

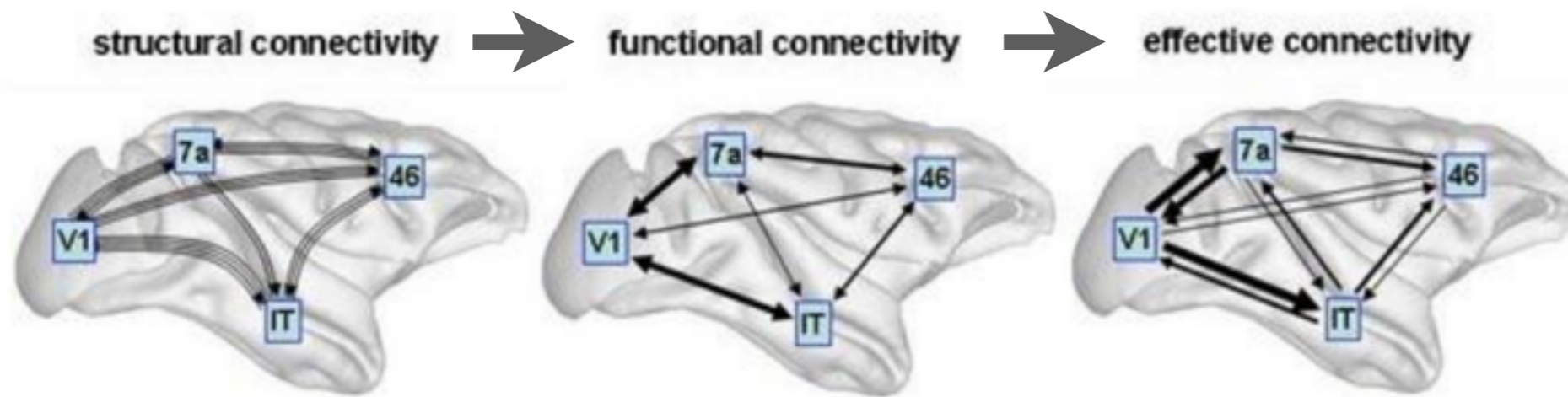
Overcoming confounds and improving the interpretability of connectivity analyses

Eugene Duff

GlaxoSmithKline - Neurophysics Workshop on Skeptical Neuroimaging

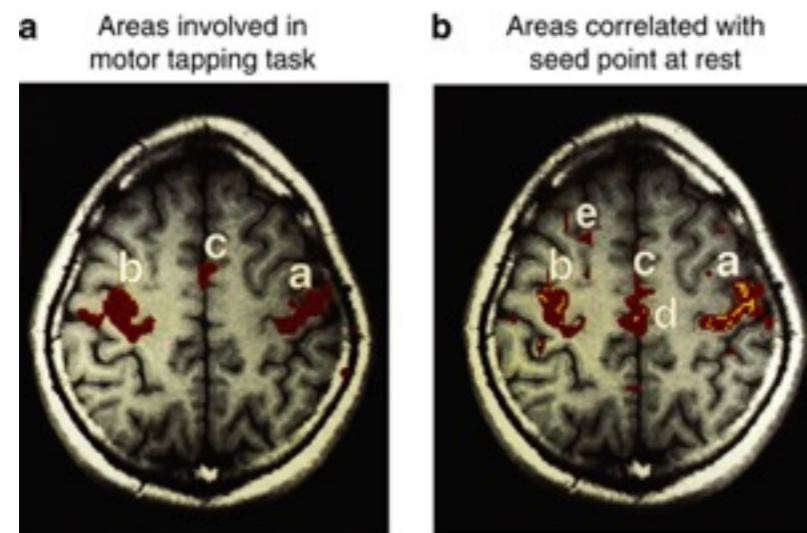


Brain connectivity in neuroimaging

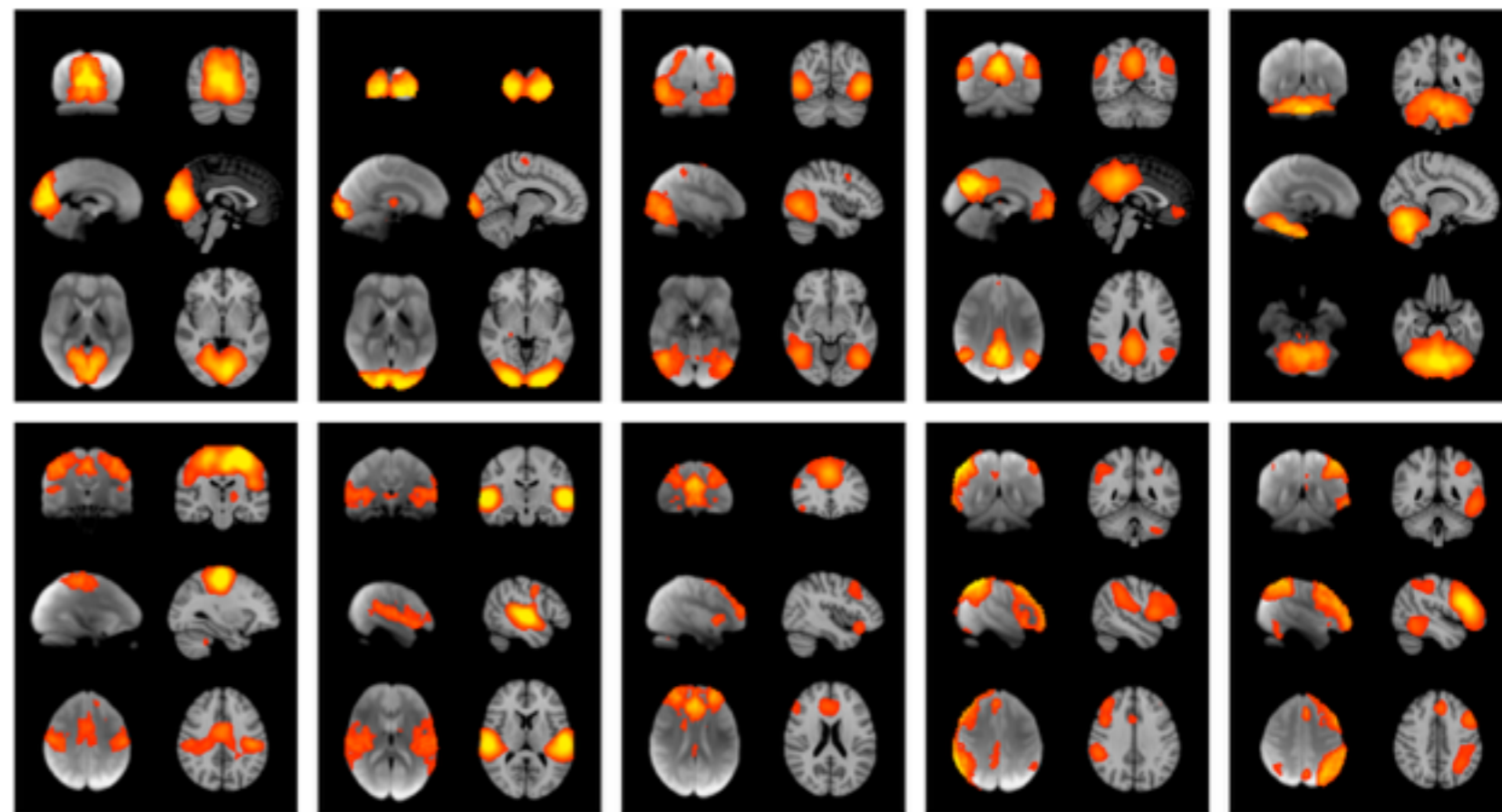


Sporns, 2007
Friston, 1995

Connectivity from uncontrolled fluctuations



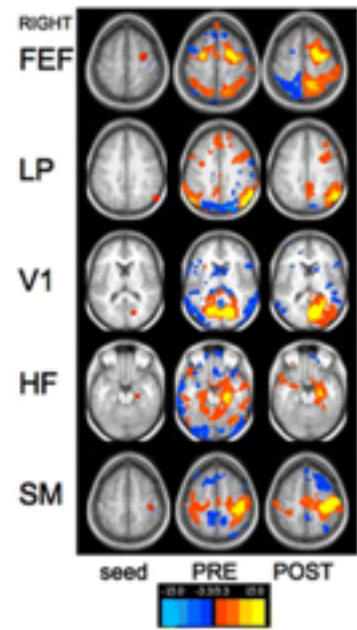
Biswal 1995



Smith 2009

Brain Connectivity from uncontrolled fluctuations

Functional connectivity analyses



Johnstone JM 2008

Seed region

Distinct patterns of brain activity in young carriers of the APOE-ε4 allele

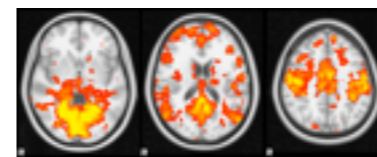
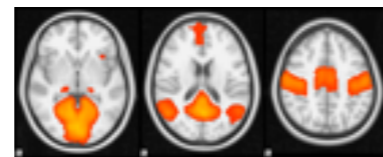
Nicola Filippi^{1,2,3,4}, Bradley J. MacIntosh⁵, Morgan G. Hough⁶, Guy M. Goodwin⁷, Giovanni B. Frisoni⁸, Stephen M. Smith⁹, Paul M. Matthews^{4,6}, Christian F. Beckmann^{4,6}, and Clare E. Mackay^{4,3,1}

¹University Department of Psychiatry and ²Functional Magnetic Resonance Imaging of the Brain Centre, University of Oxford, Oxford OX3 9DU, United Kingdom; ³Laboratory of Epidemiology, Neuroimaging, and Telemedicine, Istituto di Ricovero e Cura a Carattere Scientifico San Giovanni di Dio Fatebenefratelli, Brescia 25125, Italy; ⁴Cisaxom/InKine Research and Development, Clinical Imaging Centre, London W12 0NN, United Kingdom; ⁵Department of Clinical Neuroscience, Imperial College, Hammersmith Campus London W12 0NN, United Kingdom

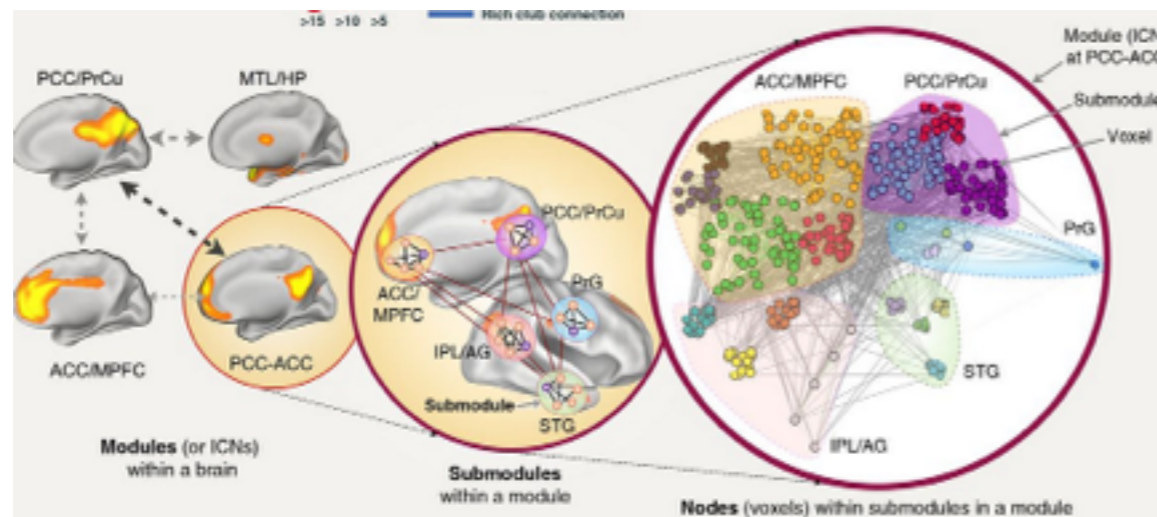
Edited by Robert W. Mahley, The J. David Gladstone Institutes, San Francisco, CA, and approved March 6, 2009 (received for review November 25, 2008)

The APOE ε4 allele is a risk factor for late-life pathological changes that is also associated with anatomical and functional brain changes in middle-aged and elderly healthy subjects. We investigated structural and functional effects of the APOE polymorphism in 18 young healthy APOE ε4-carriers and 18 matched noncarriers (age range: 20–35 years). Brain activity was studied both at rest and during an encoding memory paradigm using blood oxygen level-dependent fMRI. Resting fMRI revealed increased “default mode network” (involving retrosplenial, medial temporal, and medial-prefrontal cortical areas) coactivation in ε4-carriers relative to noncarriers. The encoding task produced greater hippocampal activation in ε4-carriers relative to noncarriers. Neither result could be explained by differences in memory performance, brain morphology, or resting cerebral blood flow. The APOE ε4 allele modulates brain function decades before any clinical or neurophysiological expression of neurodegenerative processes.

fMRI studies have tested for early life associations of the APOE polymorphism with changes in brain function. Filbey et al. (18) reported greater activation in 8 APOE ε4-carriers compared with 8 noncarriers during a working memory task. Both studies reported greater brain activity in ε4-carriers relative to noncarriers. Here, we used structural and functional MRI to investigate the APOE ε4-carrier to 35 years of age. We found that ε4-carriers showed greater spontaneous activity relative to noncarriers in the default mode network (DMN) and state networks” (RSNs), and they reflect intrinsic properties of functional brain organization (21). We were specifically inter-



Dual Regression



Analysis of graph theoretic measures

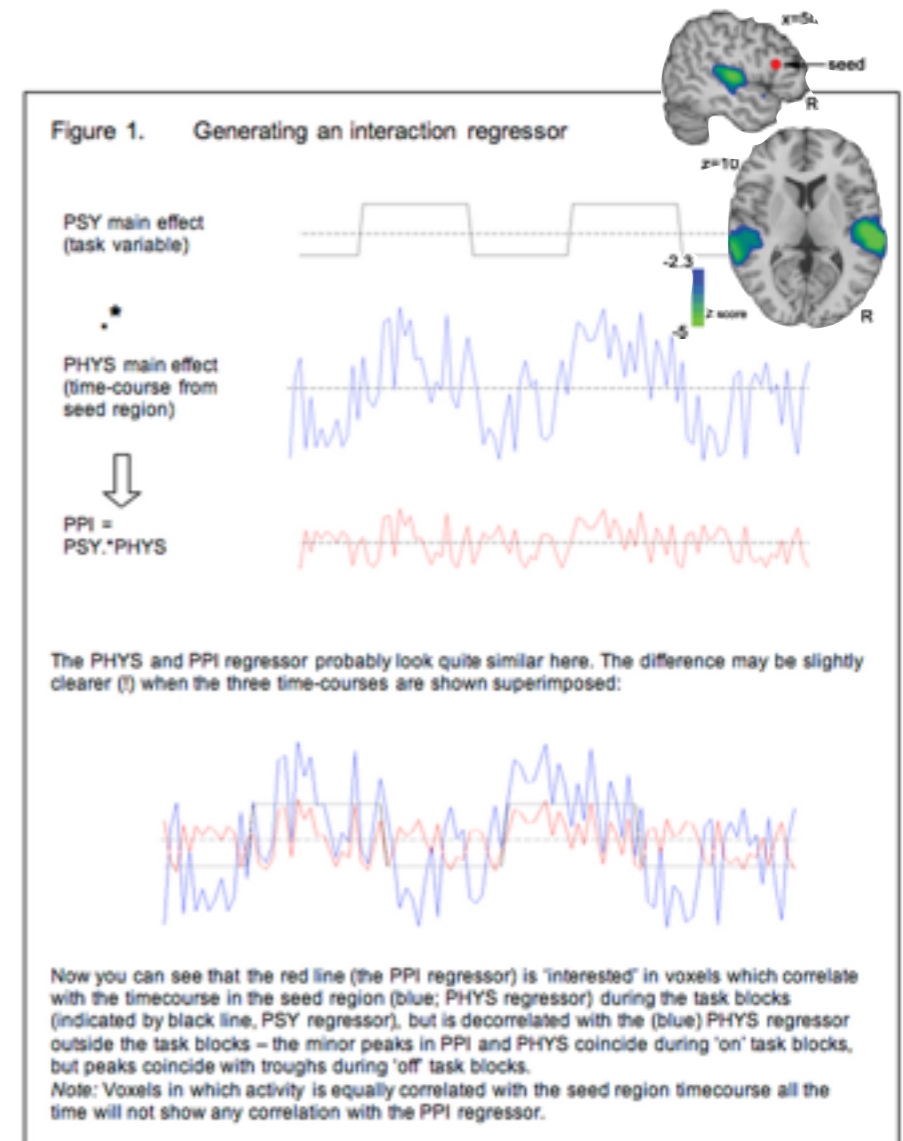
Psychophysiological and Modulatory Interactions in Neuroimaging

K. J. Friston,^{1,2} C. Büchel,³ G. R. Fink,⁴ J. Morris,⁵ E. Rolls,⁶ and R. J. Dolan^{1,2}

¹Wellcome Department of Cognitive Neurology, London, United Kingdom; ²Department of Psychology, Oxford University, Oxford, United Kingdom; and ³Royal Free Hospital School of Medicine, London, United Kingdom

Received February 19, 2007

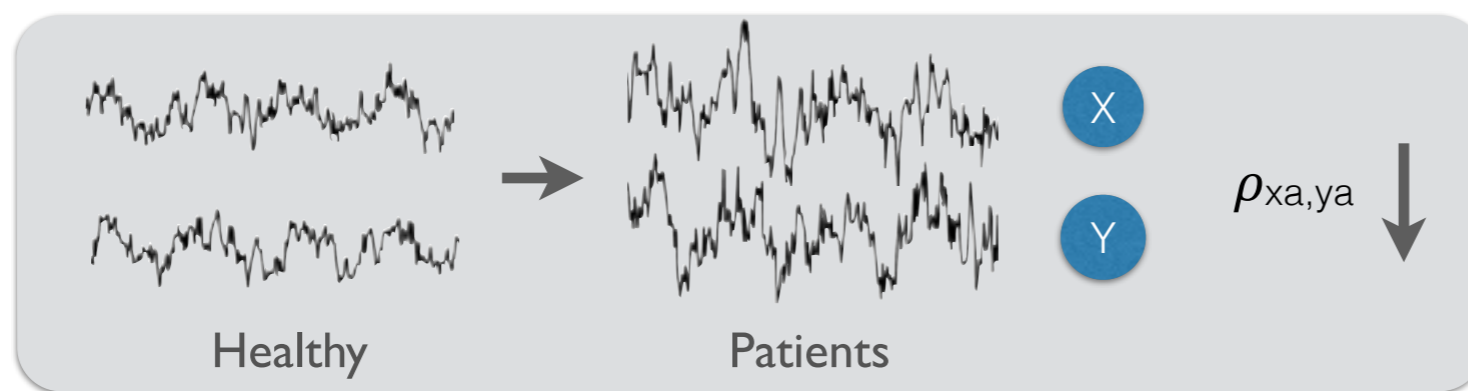
Psychophysiological interaction



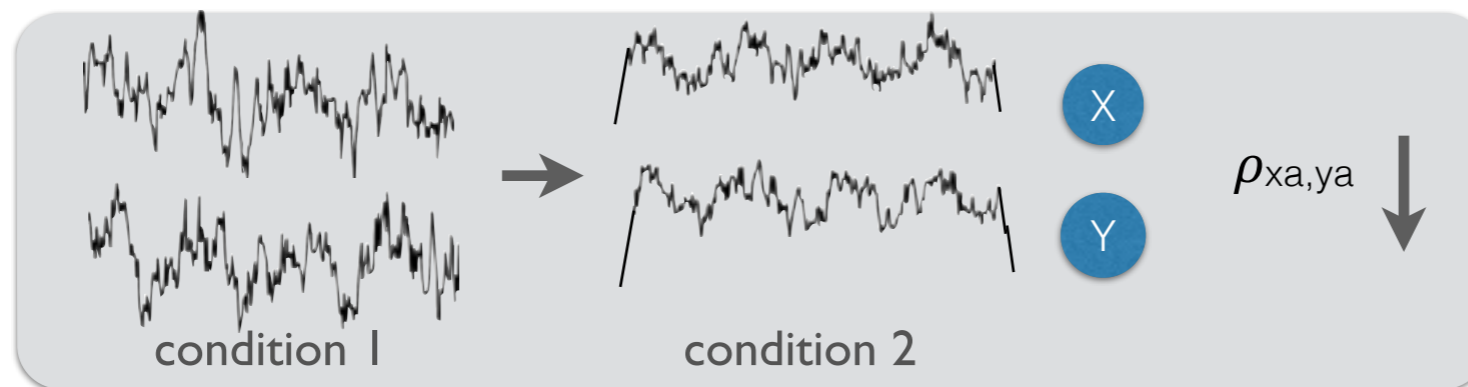
Psycho-physiological interactions

Reasons for skepticism..

