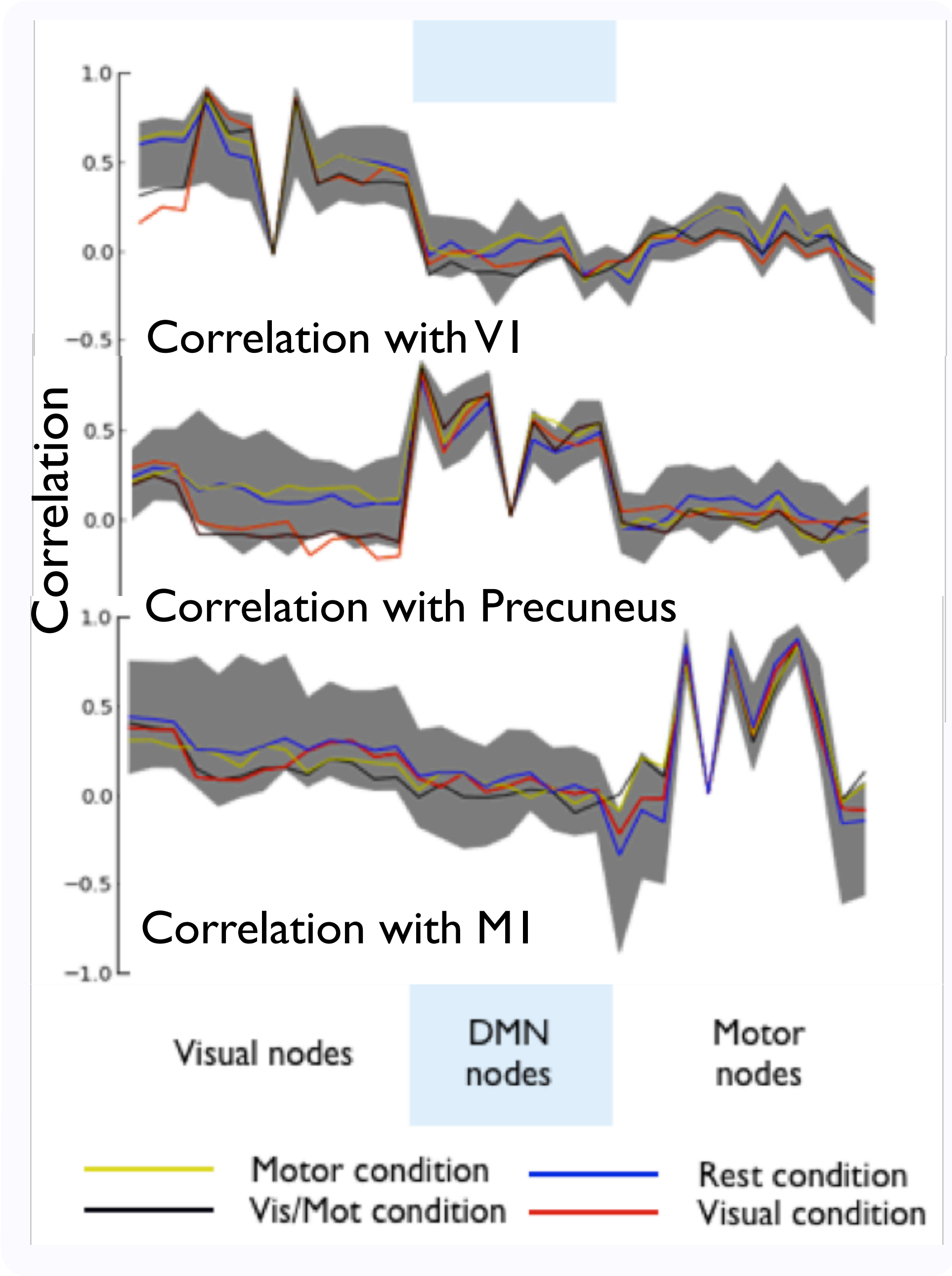
Results



Variance changes from rest for visual



Variance changes from rest for motor



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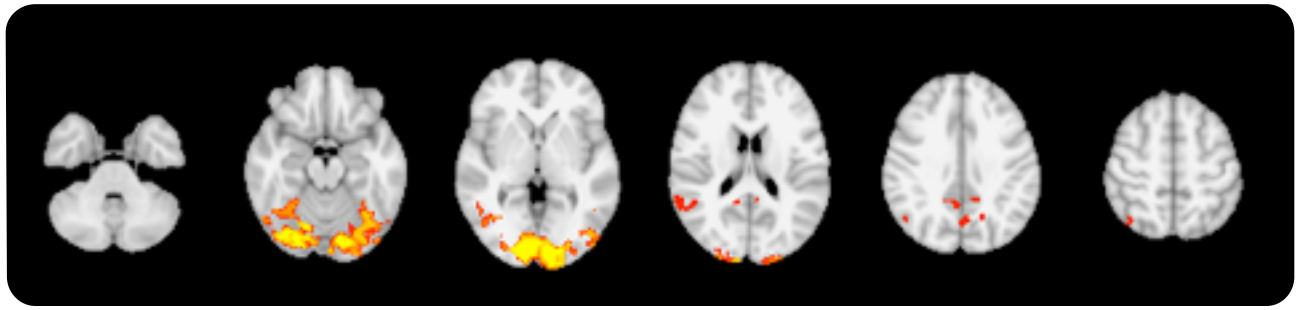
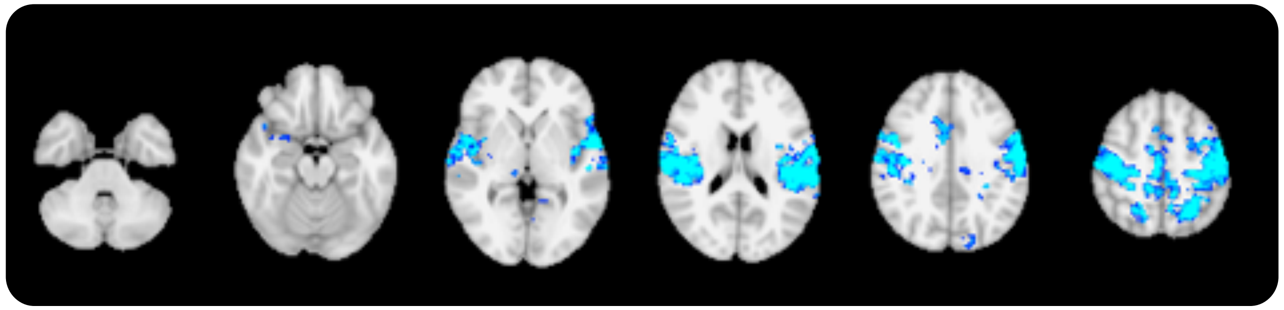
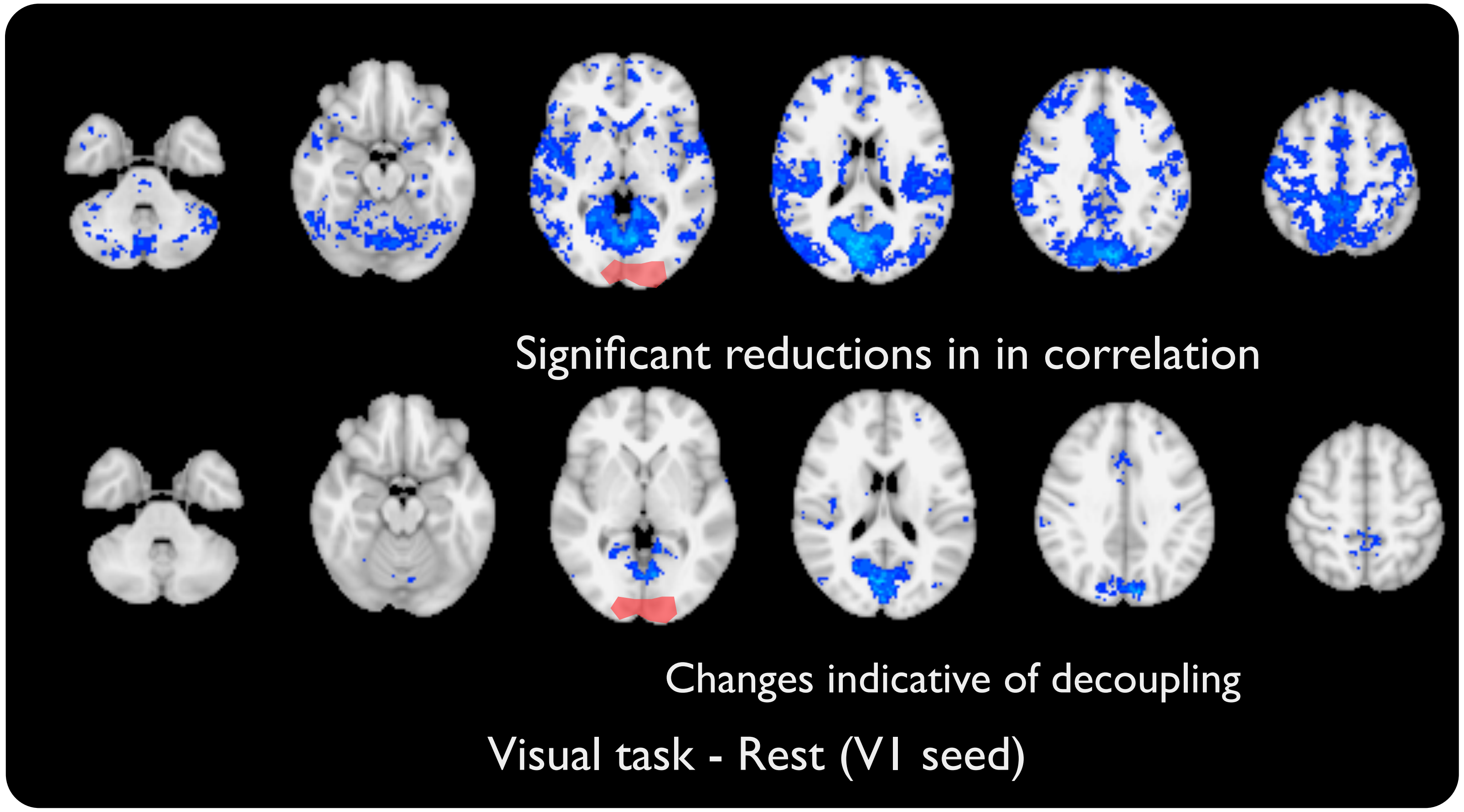