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



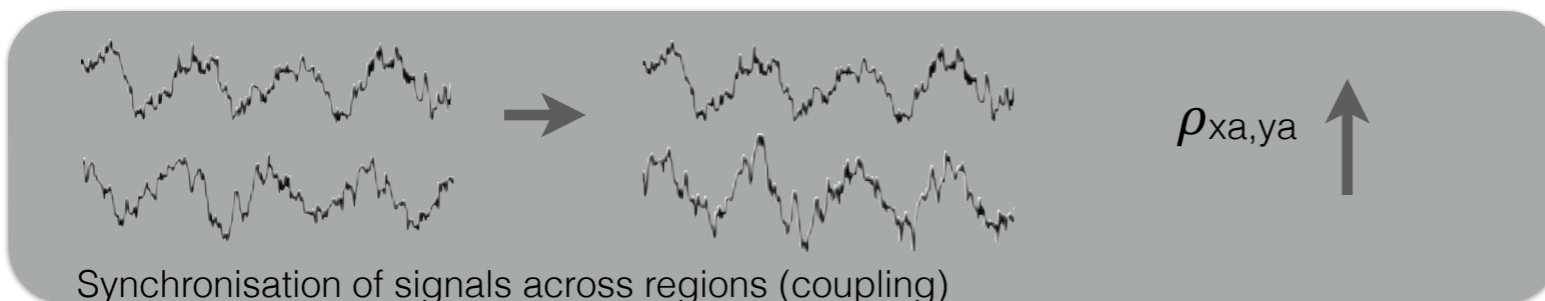
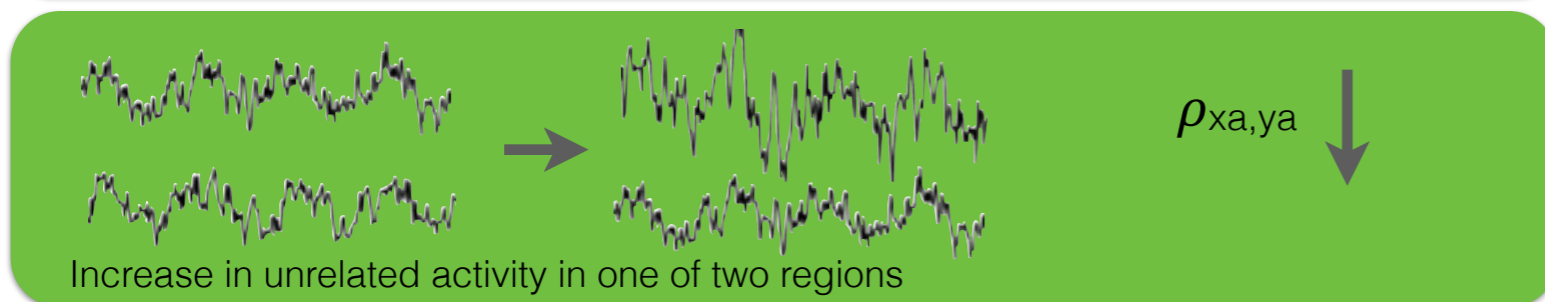
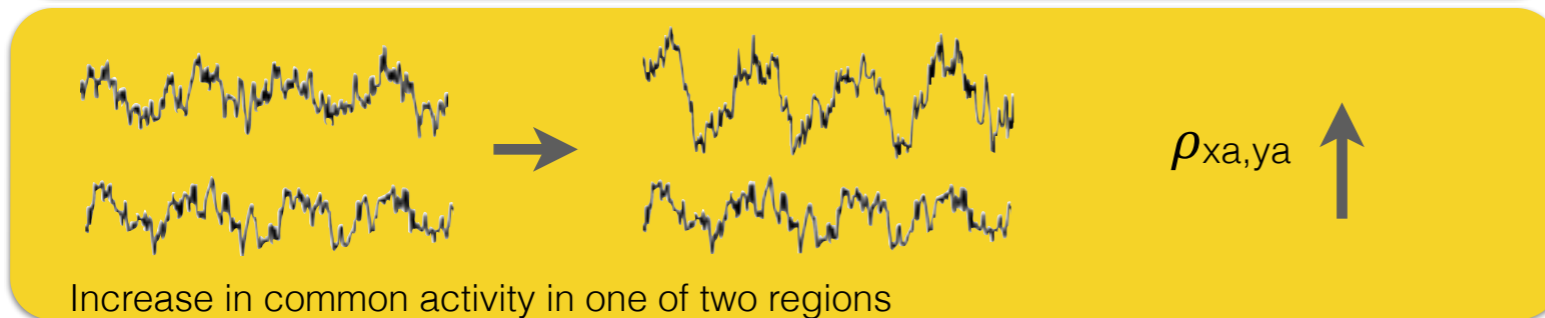
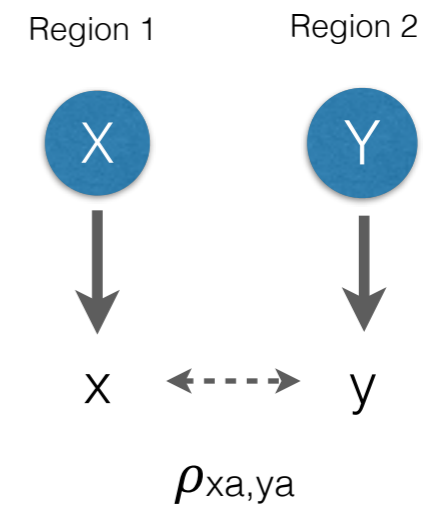
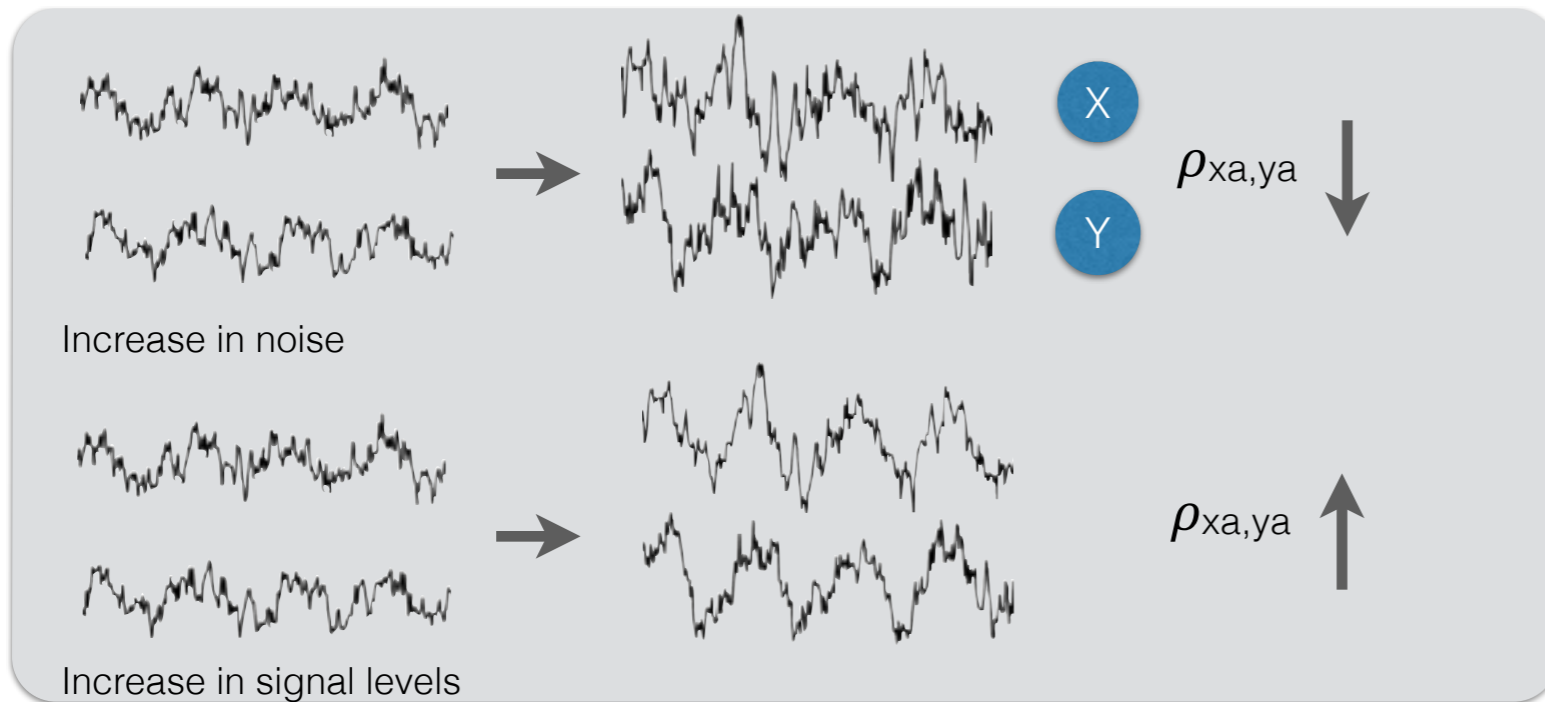
Differences in patient groups (e.g. vascular tone)



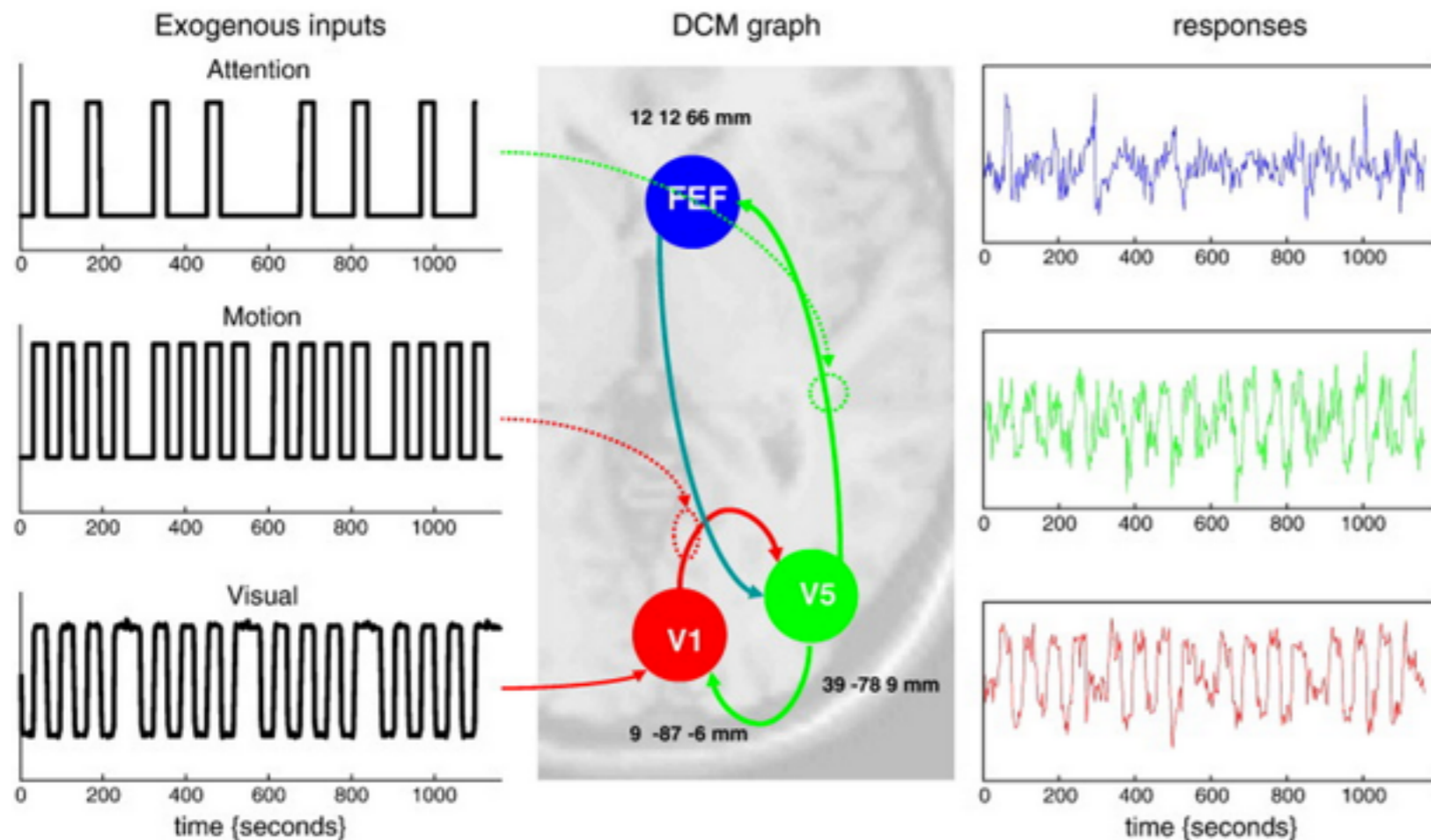
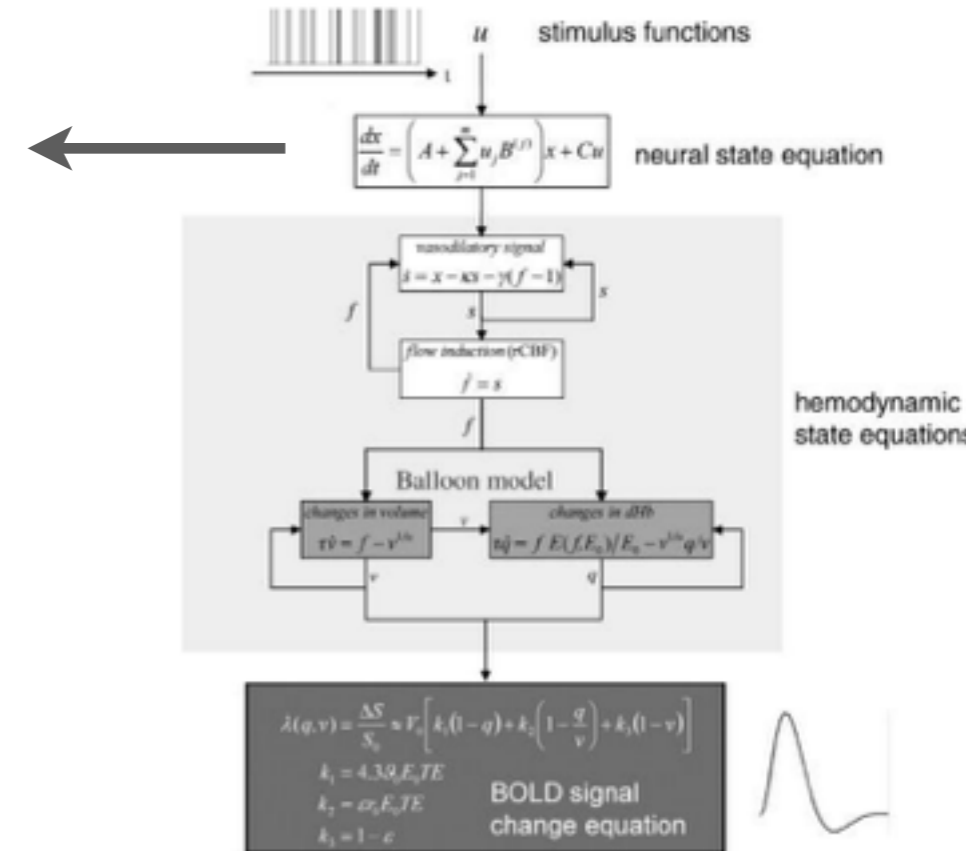
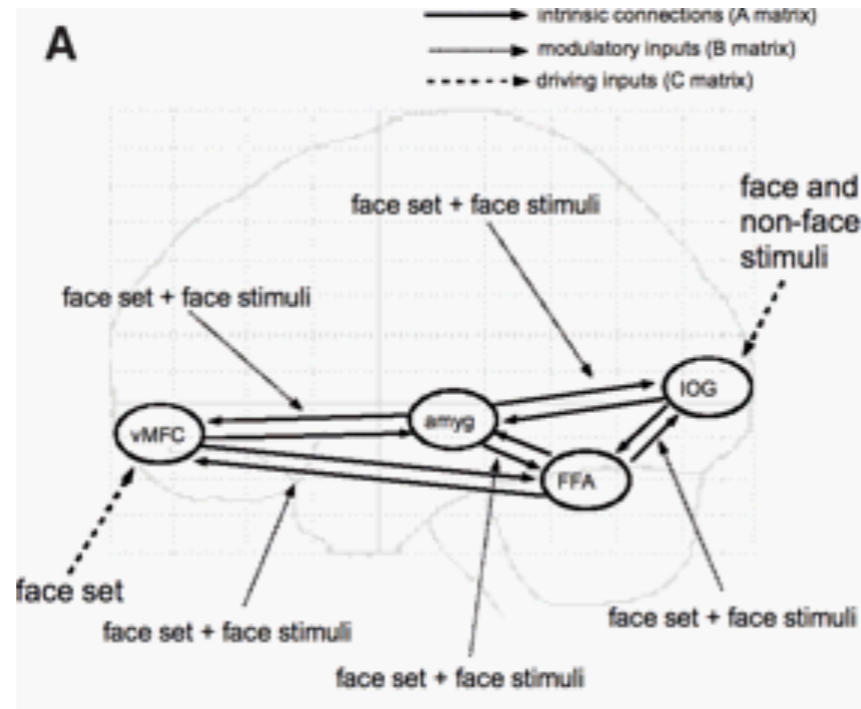
Differences across activation states (e.g. BOLD ceiling)

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

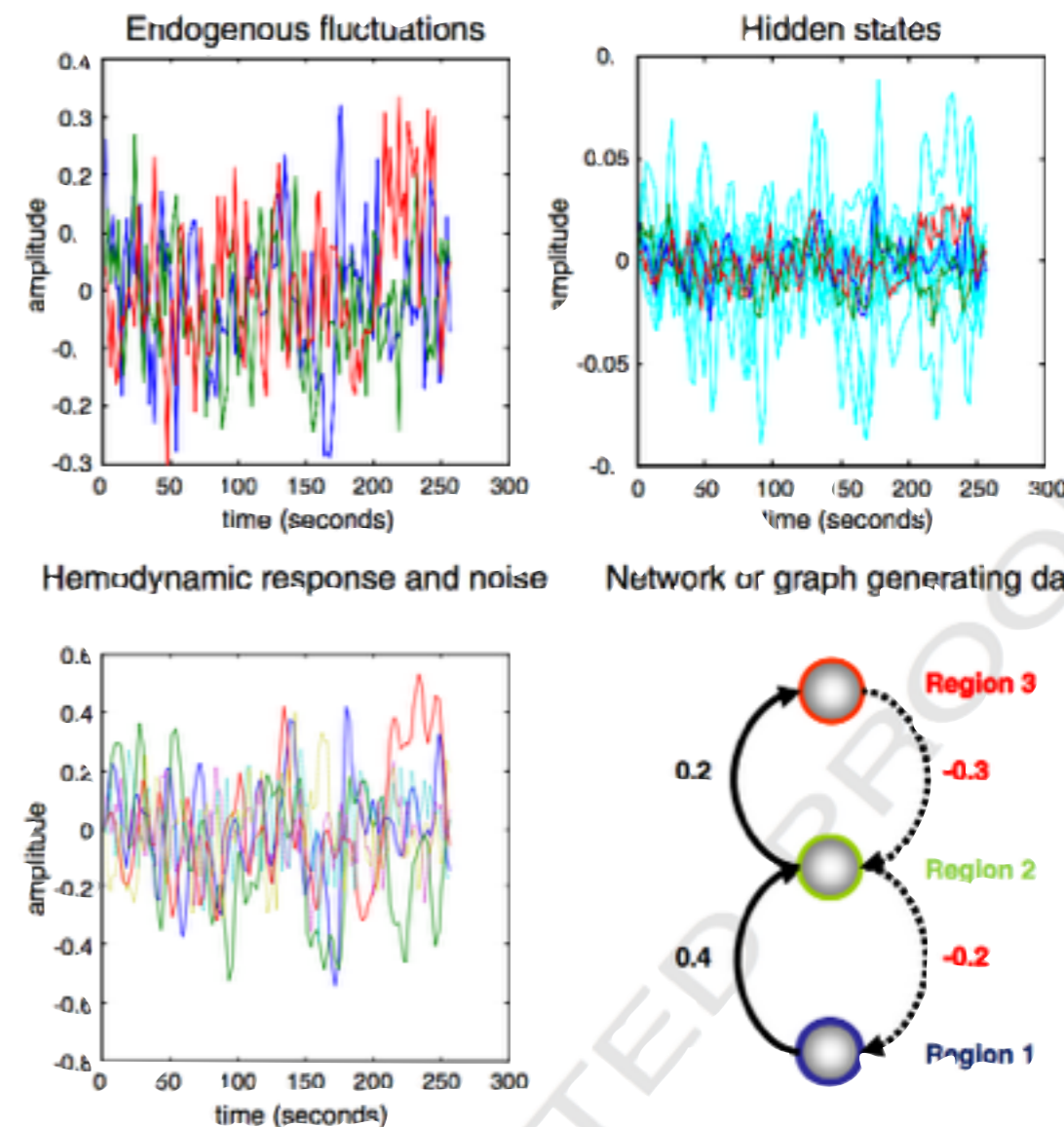
Recent alternate approach uses deterministic model using on cross-spectra of time series.

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.



DCM of random fluctuations

Stochastic DCM: models endogenous stochastic fluctuations

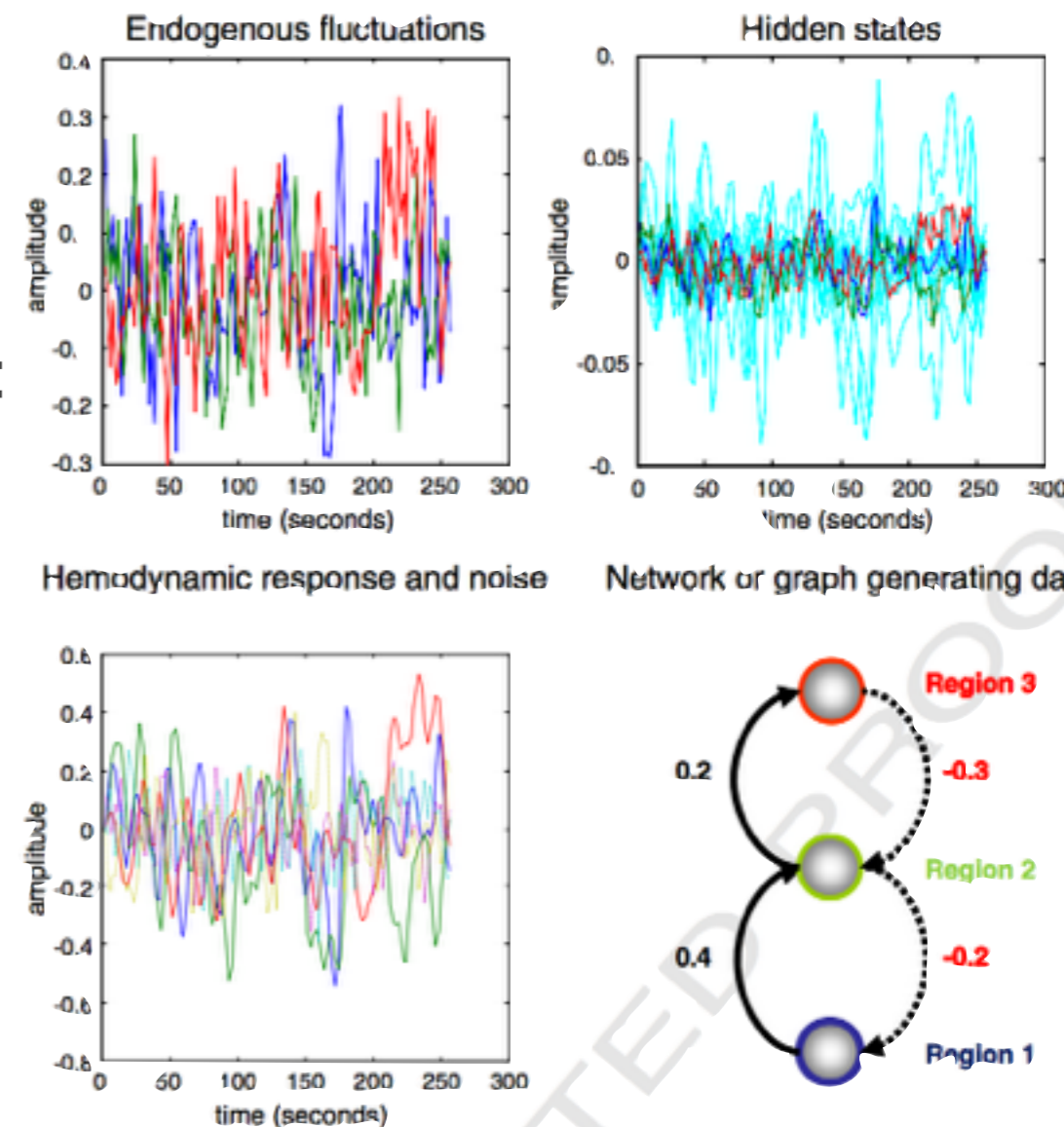
- Variational Bayesian generalised filtering estimation
- Communicated dynamics are modelled to have low frequency dynamics

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

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



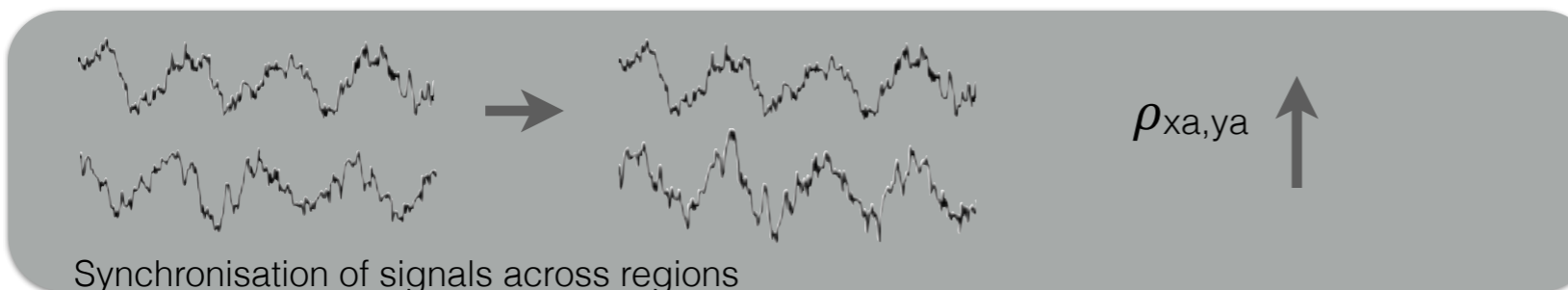
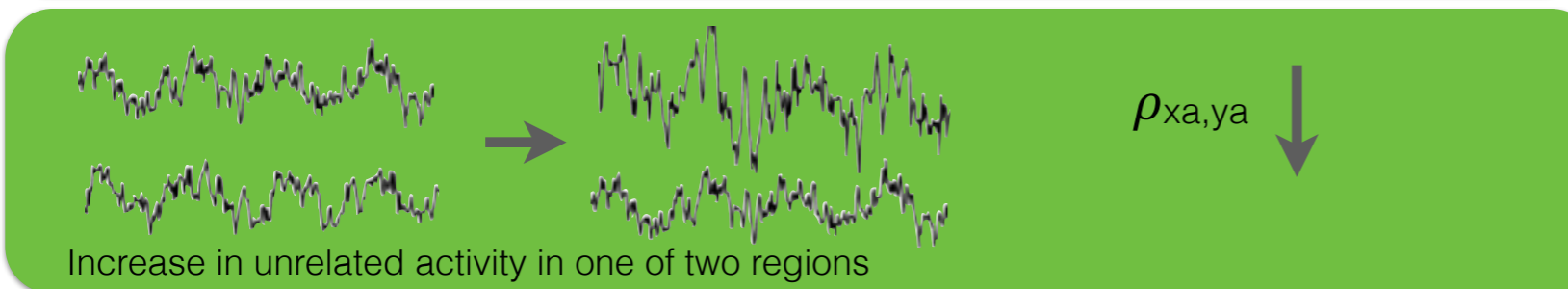
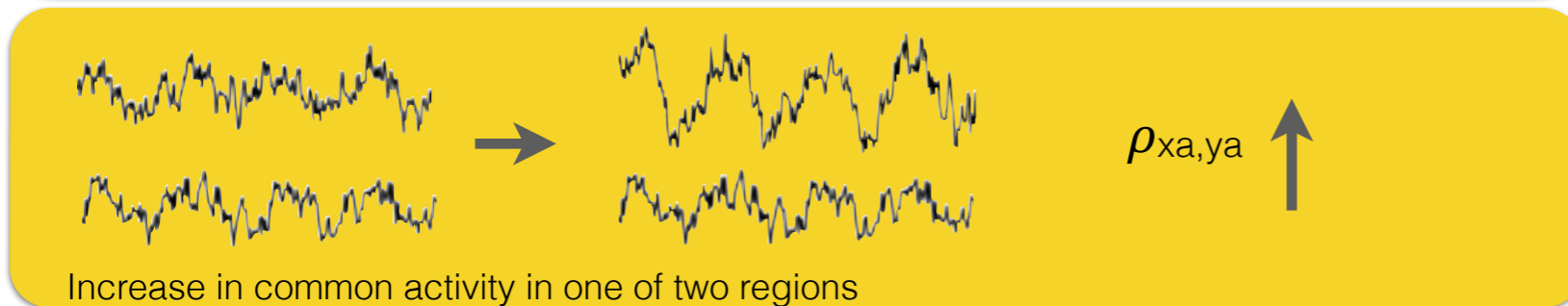
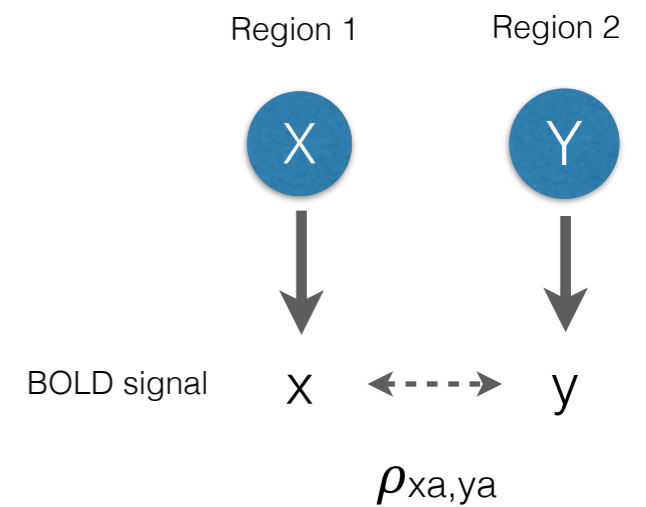
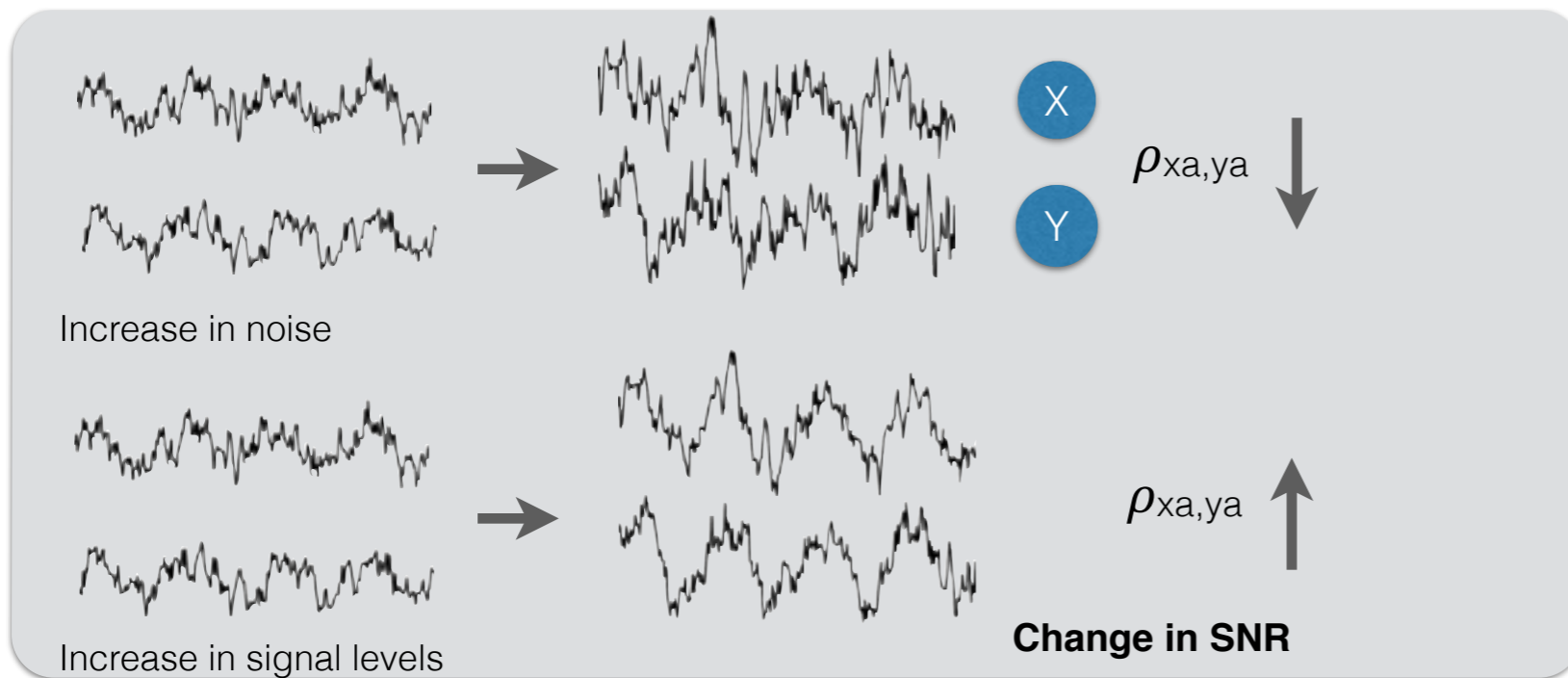
Goal