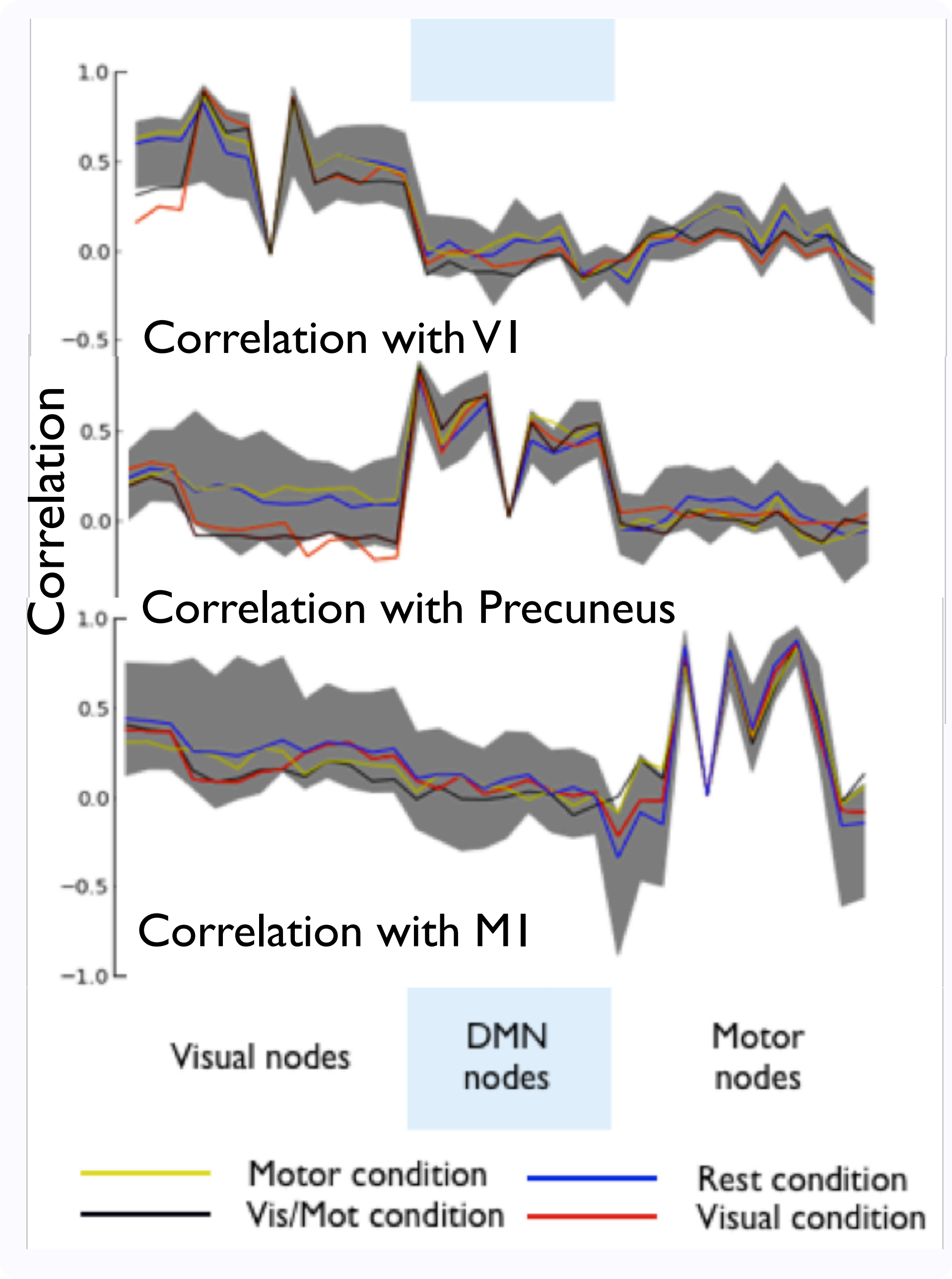
Variance changes from rest for visual



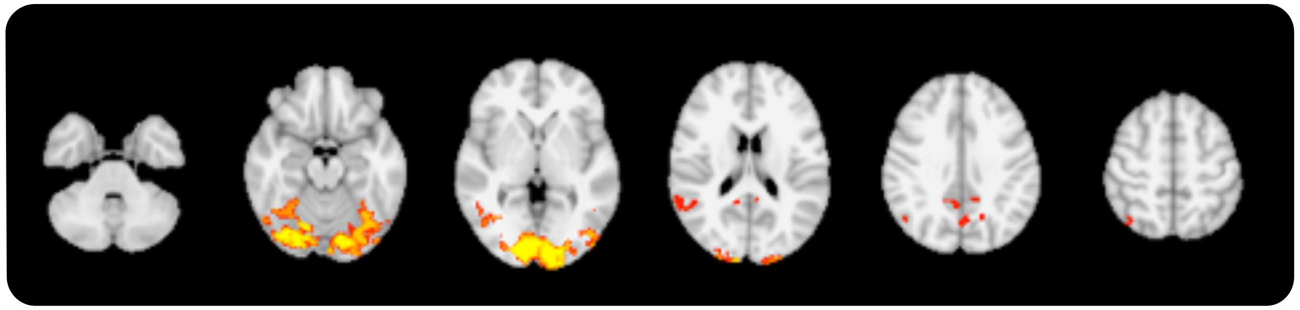
Variance changes from rest for motor



Correlation changes from rest for visual