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

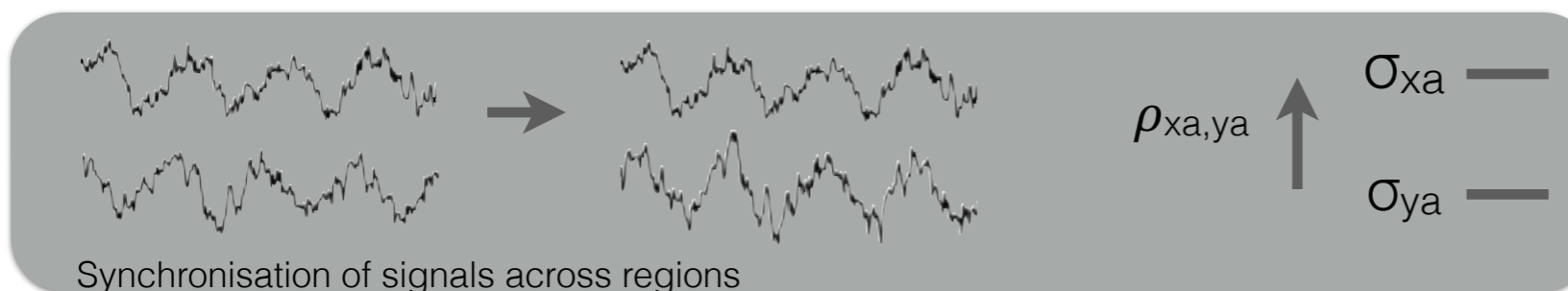
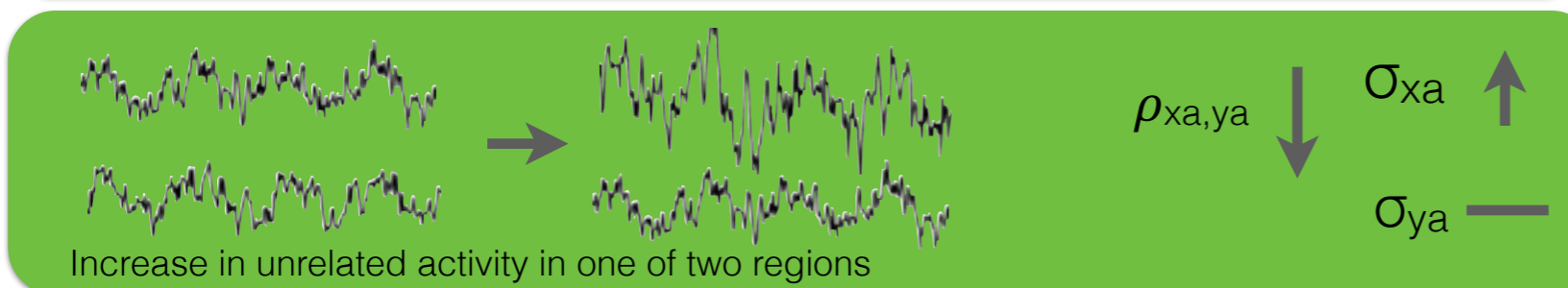
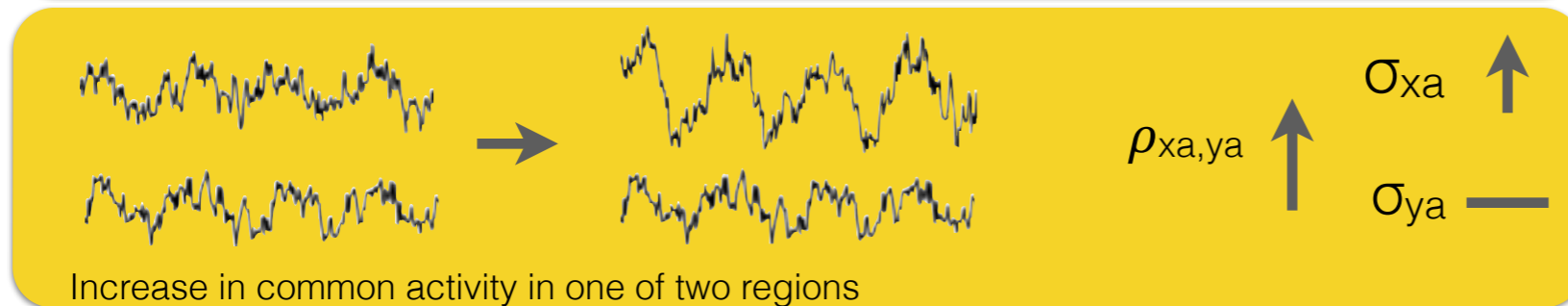
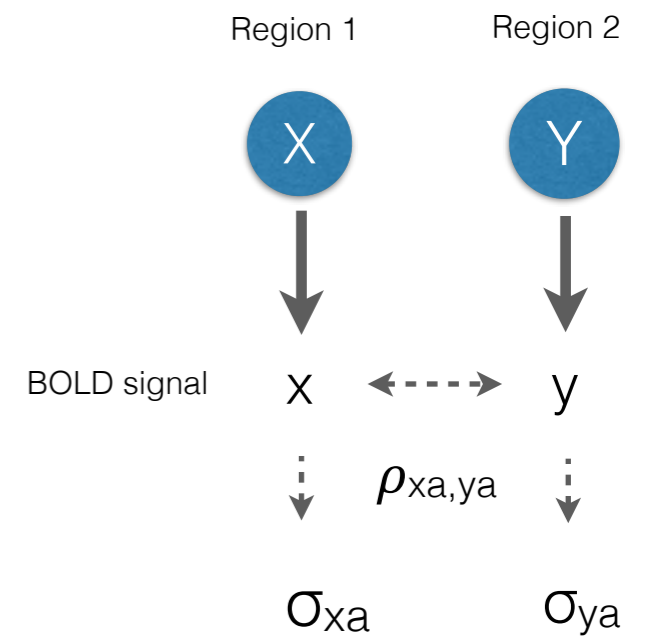
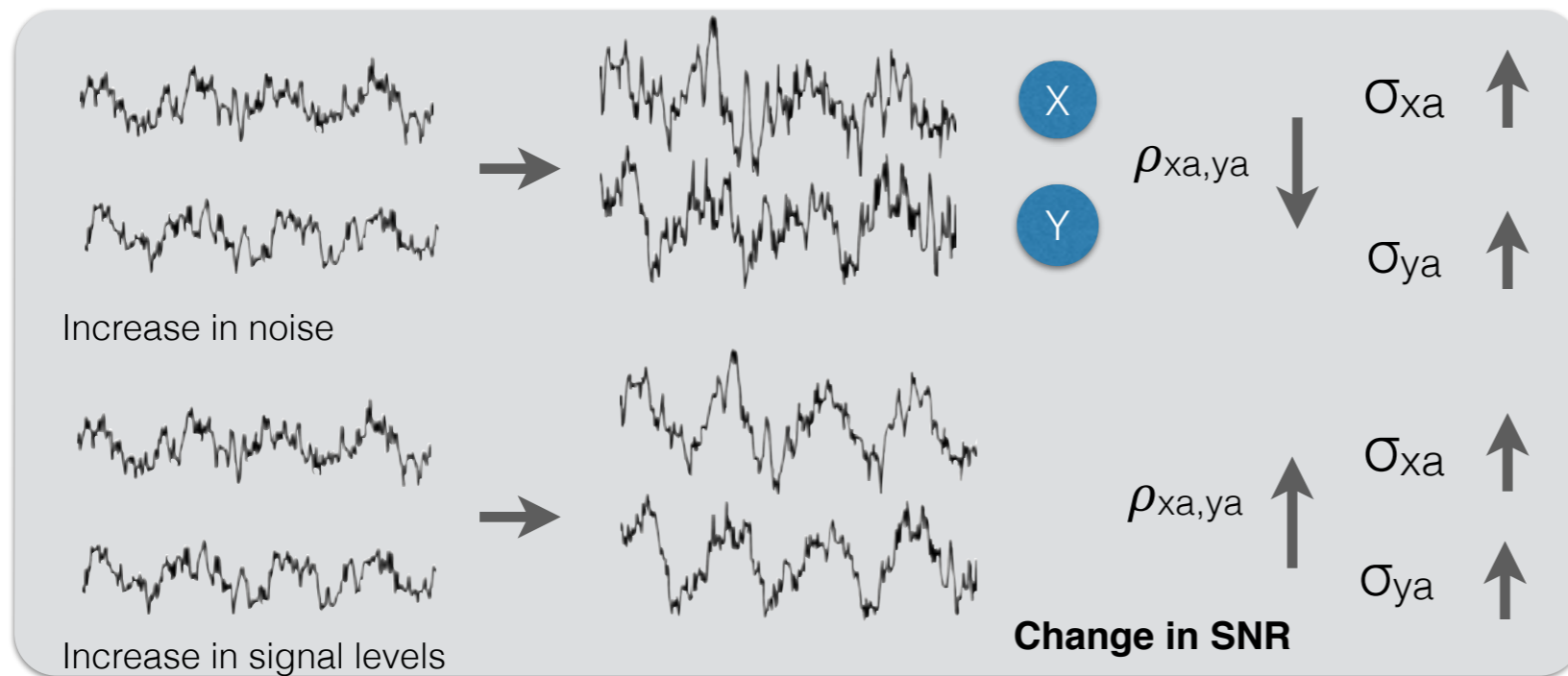
Strategy:

Focus on identification of types of pairwise changes in relationship

Basic features of dynamics affecting connectivity

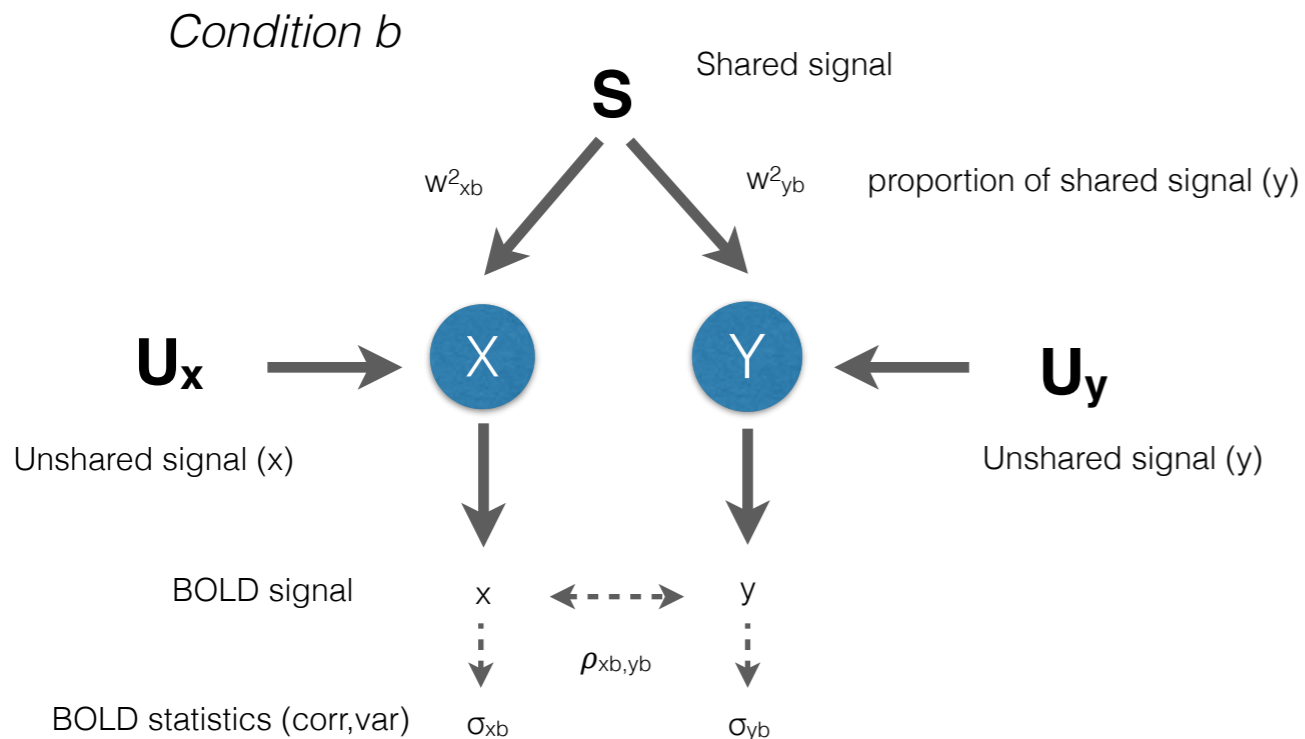
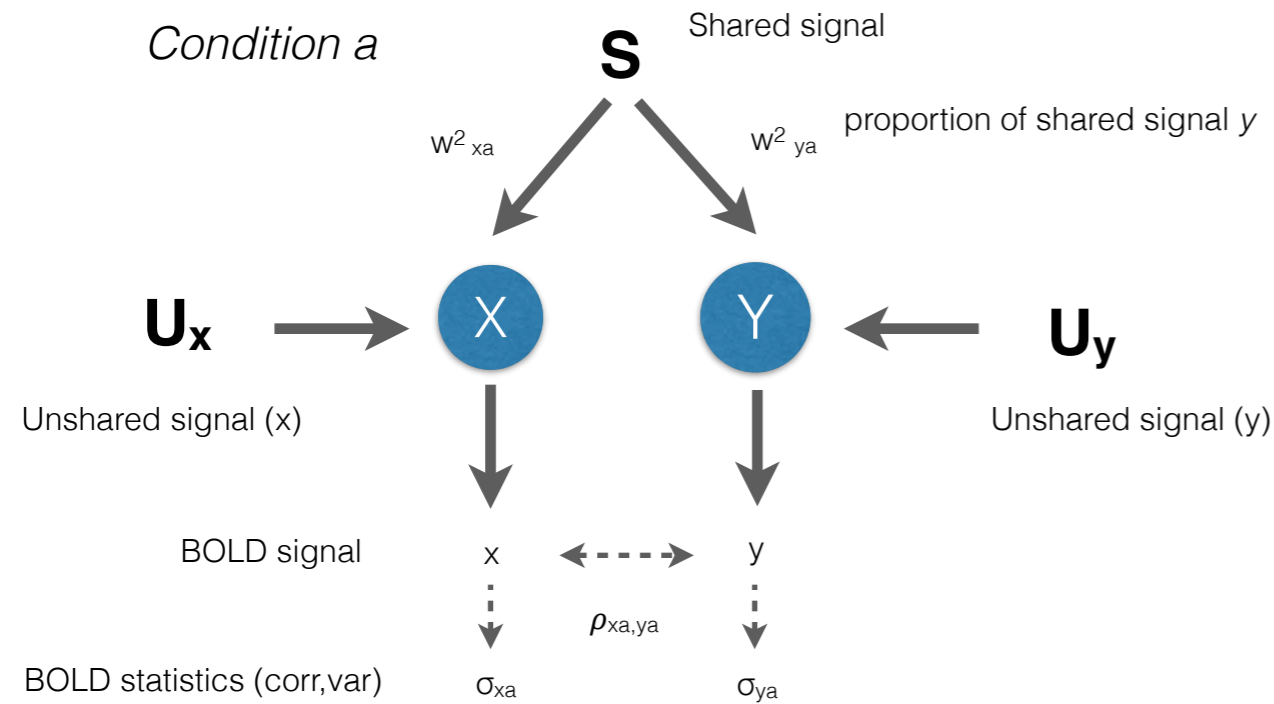


Basic features of dynamics affecting connectivity



Shared/Unshared Signal Model

Pairwise model linking regions X and Y.



Model Formulation

BOLD signal for condition a as a function of S and U_x U_y.

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

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

Proportion of shared signal in each region is bounded by correlation

$$\rho_{x_a,y_a} = \frac{COV(x_a, y_a)}{\sigma_{x_a} \sigma_{y_a}} \quad (3)$$

$$\rho_{x_a,y_a} = \frac{w_{x_a} \sigma_{x_a} w_{y_a} \sigma_{y_a}}{\sigma_{x_a} \sigma_{y_a}} \quad (4)$$

$$\rho_{x_a,y_a} = w_{x_a} w_{y_a} \rightarrow \rho_a < w_{x_a} < 1 \quad (5)$$

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:

$$x_b = \sigma_{x_b} (c_x w_{x_a} S + u_x \sqrt{1 - w_{x_a}^2} \cdot U_x) \quad (6)$$

$$= \sigma_{x_b} \left(\frac{\sigma_{x_a} c_x w_{x_a}}{\sigma_{x_b}} S + \frac{\sigma_{x_a} u_x \sqrt{1 - w_{x_a}^2}}{\sigma_{x_b}} \cdot U_x \right)$$

New observed variance can be expressed:

$$\sigma_{x_b}^2 = \sigma_{x_a}^2 (c_x^2 w_{x_a}^2 + u_x^2 (1 - w_{x_a}^2)) \quad (7)$$

ρ_{x_b,y_b} can be expressed in terms of $\sigma_{x_a}, \sigma_{x_b}, \sigma_{y_a}, \sigma_{y_b}, w_{x_a}$, and u_x

$$\rho_b = \rho_a \frac{\sigma_{x_a} \sigma_{y_a} c_x c_y}{\sigma_{x_b} \sigma_{y_b}} \quad (8)$$

$$= \rho_a \frac{\sigma_{x_a} \sigma_{y_a}}{\sigma_{x_b} \sigma_{y_b}} \sqrt{\frac{\sigma_{x_b}^2}{\sigma_{x_a}^2} - u_x^2 (1 - w_{x_a}^2)} \cdot \frac{1}{w_{x_a}} \sqrt{\frac{\sigma_{y_b}^2}{\sigma_{y_a}^2} - u_y^2 (1 - w_{y_a}^2)} \cdot \left| \frac{w_{x_a}}{\rho_a} \right| \quad (9)$$

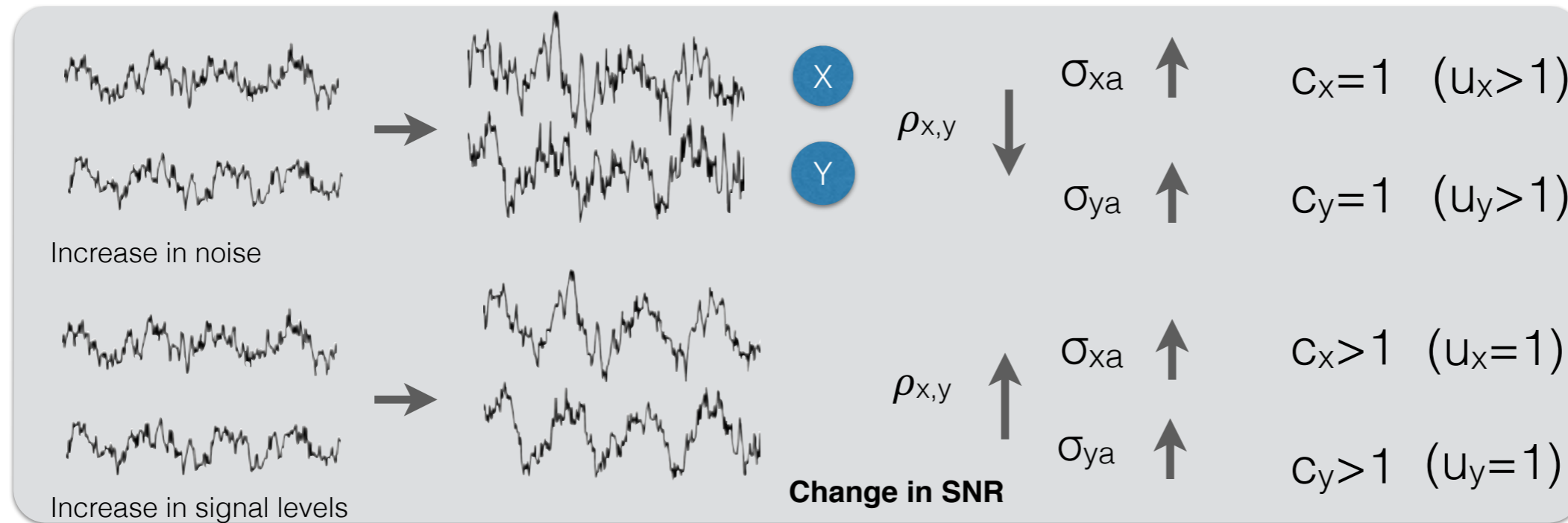
$$= \text{sign}(\rho_a) \sqrt{1 - \frac{\sigma_{x_a}^2}{\sigma_{x_b}^2} (u_x^2 - w_{x_a}^2)} \sqrt{1 - \frac{\sigma_{y_a}^2}{\sigma_{y_b}^2} (u_y^2 - \frac{\rho_a^2}{w_{x_a}^2})} \quad (10)$$

Given the limits on w_{x_a} , maximum effects of particular changes in signal and noise on ρ_{x_b,y_b} can be determined based on variance changes. E.g. if there was no change in signal levels:

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

Determining possibility of different changes

$$\rho_{x_a, y_a} \quad \sigma_{x_a}, \sigma_{x_b} \quad \sigma_{y_a}, \sigma_{y_b}, \quad \longrightarrow \quad \rho_{x_b, y_b}$$



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

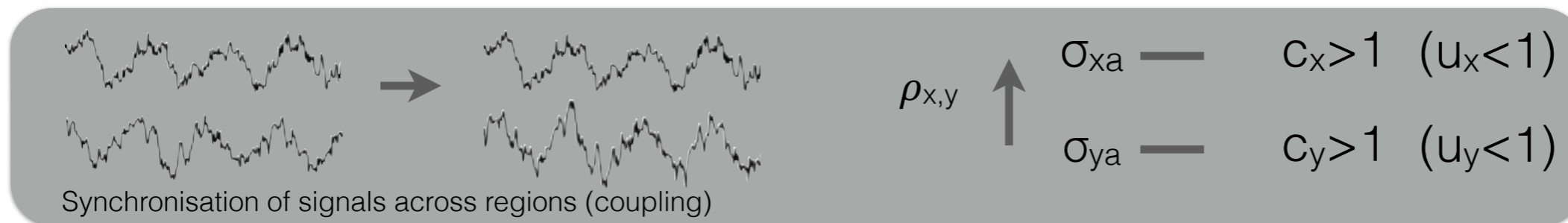


$$\max(\rho_b) = \text{sign}(\rho_a) \sqrt{1 - m(1 - \rho_a^2)}$$

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

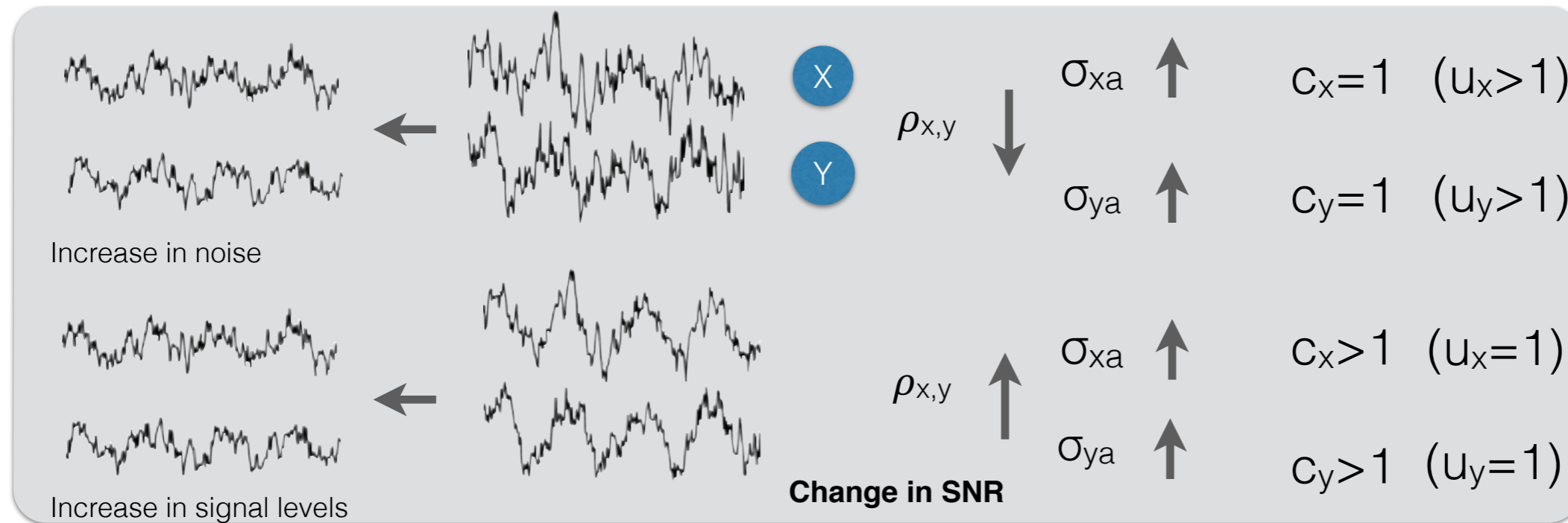


$$\rho_b = \rho_a \frac{\sigma_{x_a} \sigma_{y_a}}{\sigma_{x_b} \sigma_{y_b}}$$



Determining possibility of different changes

$$\rho_{xb,yb} \quad \sigma_{xa}, \sigma_{xb} \quad \sigma_{ya}, \sigma_{yb}, \quad \longrightarrow \quad \rho_{xa,ya}$$

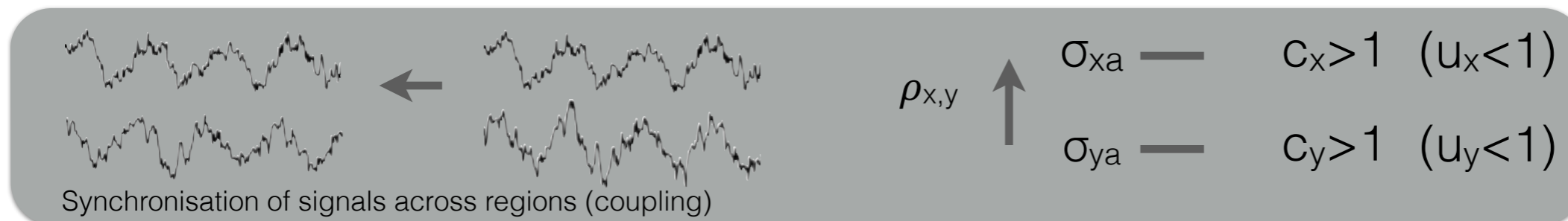


$$\rho_a \frac{\sigma_{ya}}{\sigma_{yb}} < w_{xa} < \min\left(\frac{\sigma_{xb}}{\sigma_{xa}}, 1\right)$$

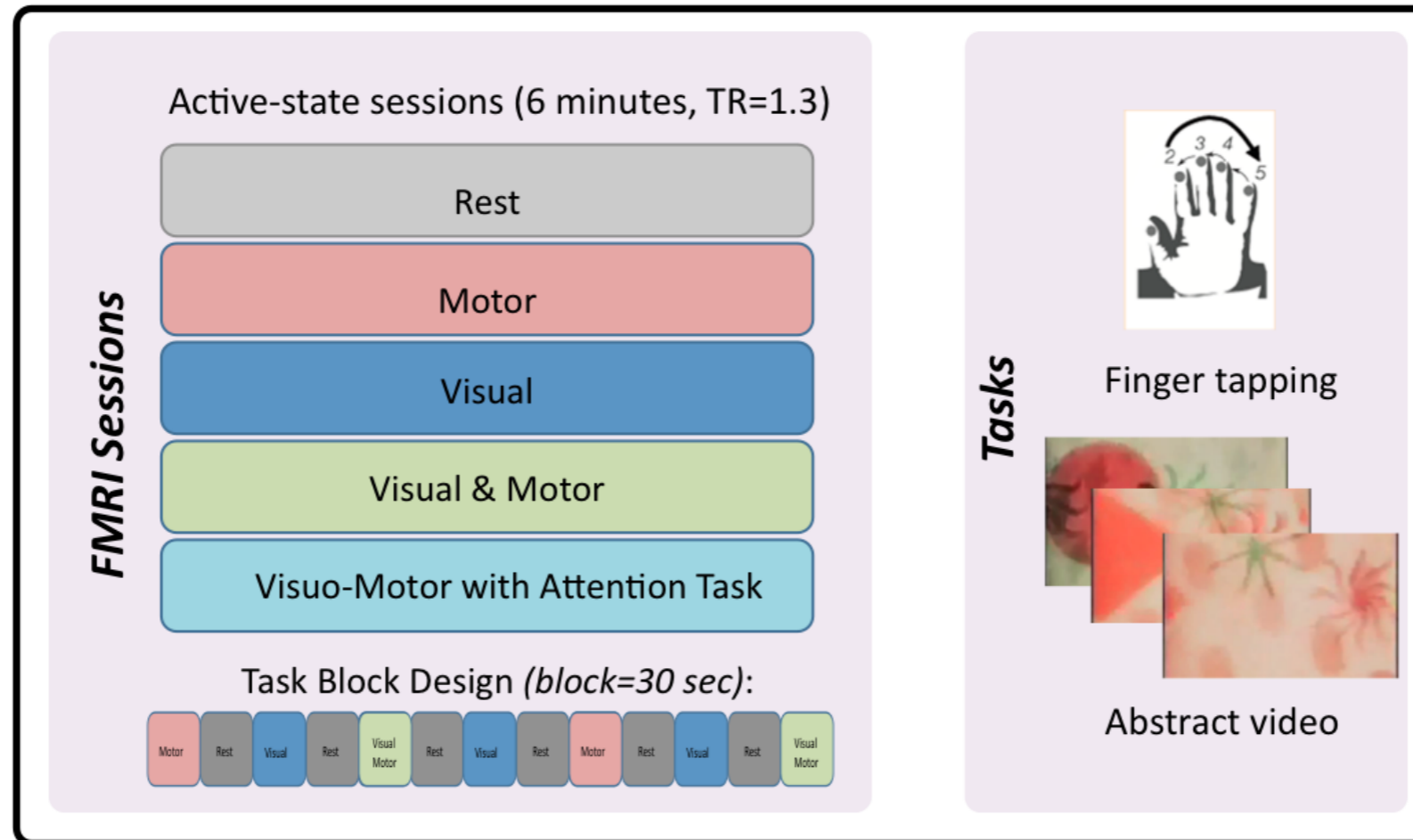
$$\max\left(\rho_a, \sqrt{1 - \frac{\sigma_{xb}^2}{\sigma_{xa}^2}}\right) < w_{xa} < \rho_a \frac{1}{\sqrt{1 - \frac{\sigma_{xb}^2}{\sigma_{xa}^2}}}$$



$$\rho_a \frac{\sigma_{ya}}{\sigma_{yb}} < w_{xa} < \min\left(\frac{\sigma_{xb}}{\sigma_{xa}}, 1\right)$$



Experiment

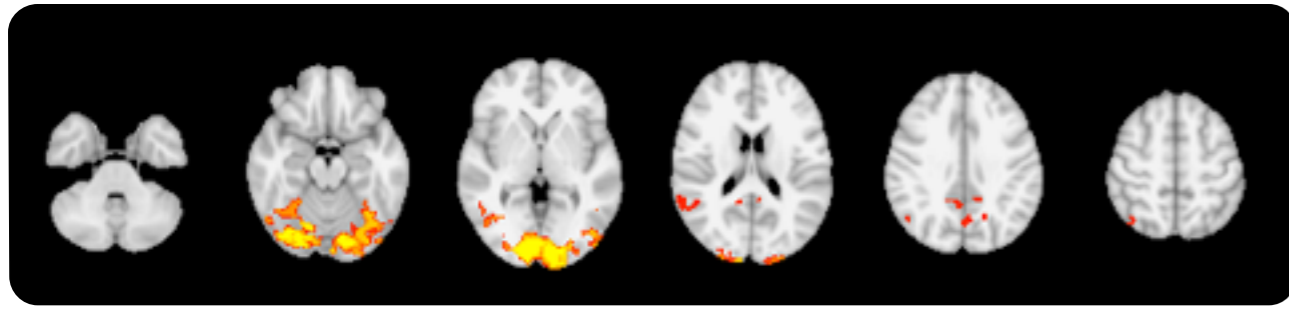


Are changes in connectivity across associated with variance changes?

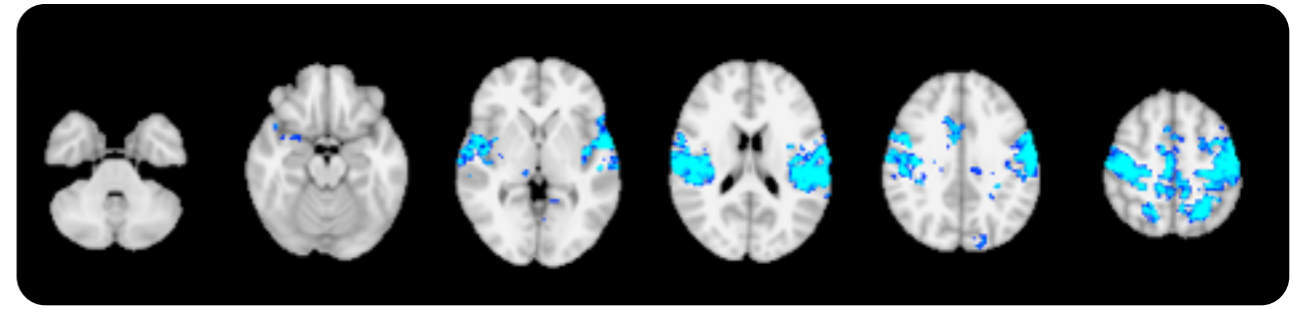
Do these changes correspond to particular types of changes in connectivity
- are they predicted by model?

How about activation levels?

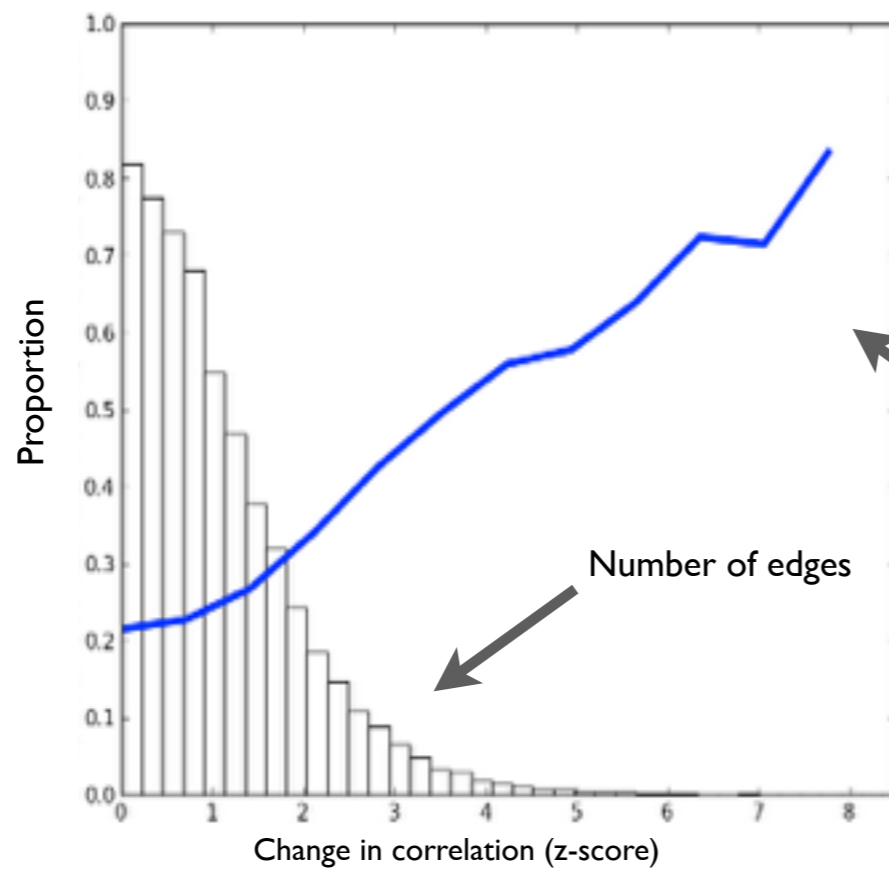
Results



Variance changes from rest for visual

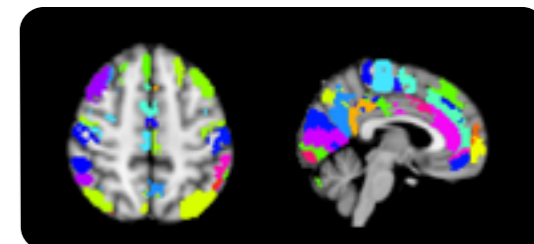


Variance changes from rest for motor

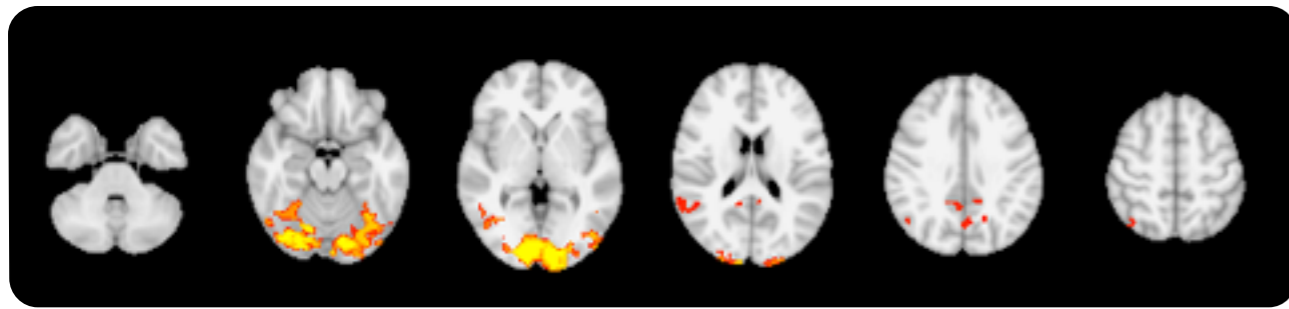


Proportion of edges with at least one region changing in variance

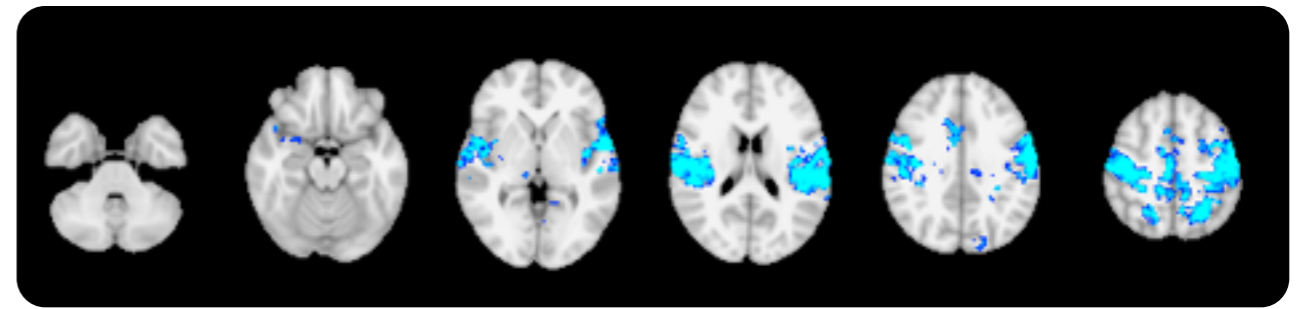
Number of edges



Results

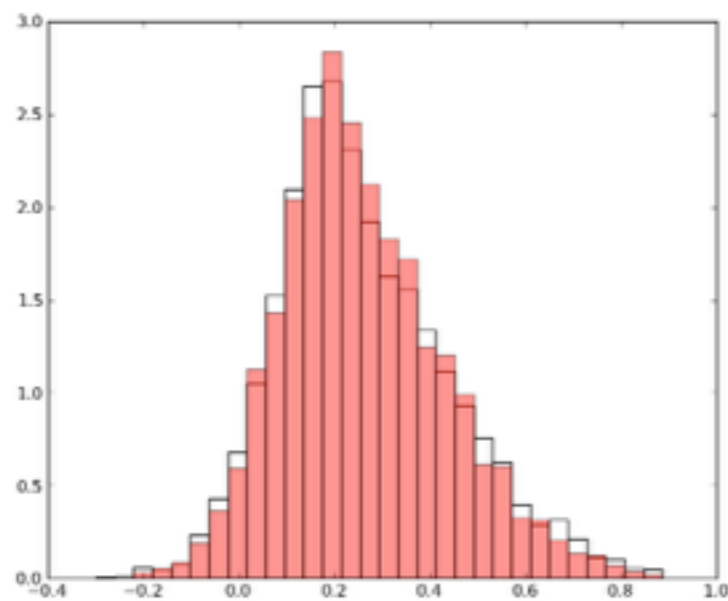


Variance changes from rest for visual

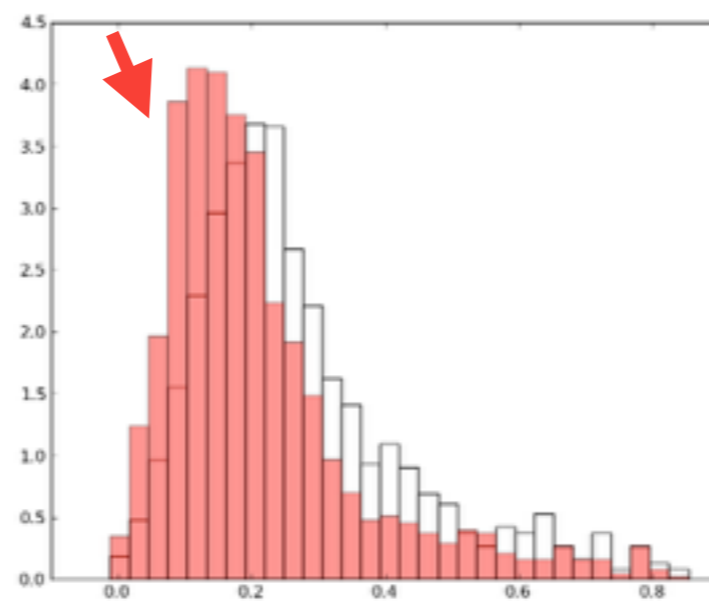


Variance changes from rest for motor

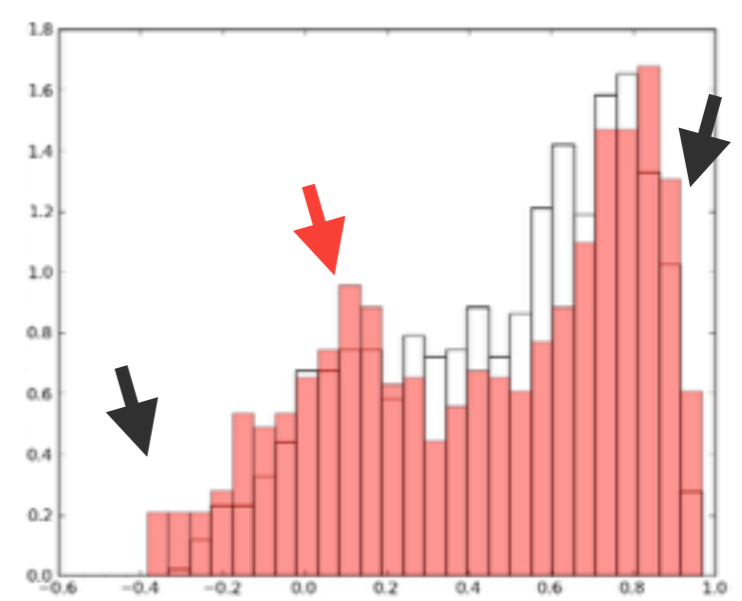
No change in variance.