Results



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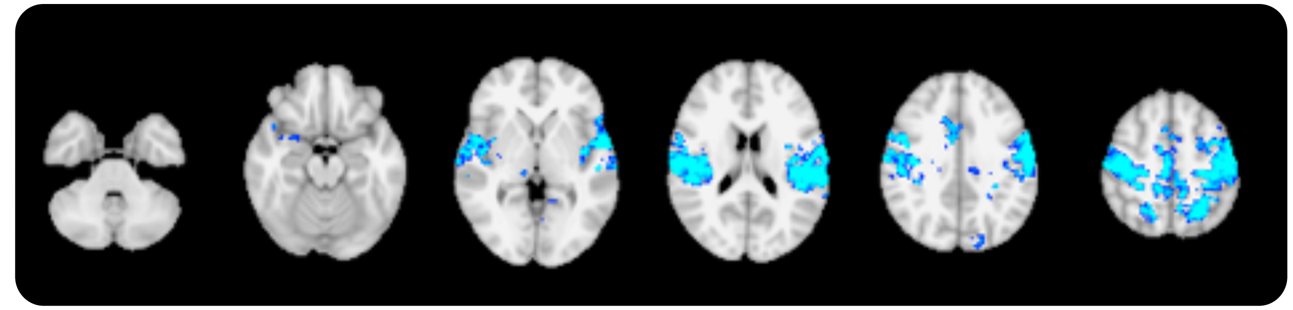
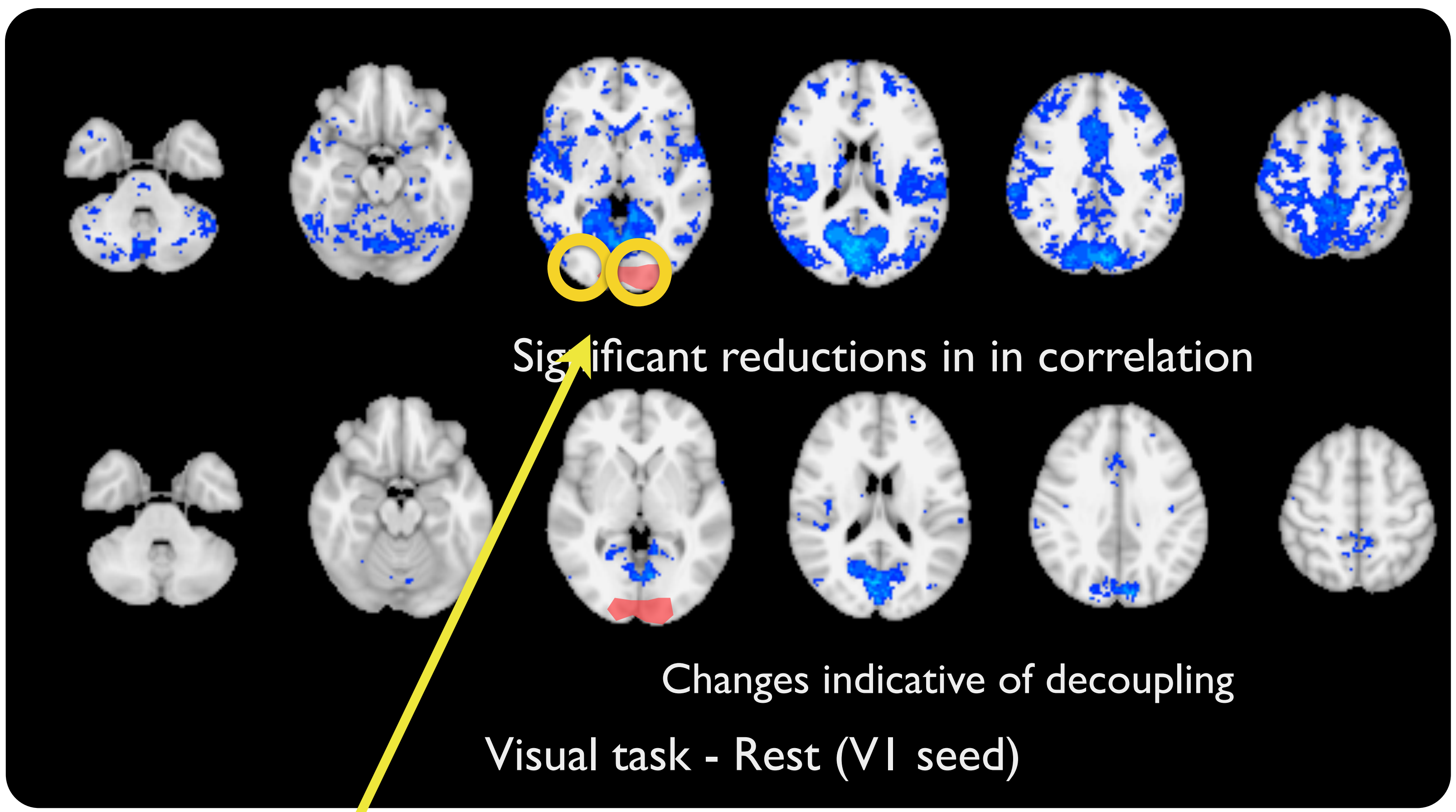
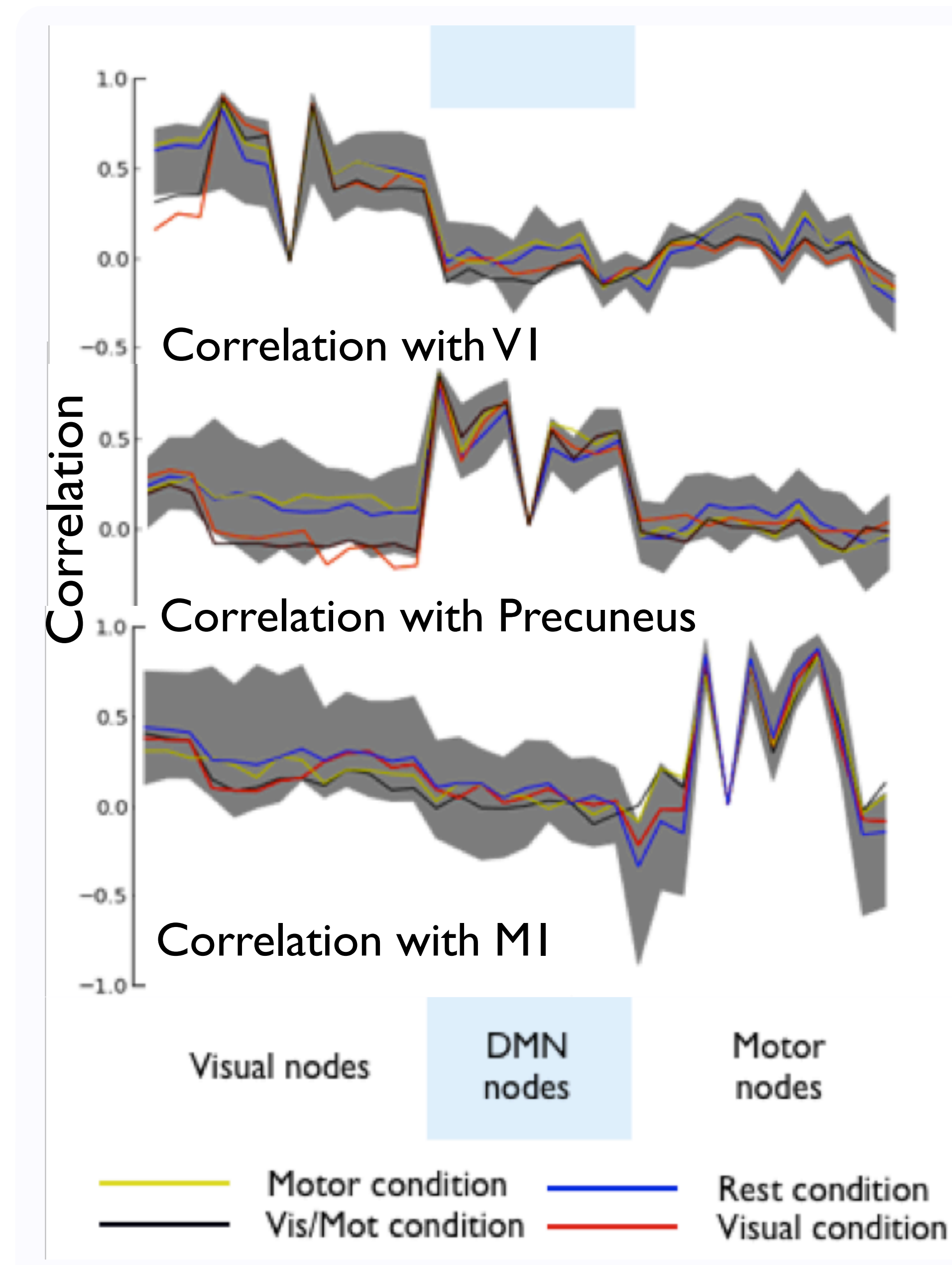