One region increases in variance

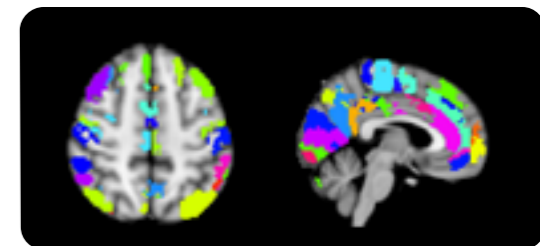


Both regions increase in variance

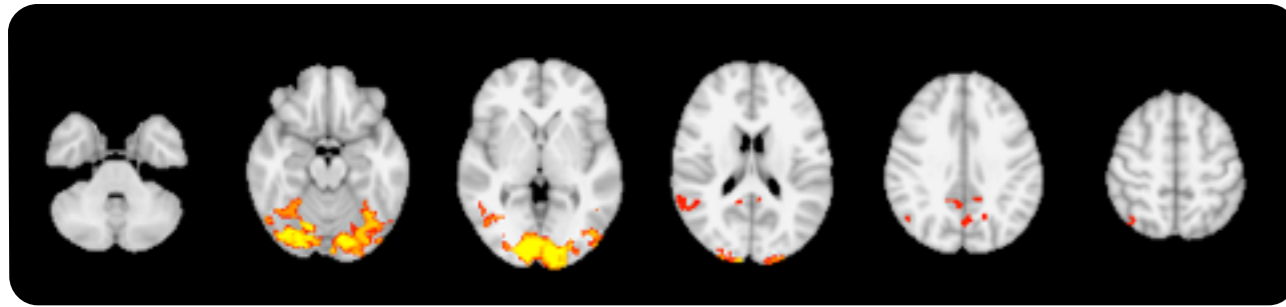


Rest

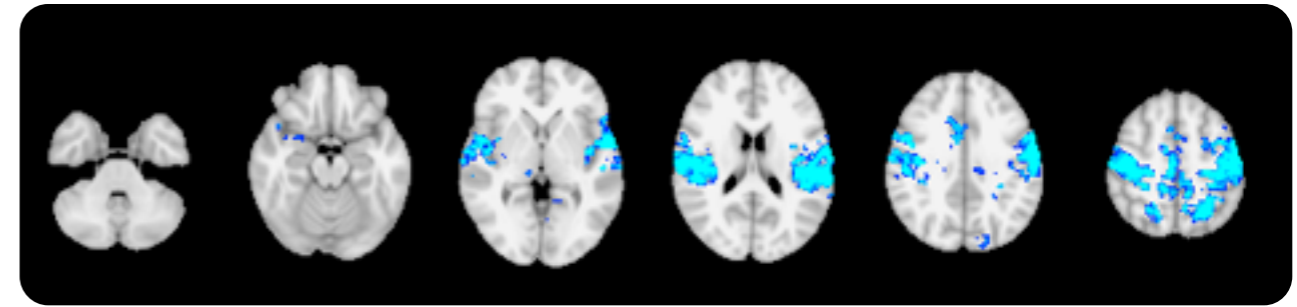
Visual movie



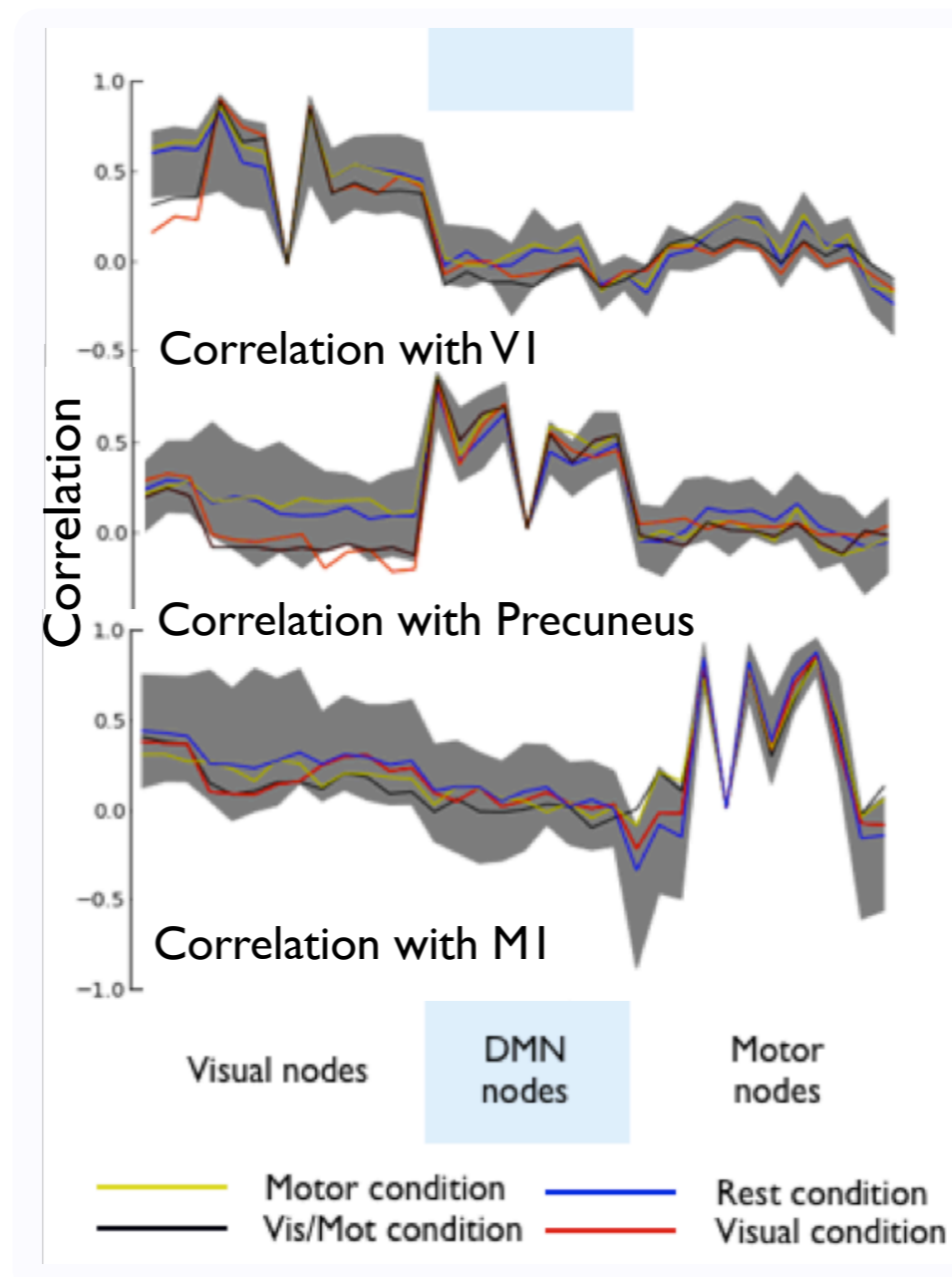
Results



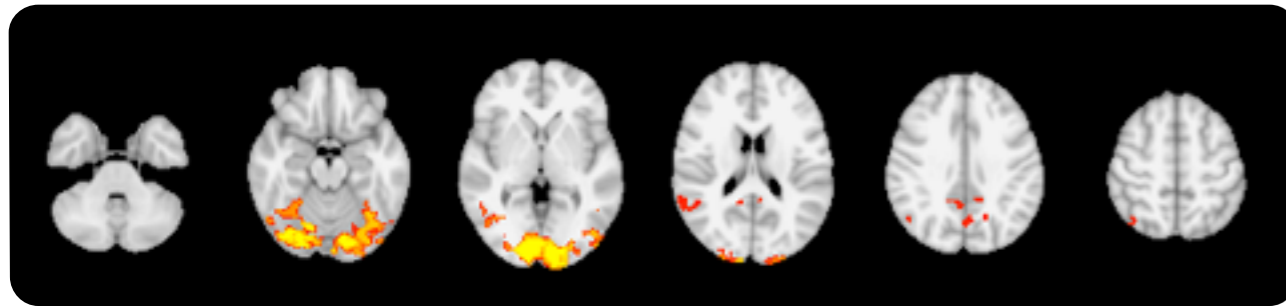
Variance changes from rest for visual



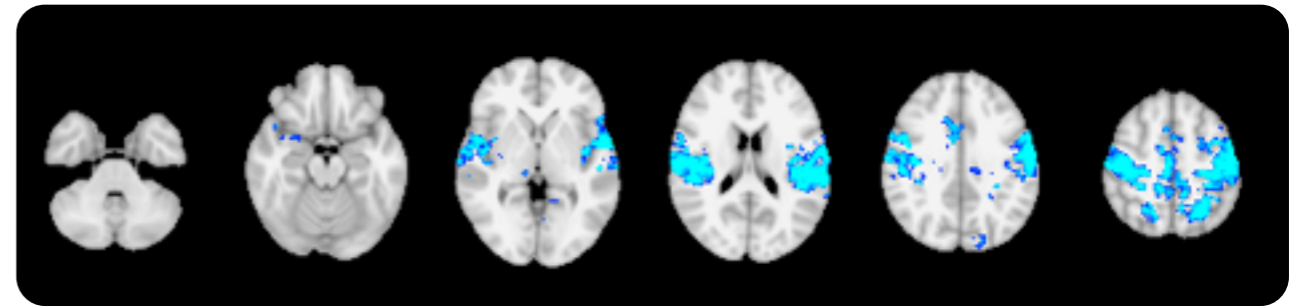
Variance changes from rest for motor



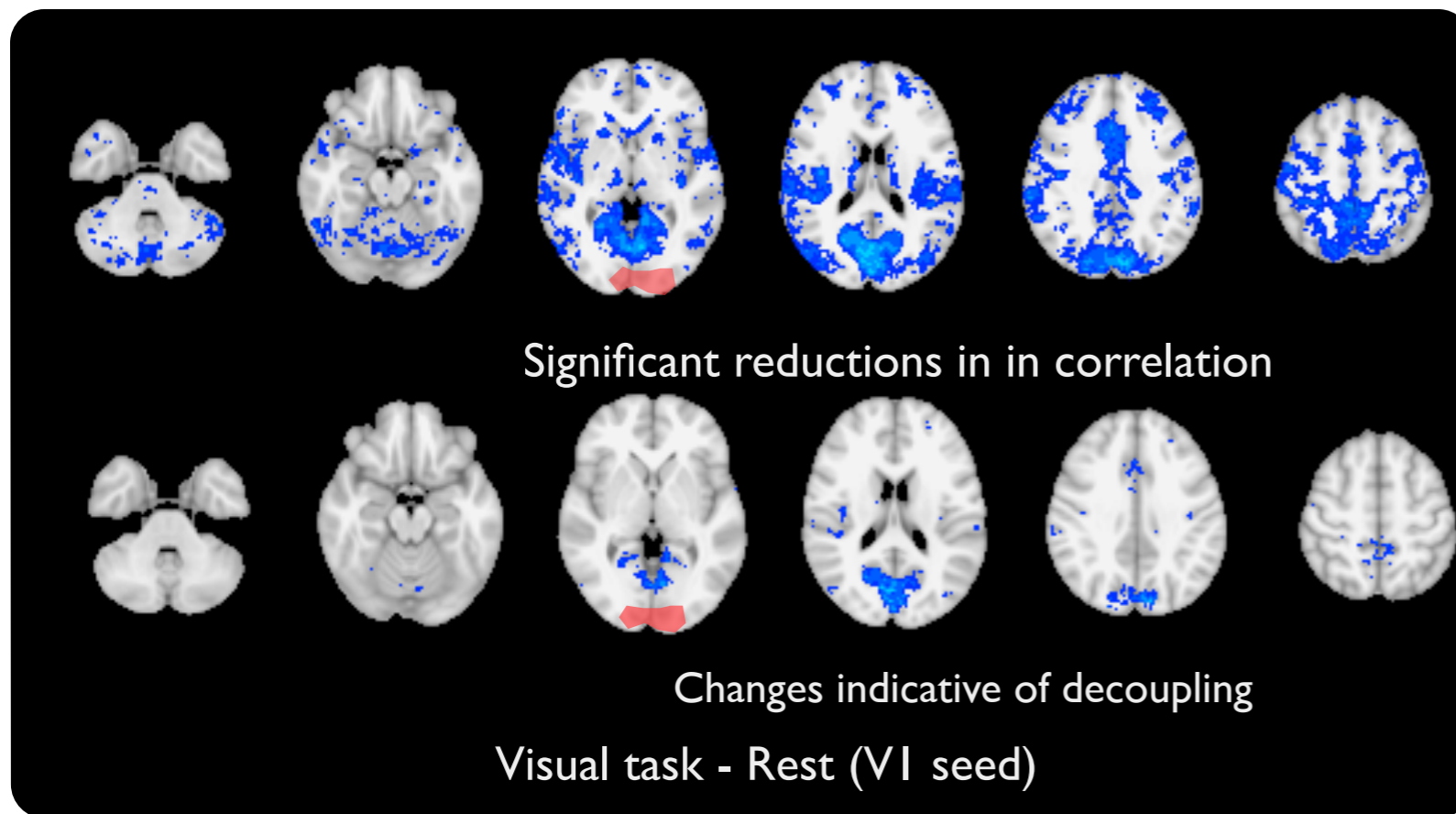
Results



Variance changes from rest for visual



Variance changes from rest for motor

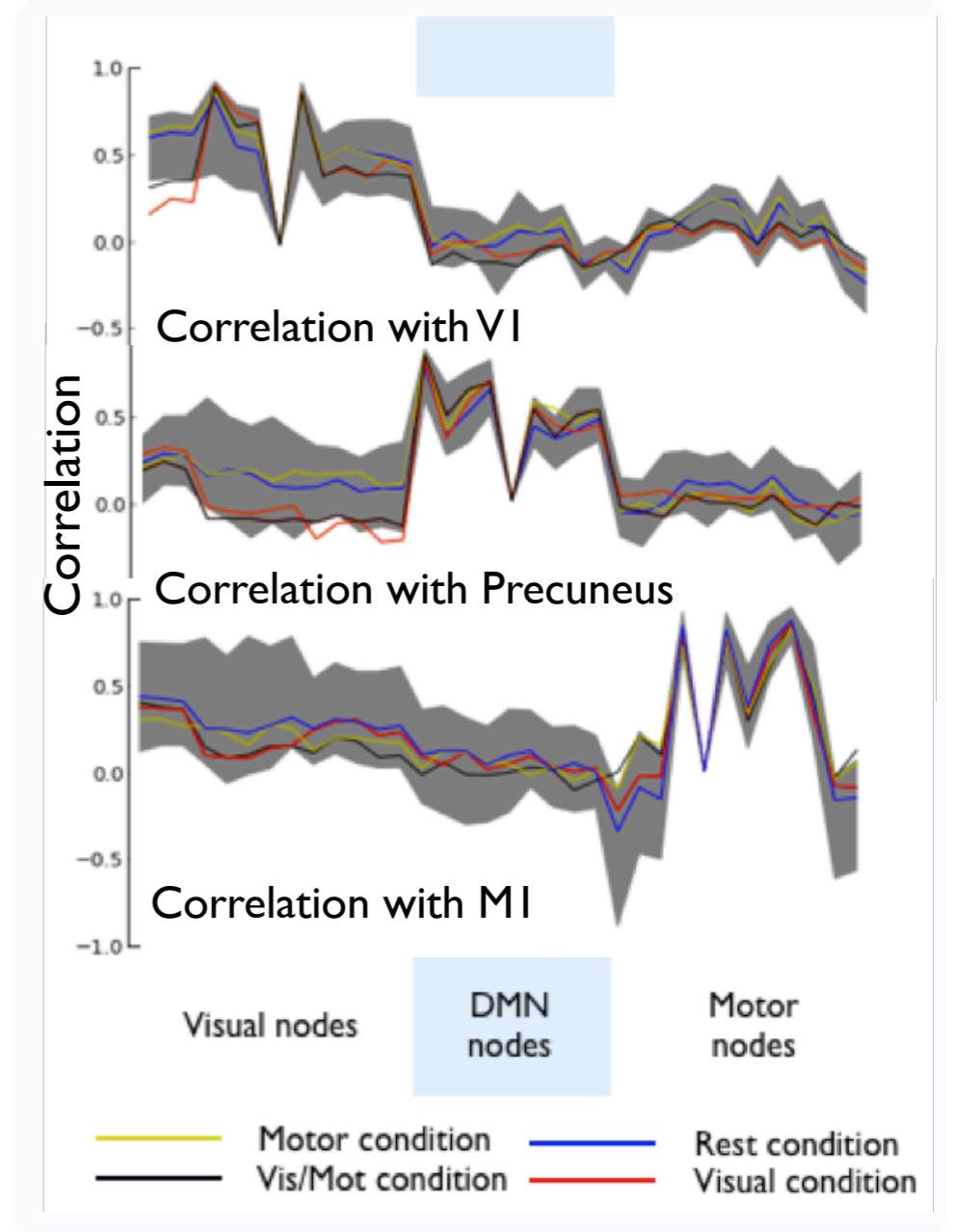


Significant reductions in in correlation

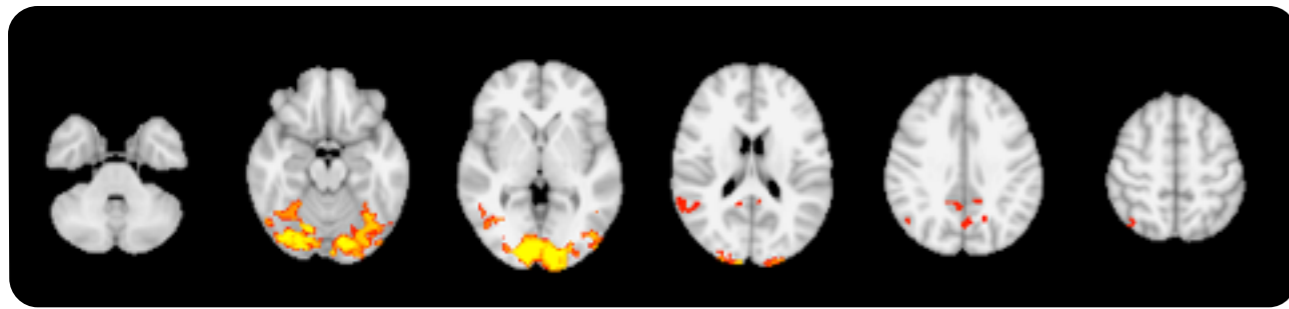
Changes indicative of decoupling

Visual task - Rest (VI seed)

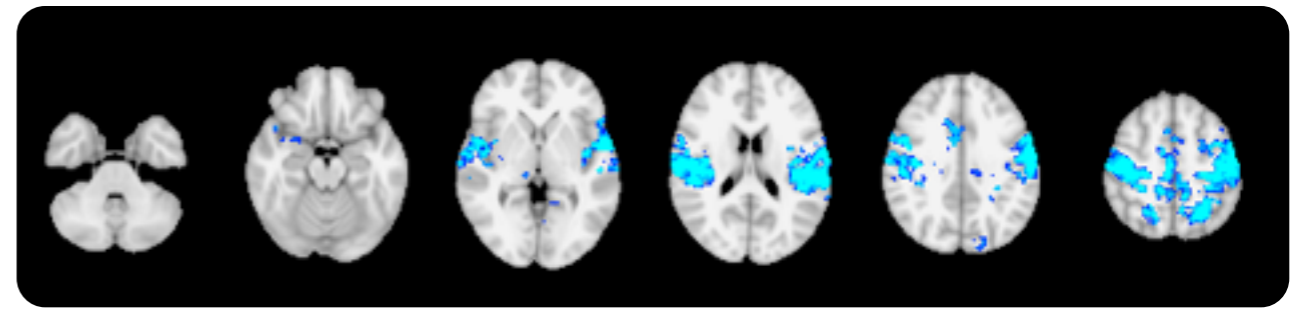
Correlation changes from rest for visual



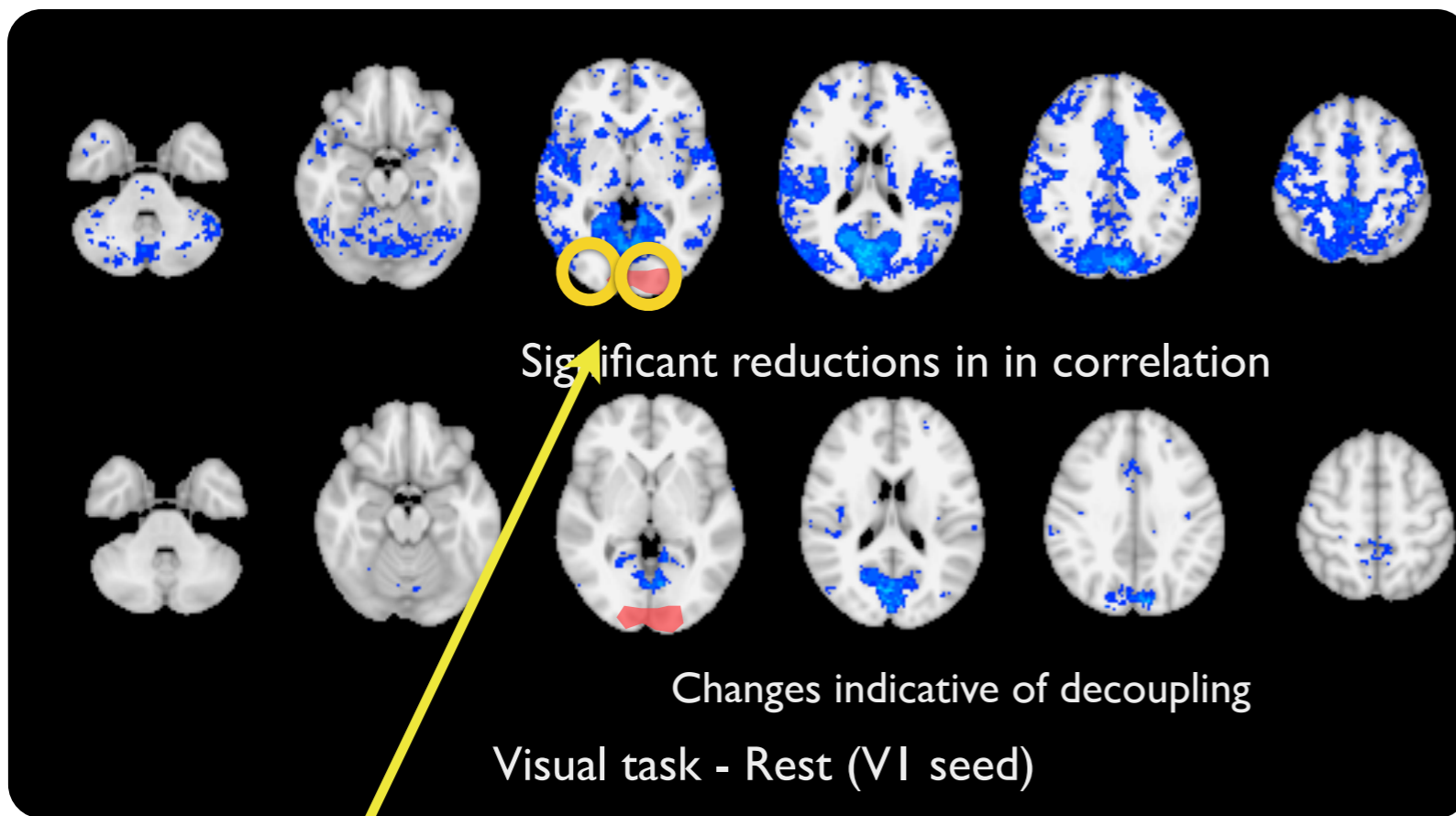
Results



Variance changes from rest for visual



Variance changes from rest for motor



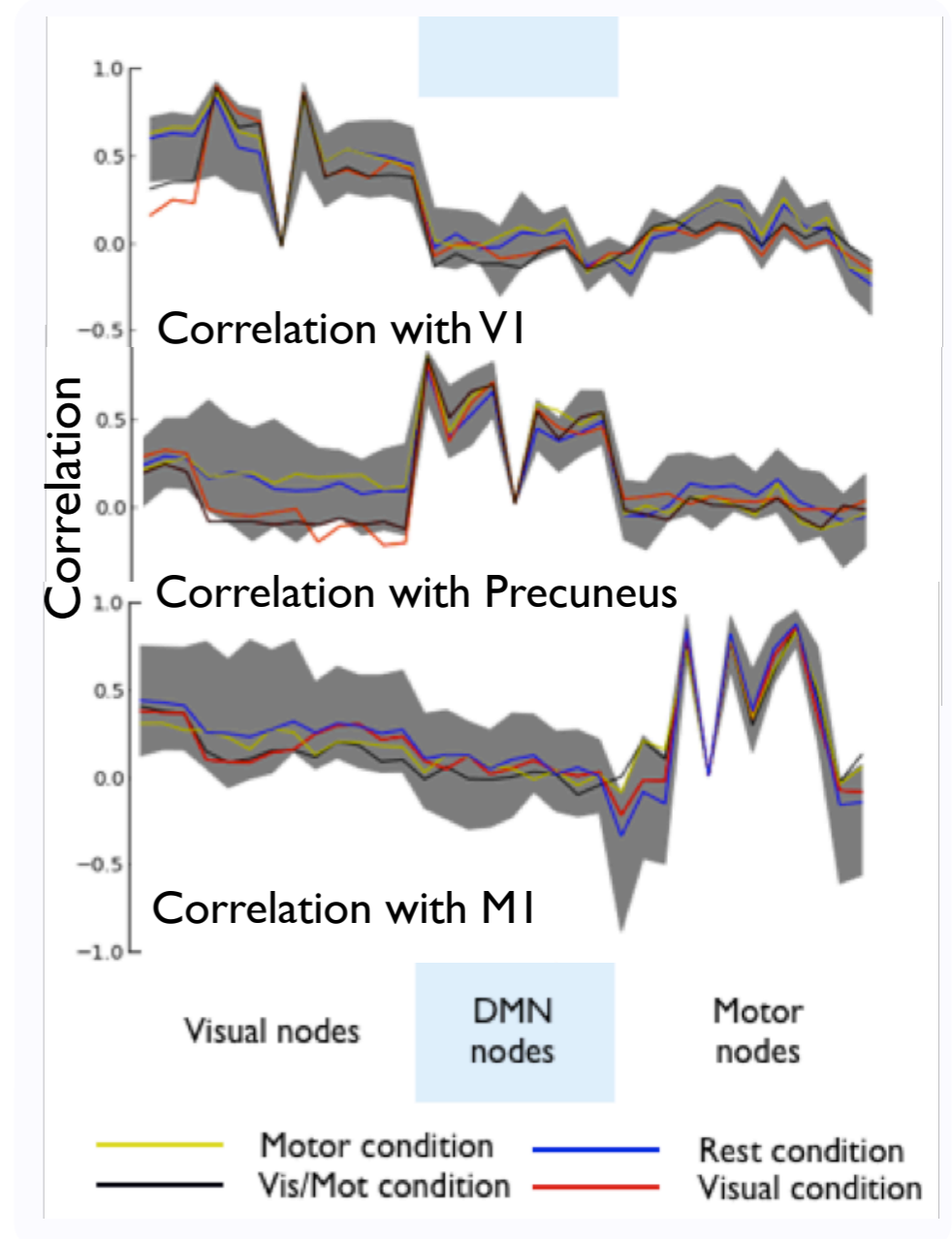
Significant reductions in in correlation

Changes indicative of decoupling

Visual task - Rest (VI seed)