Variance changes from rest for motor

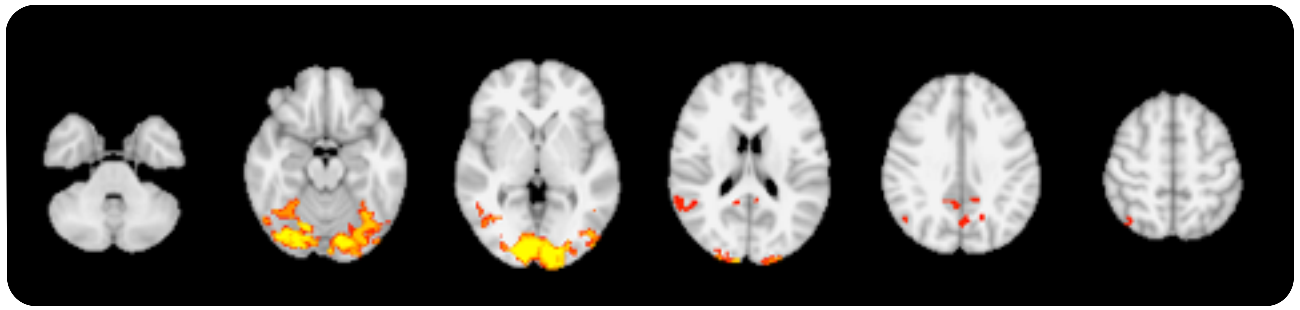


Correlation changes from rest for visual

Increase in signal levels



Results



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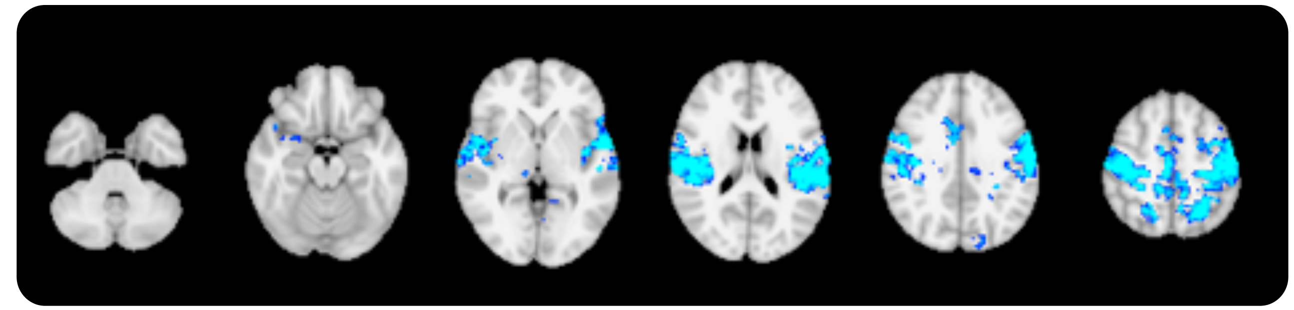
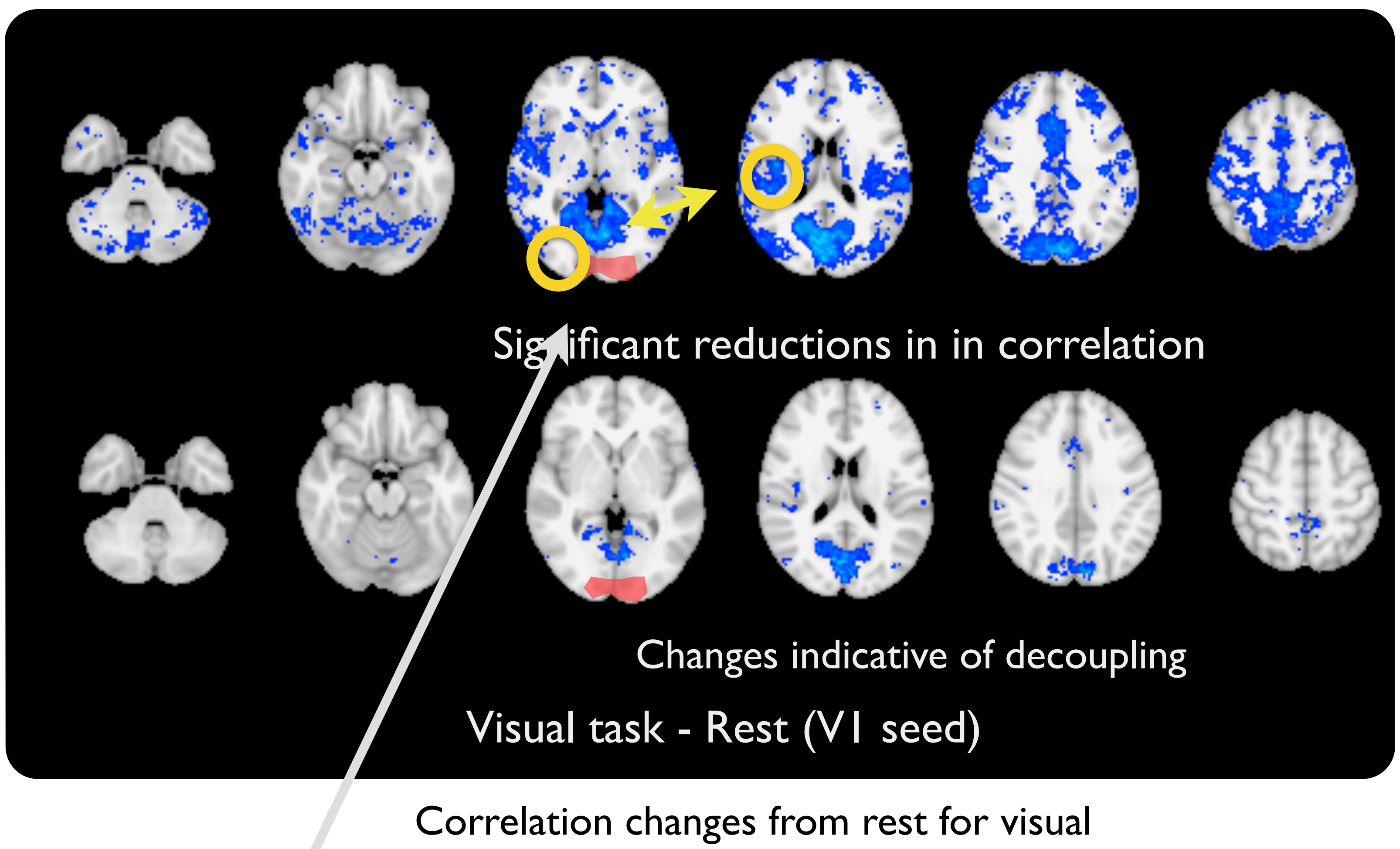
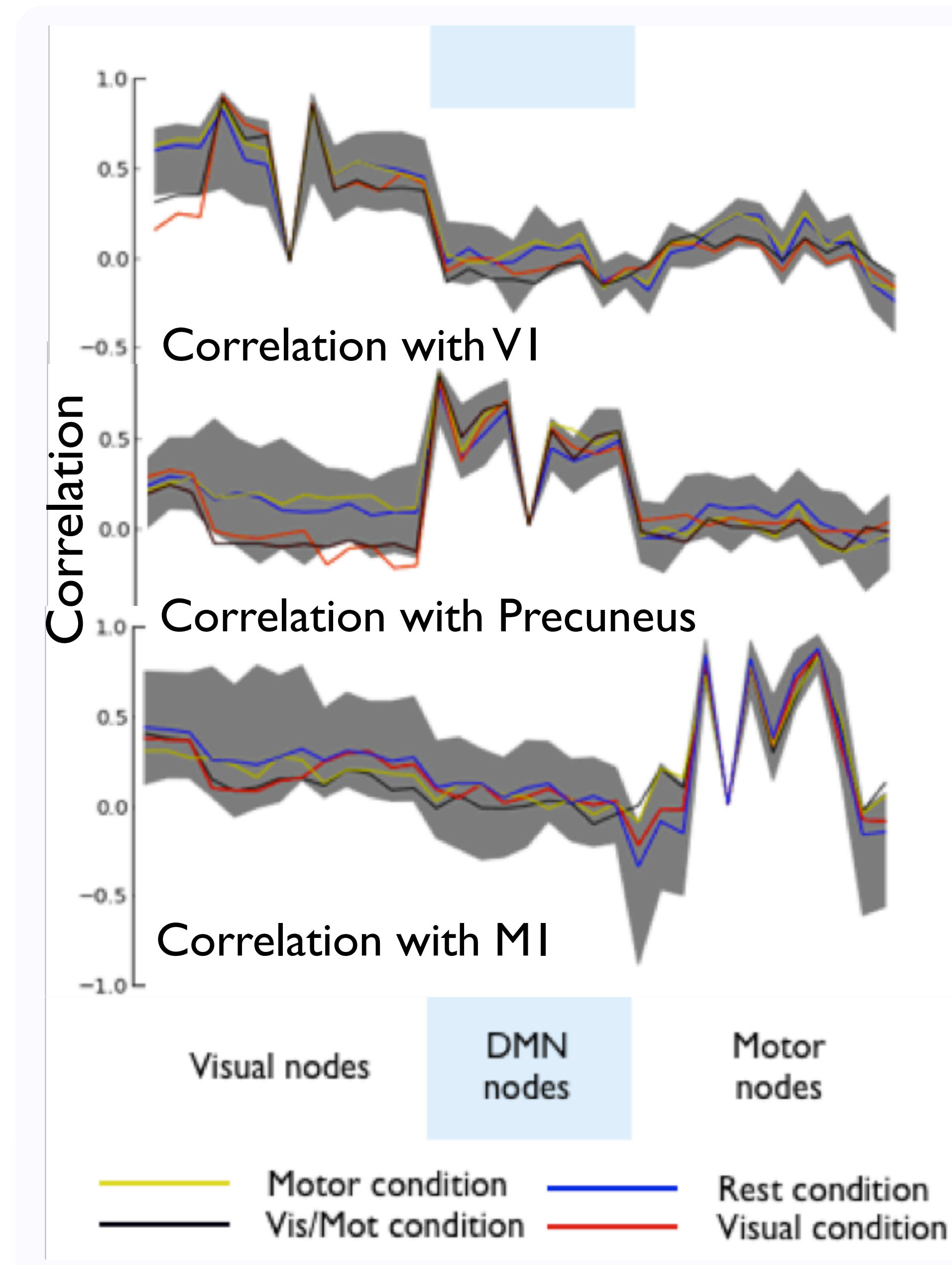