Correlation changes from rest for visual

Increase in signal levels



Correlation with VI

Correlation with Precuneus

Correlation with MI

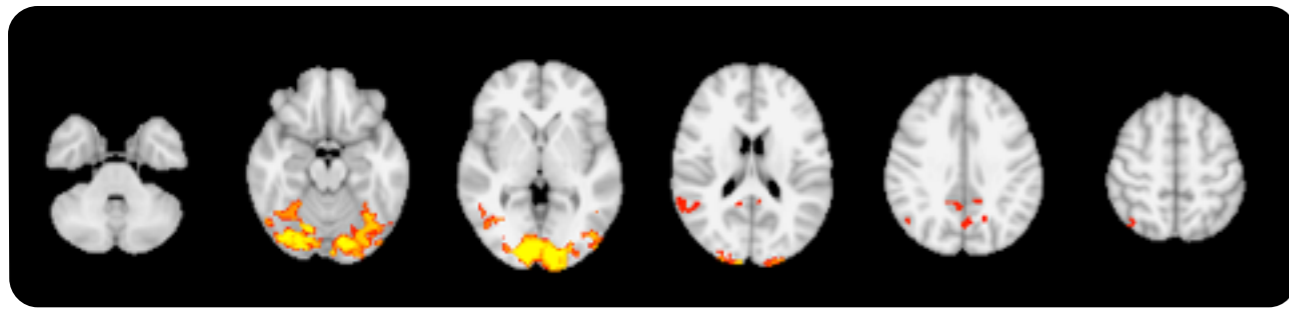
Visual nodes

DMN nodes

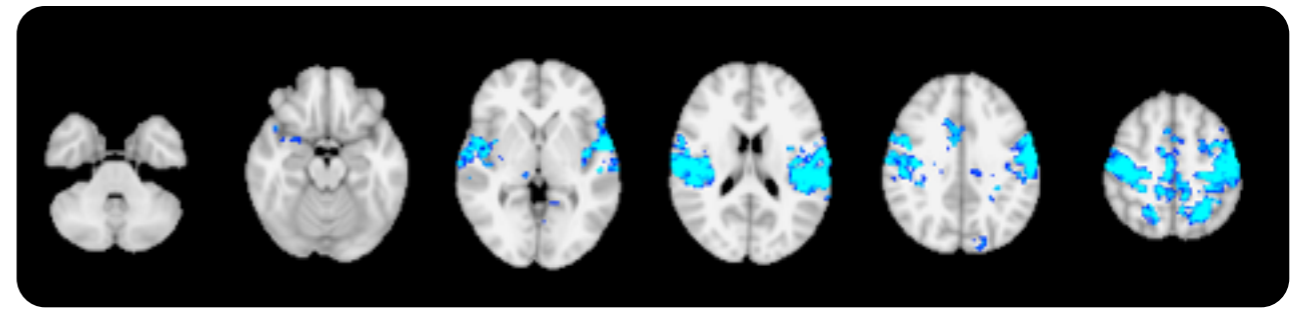
Motor nodes

Motor condition Rest condition
Vis/Mot condition Visual condition

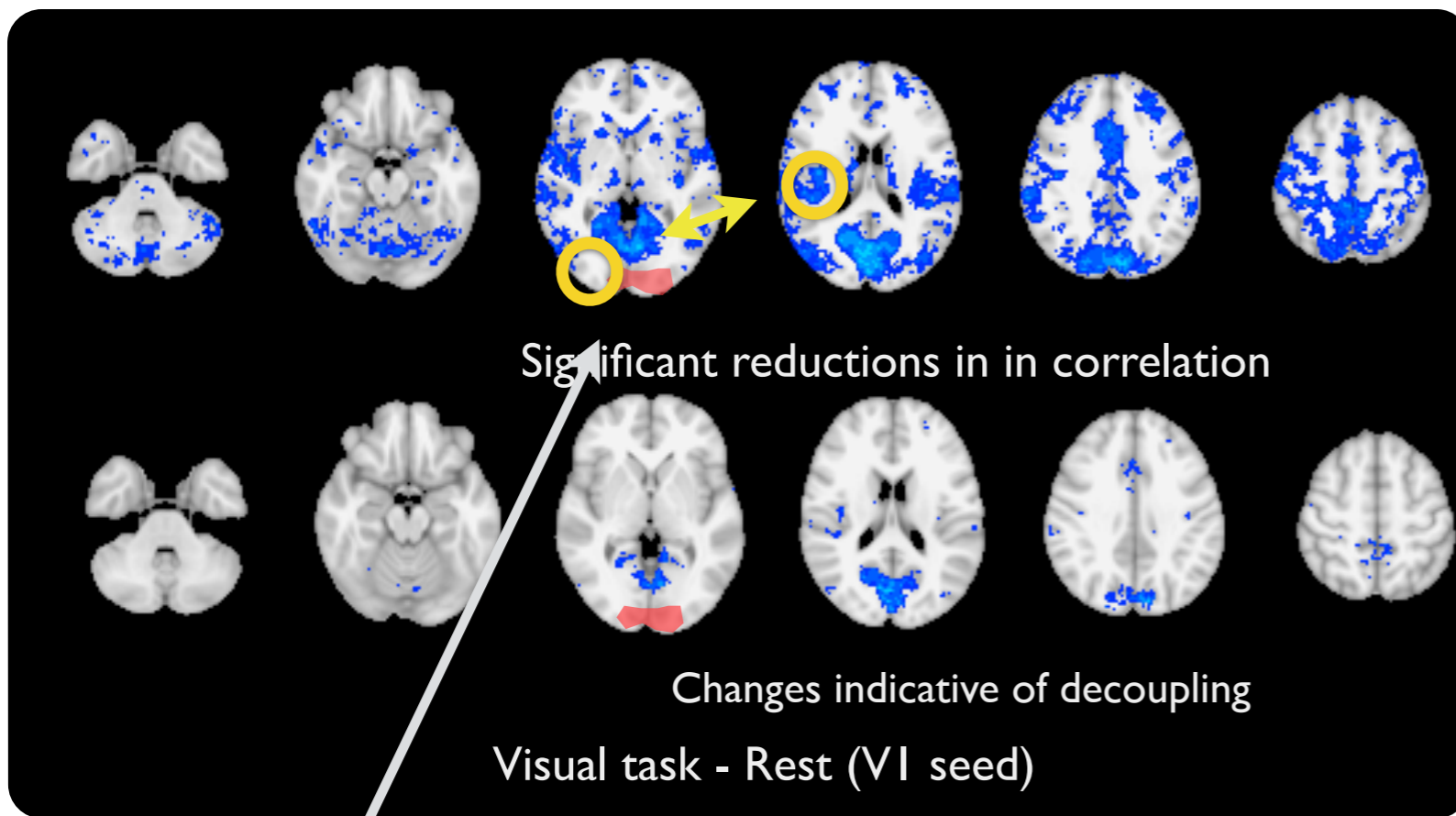
Results



Variance changes from rest for visual

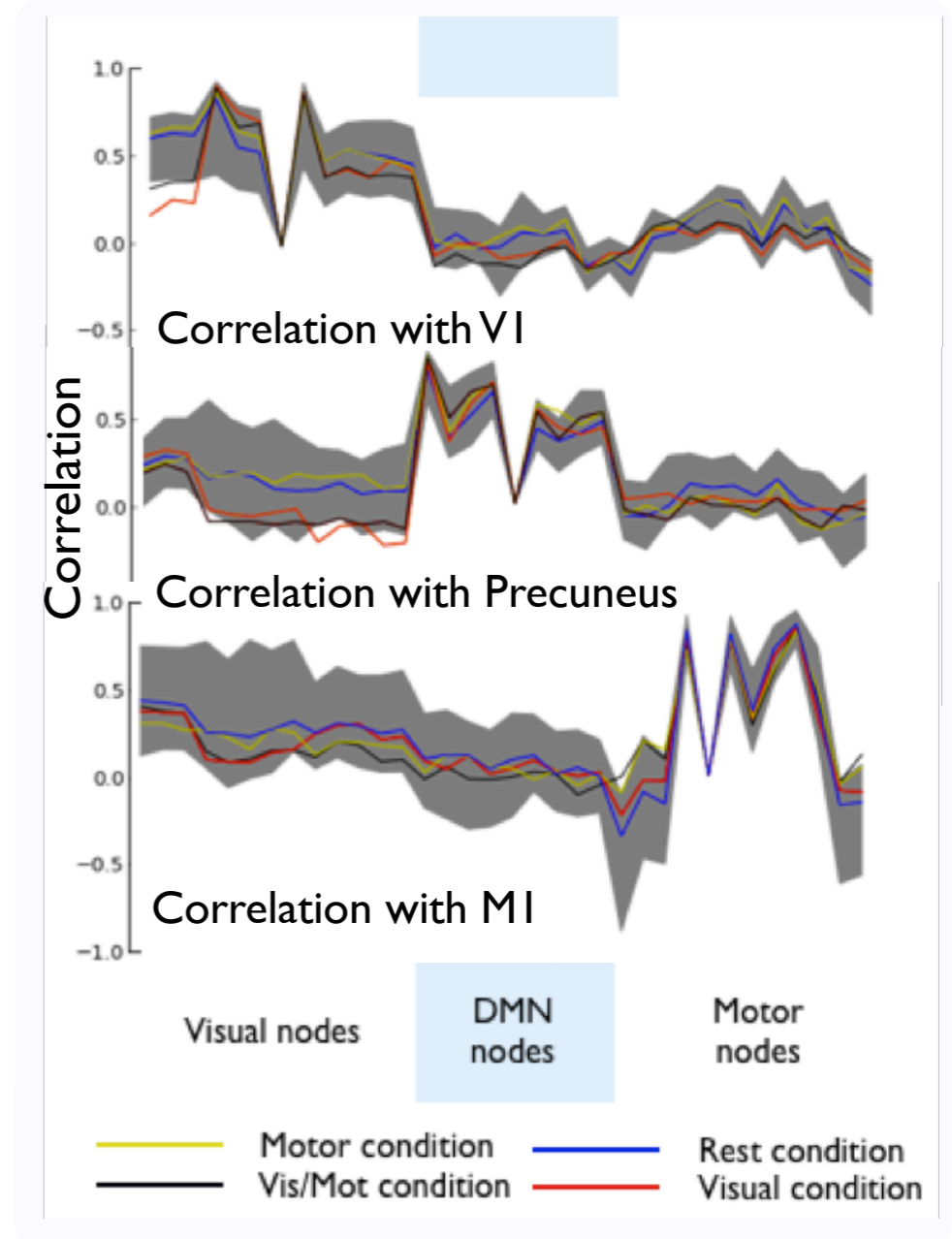


Variance changes from rest for motor

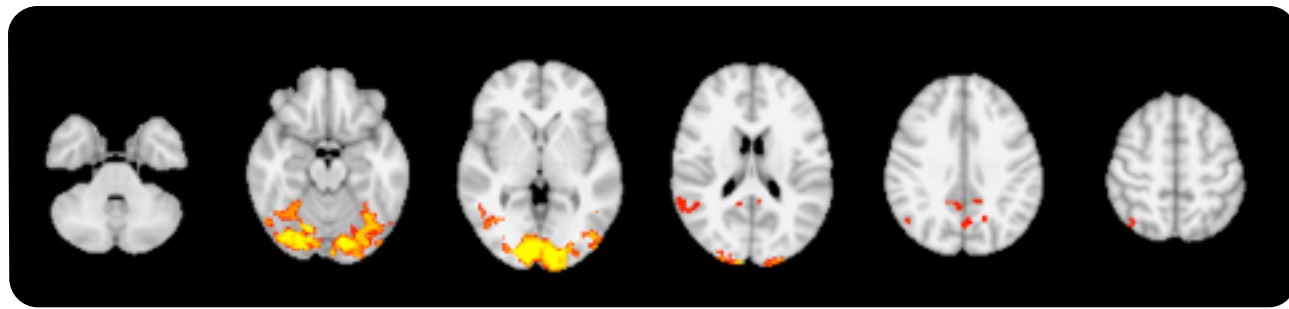


Correlation changes from rest for visual

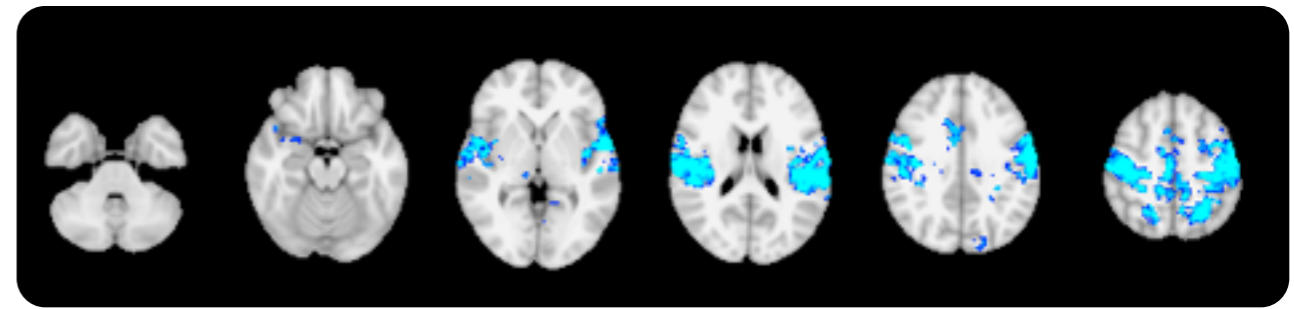
Increase in unshared signal



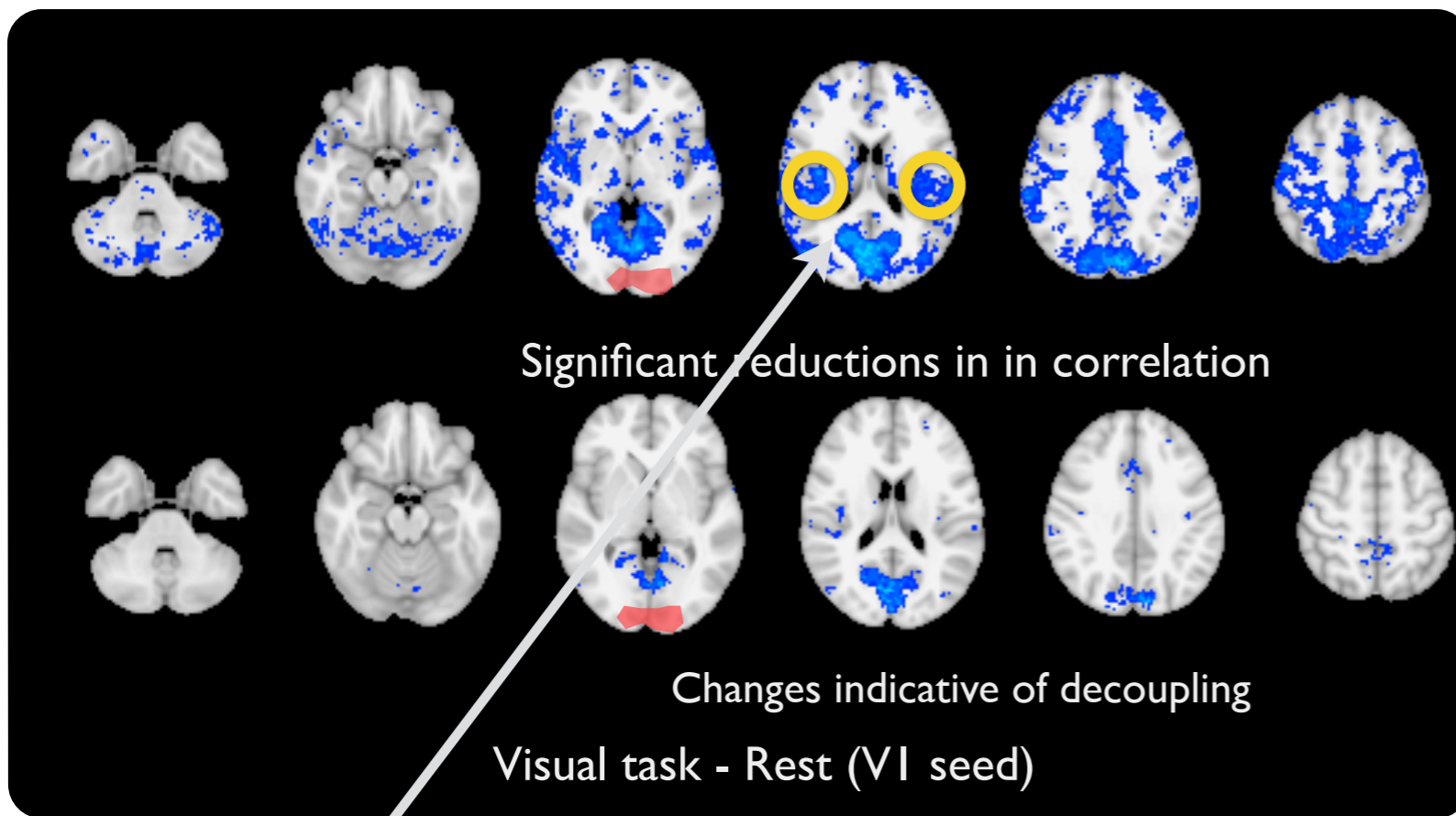
Results



Variance changes from rest for visual



Variance changes from rest for motor



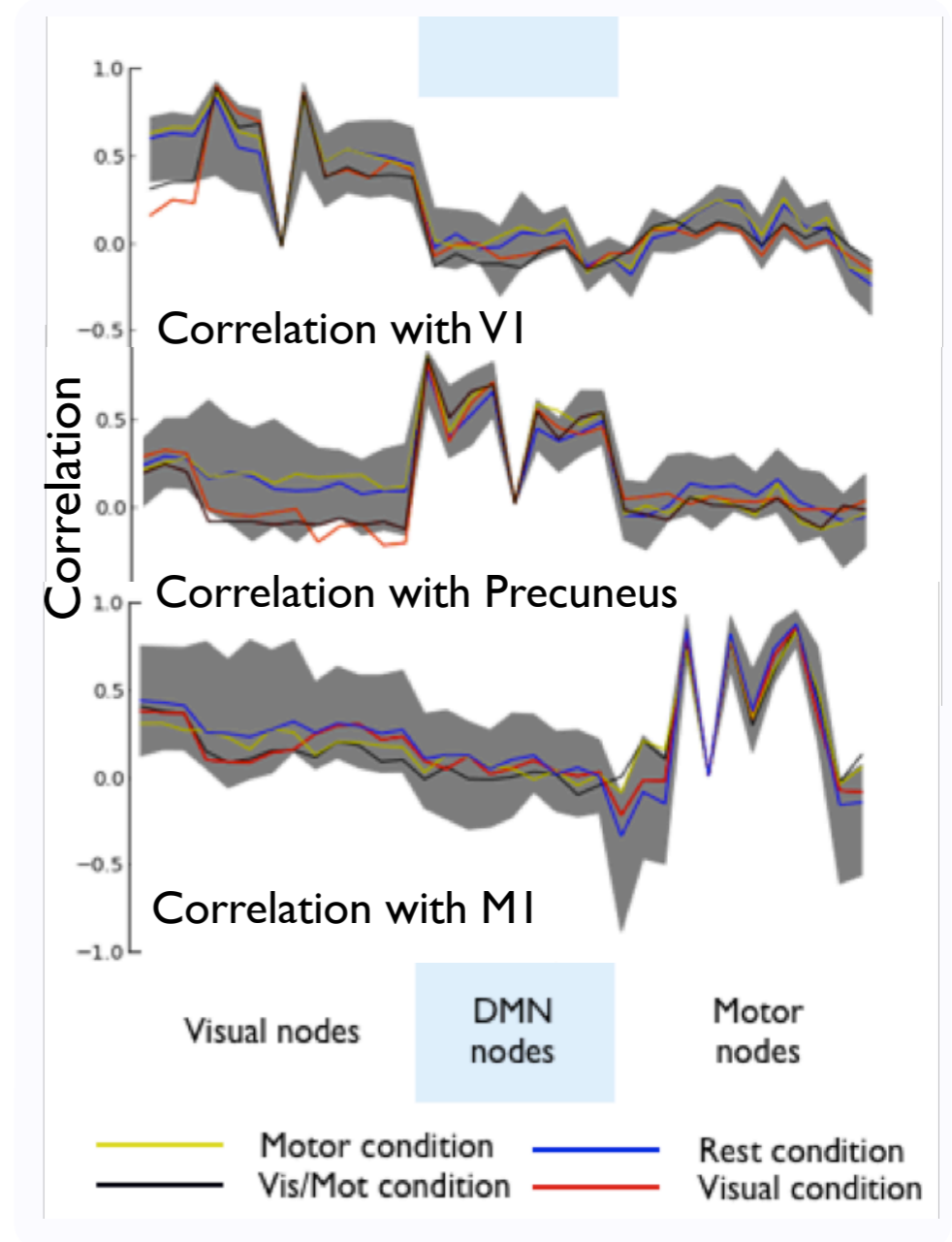
Significant reductions in in correlation

Changes indicative of decoupling

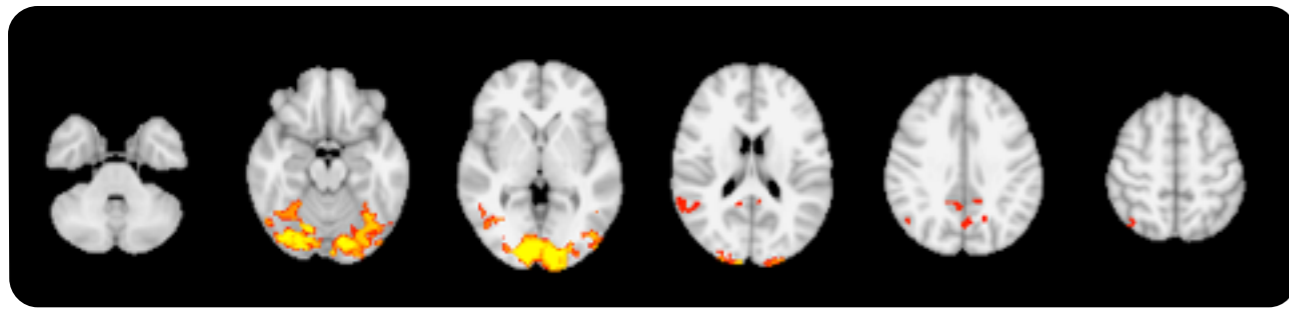
Visual task - Rest (VI seed)

Correlation changes from rest for visual

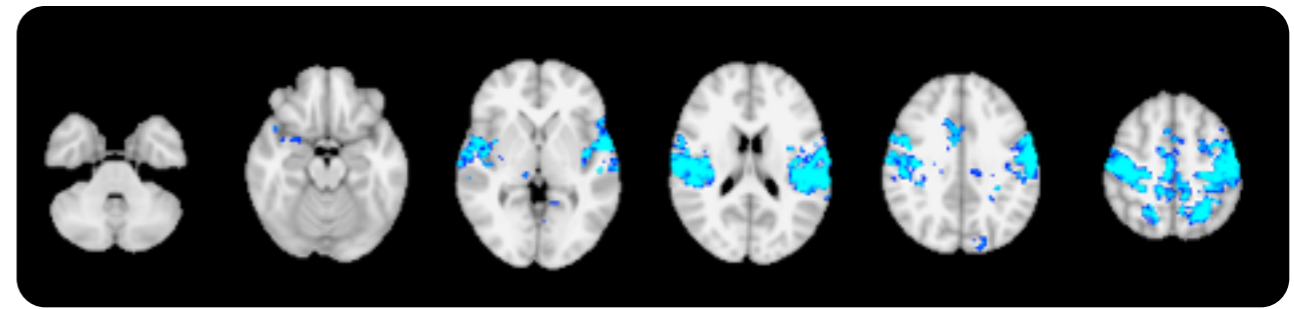
Reduction in shared signal



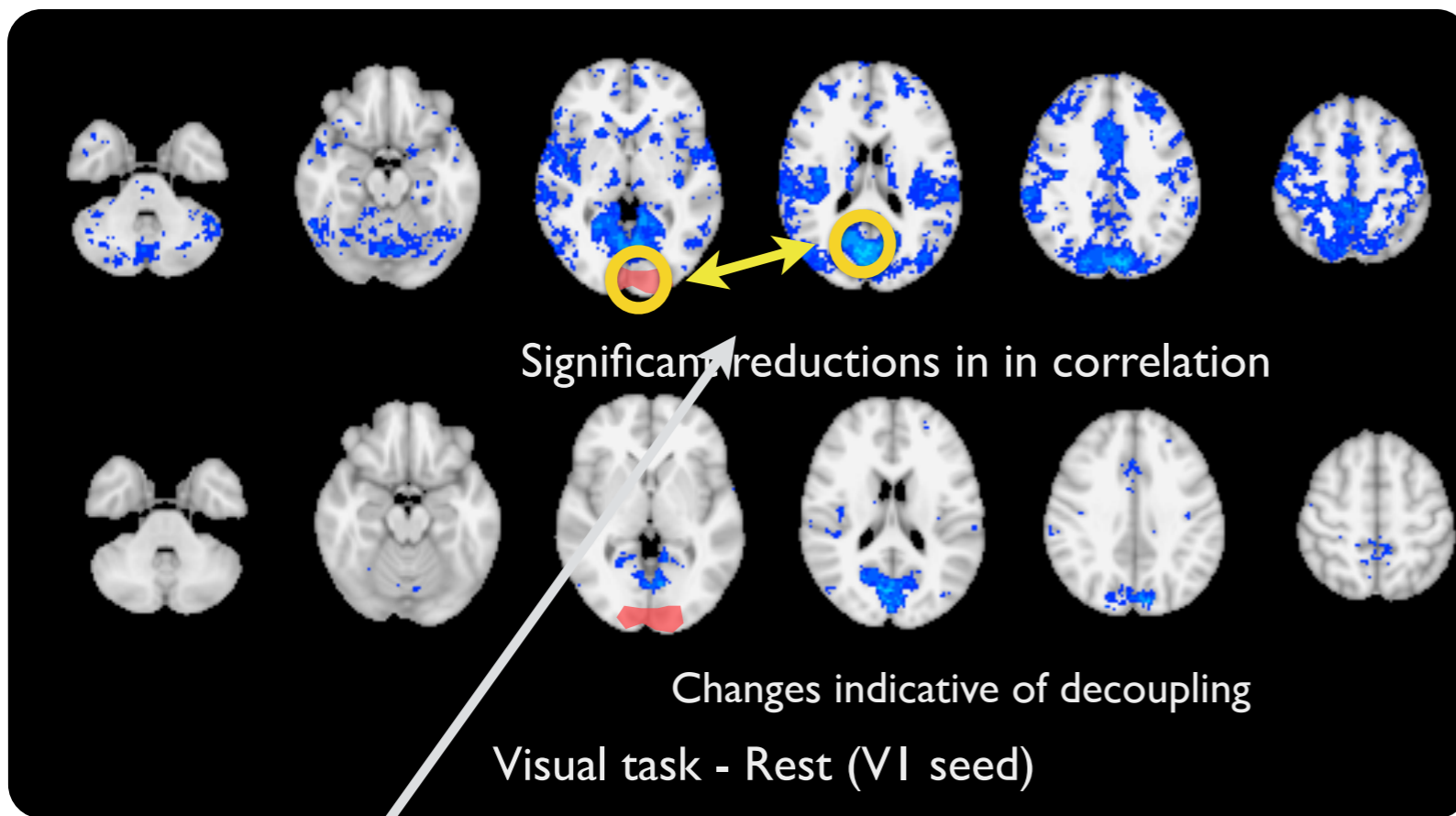
Results



Variance changes from rest for visual

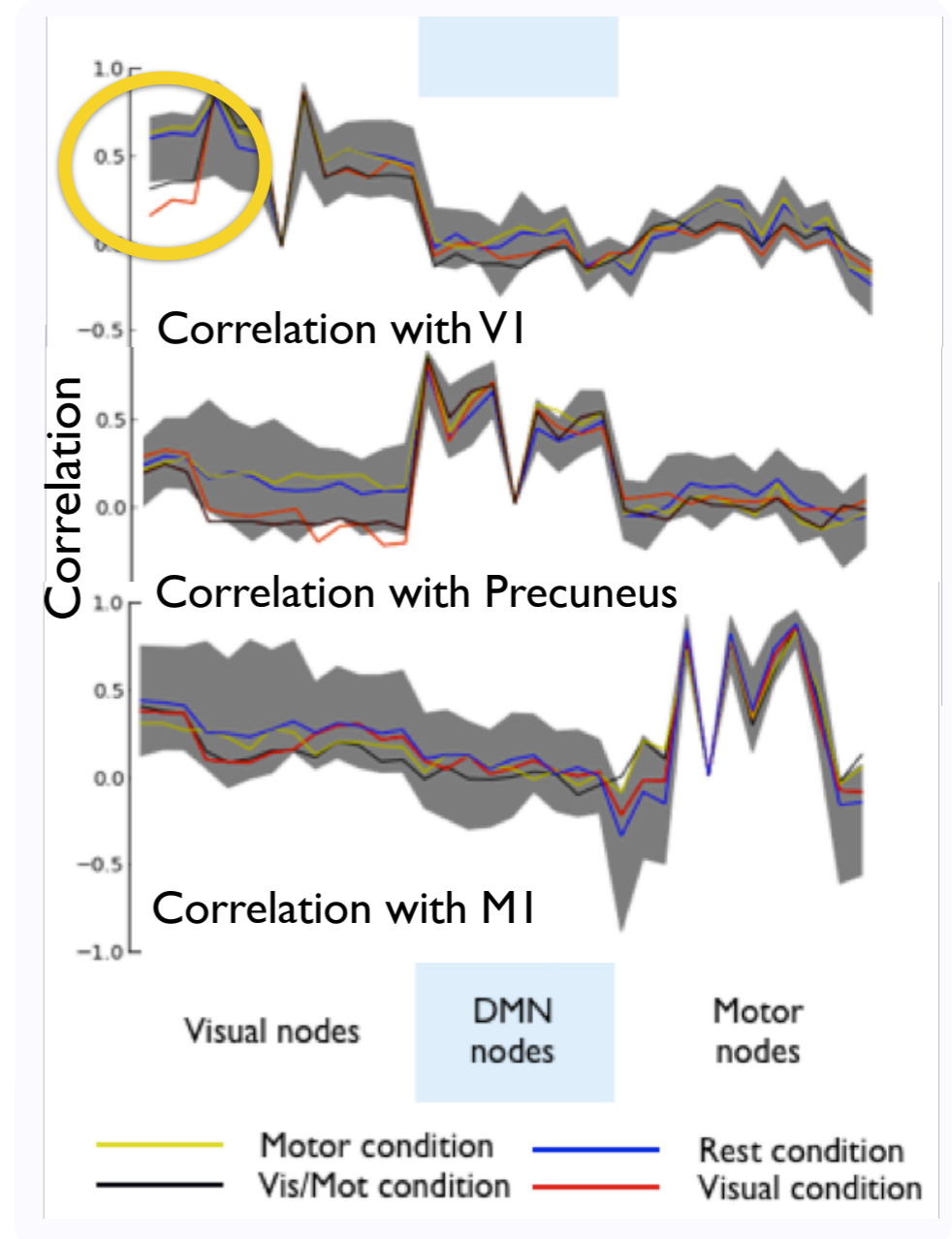


Variance changes from rest for motor



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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