Variance changes from rest for motor

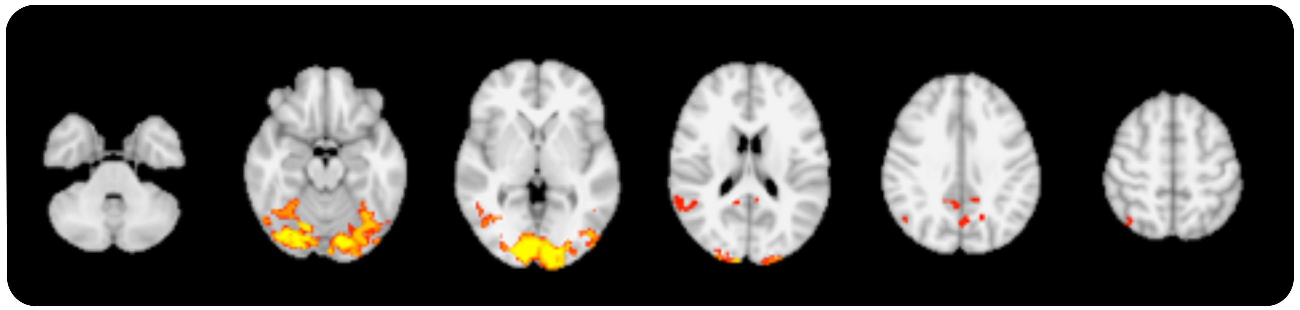


Correlation changes from rest for visual

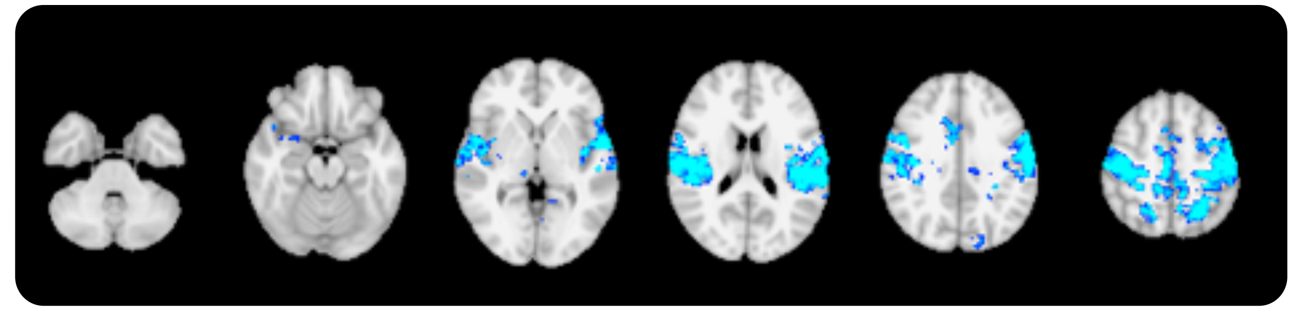
Increase in unshared signal



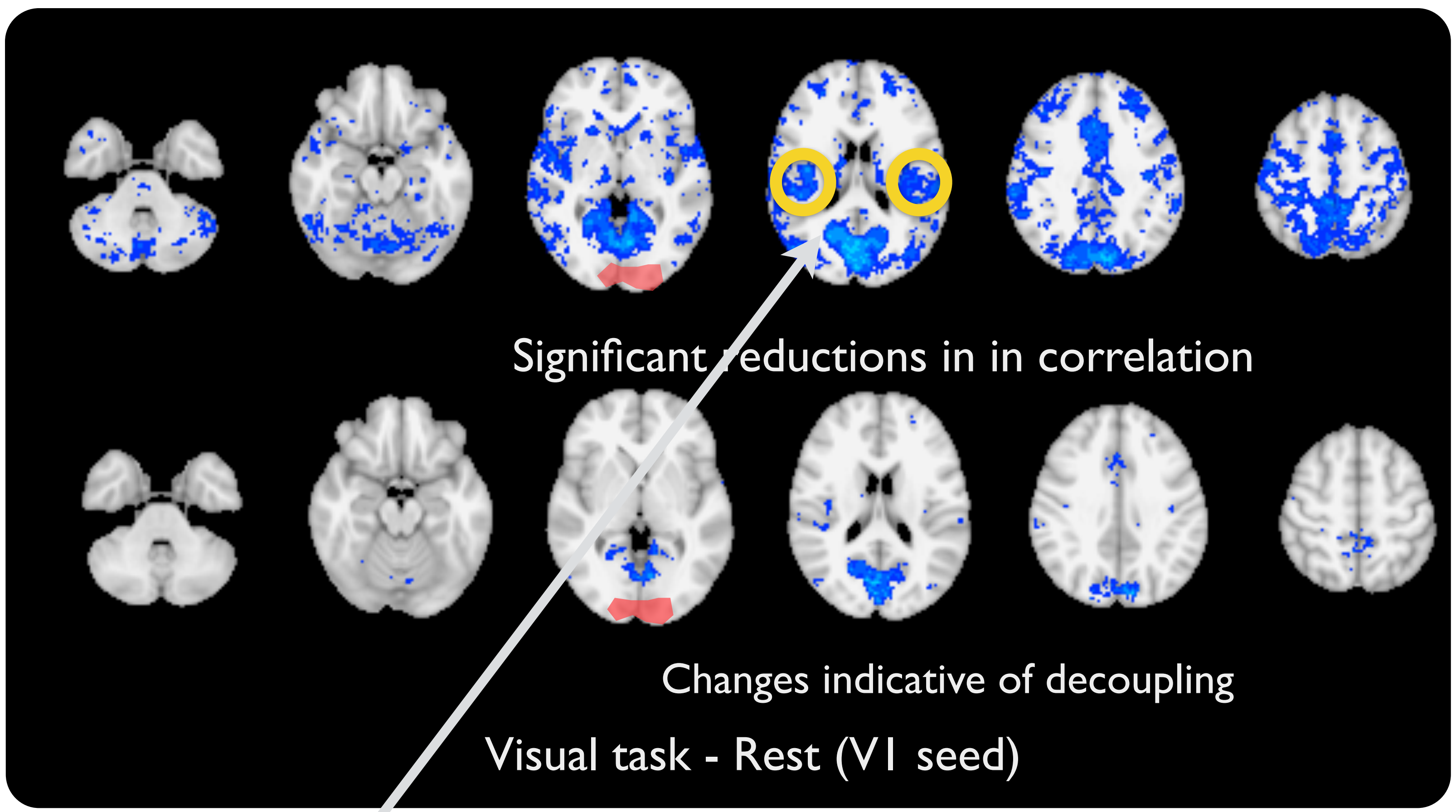
Results



Variance changes from rest for visual

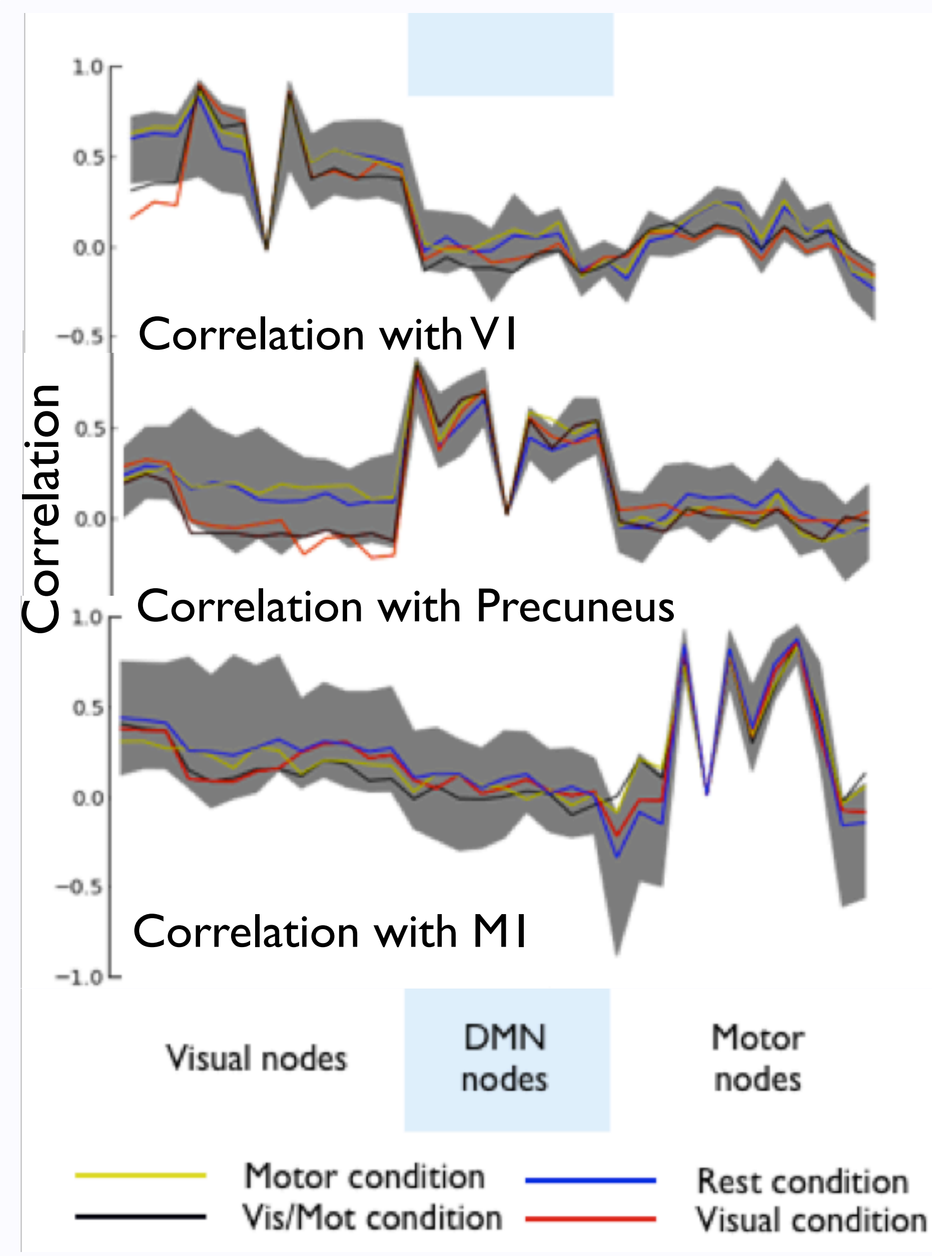


Variance changes from rest for motor

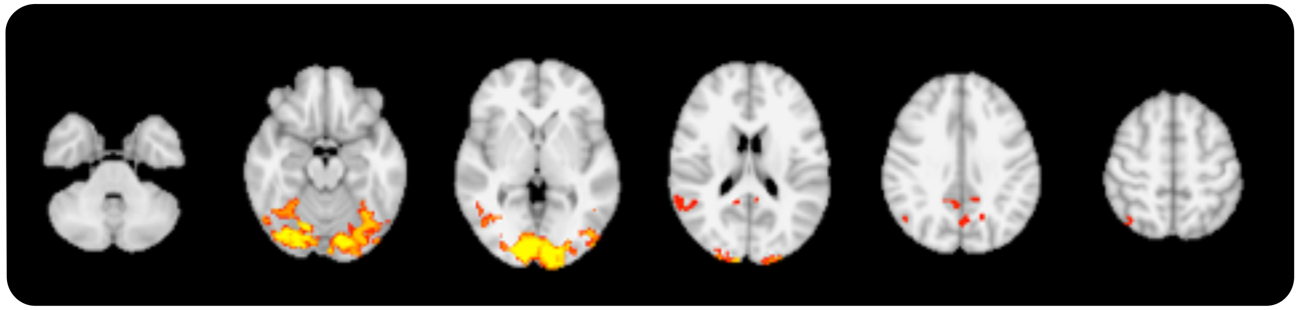


Correlation changes from rest for visual

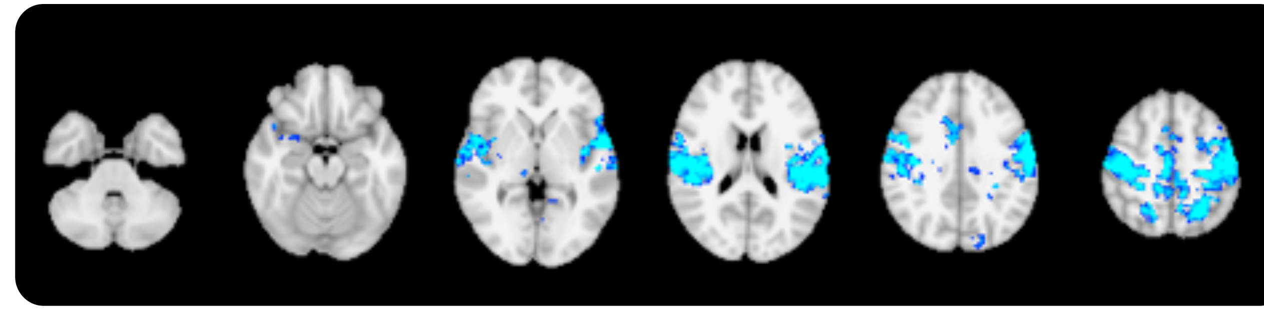
Reduction in shared signal



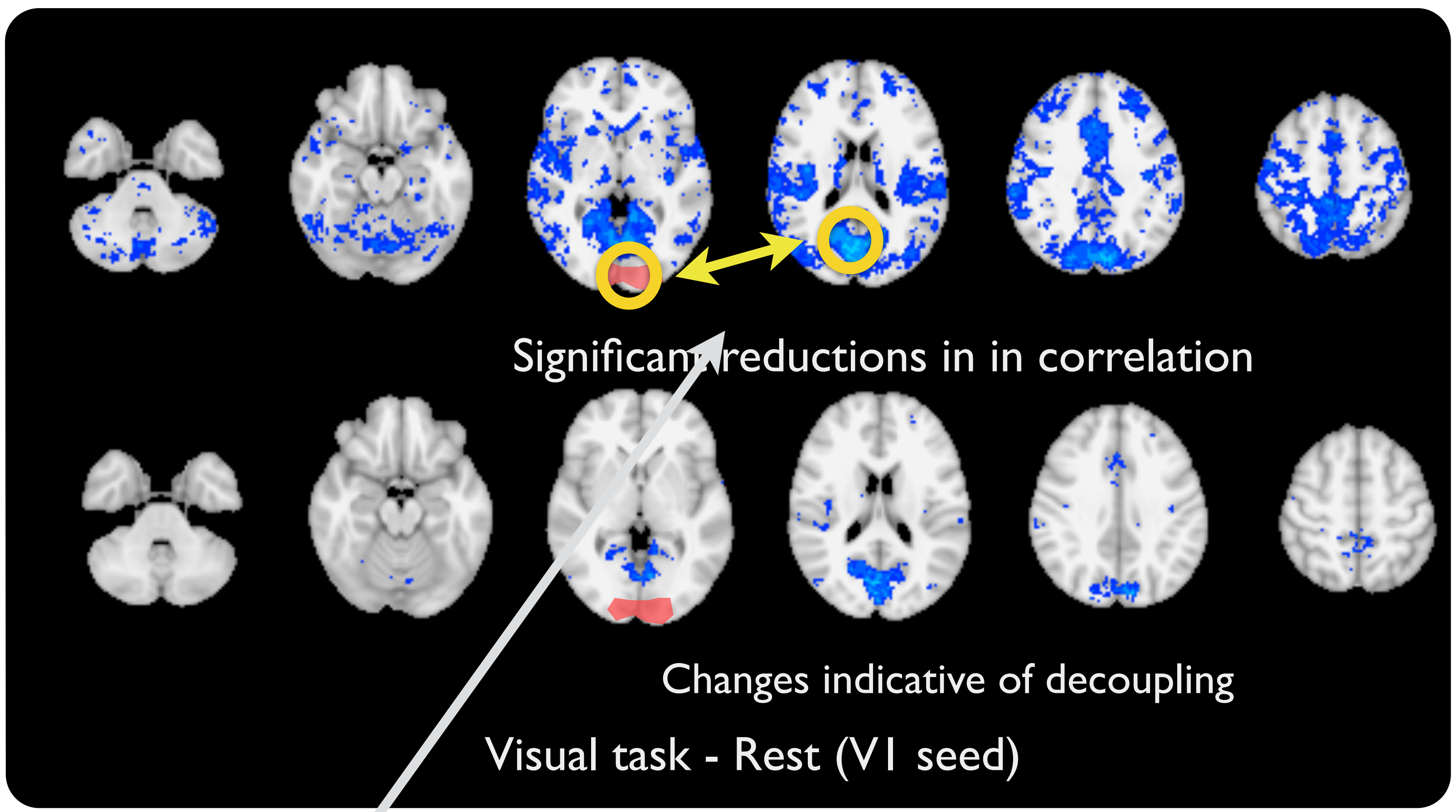
Results



Variance changes from rest for visual

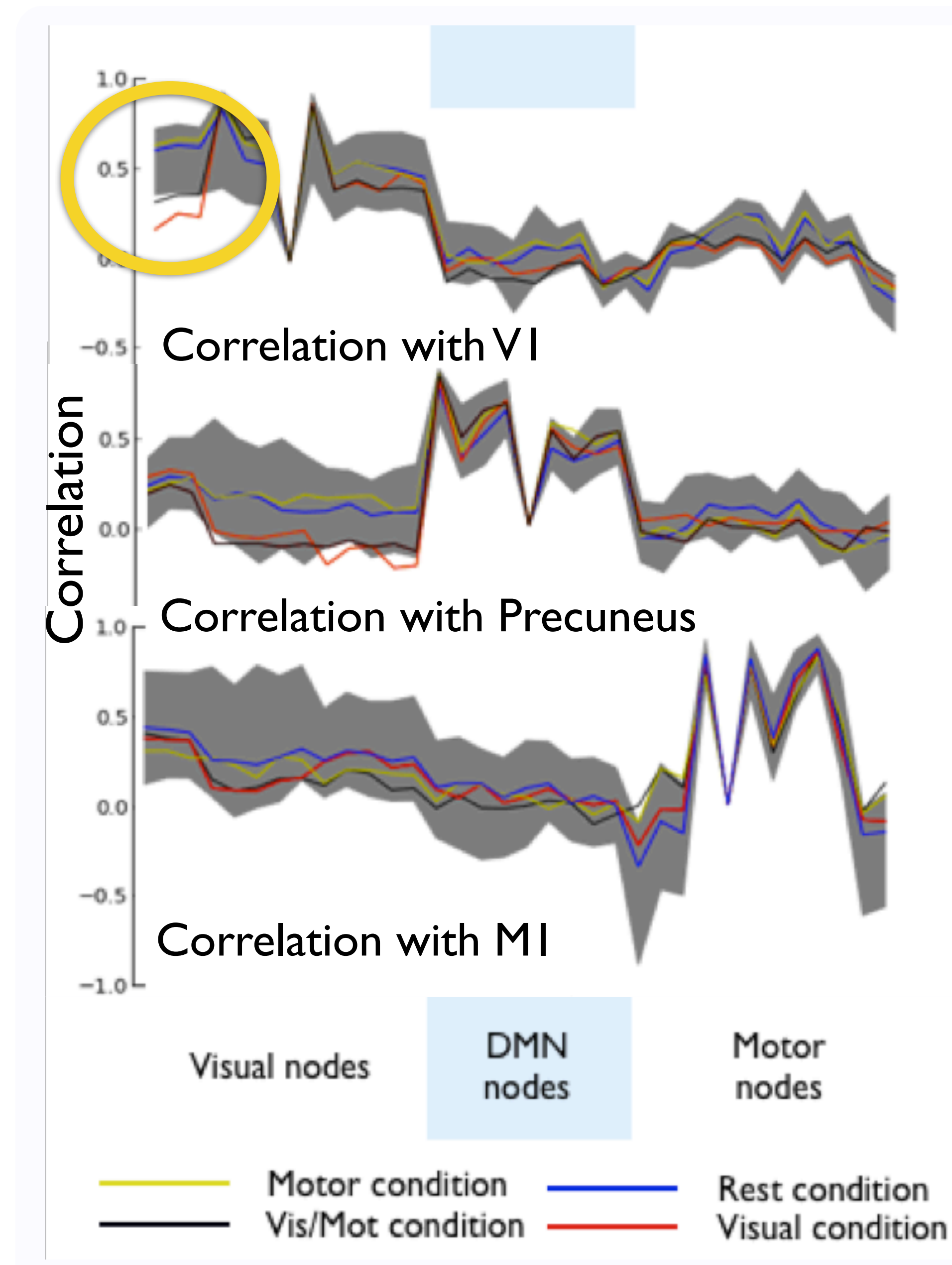


Variance changes from rest for motor



Correlation changes from rest for visual

Decoupling



Summary

We have identified a simple model that links correlation and variance to provides insight into the types of dynamics underlying connectivity changes

In a test dataset we could find almost every proposed feature of dynamics

Most changes in correlation are accompanied by some change in variance

DCM models typically predict variance changes, so are validated by these results

Software is under development

Future directions

Smooth integration with functional connectivity and DCM analyses

More signal components: relationship to ICA?

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