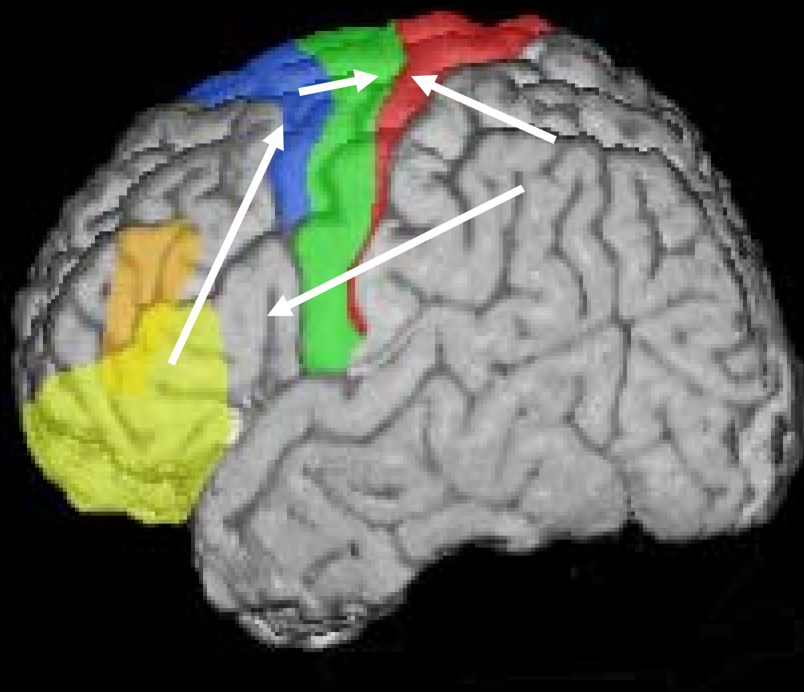
Brain Connectivity Overview

Thomas Zeffiro M.D. Ph.D.

- SPM 8/12
- ART Toolbox
- PPI
- GIFT
- DCM
- Connectivity Toolbox
- Brainwaver

regional specialization



regional interaction

Regional Interactions

Functional connectivity

= the temporal correlation between spatially remote areas

MODEL-FREE

Exploratory

Data Driven

No Causation

Whole brain connectivity

Effective connectivity

= the influence one area exerts over another

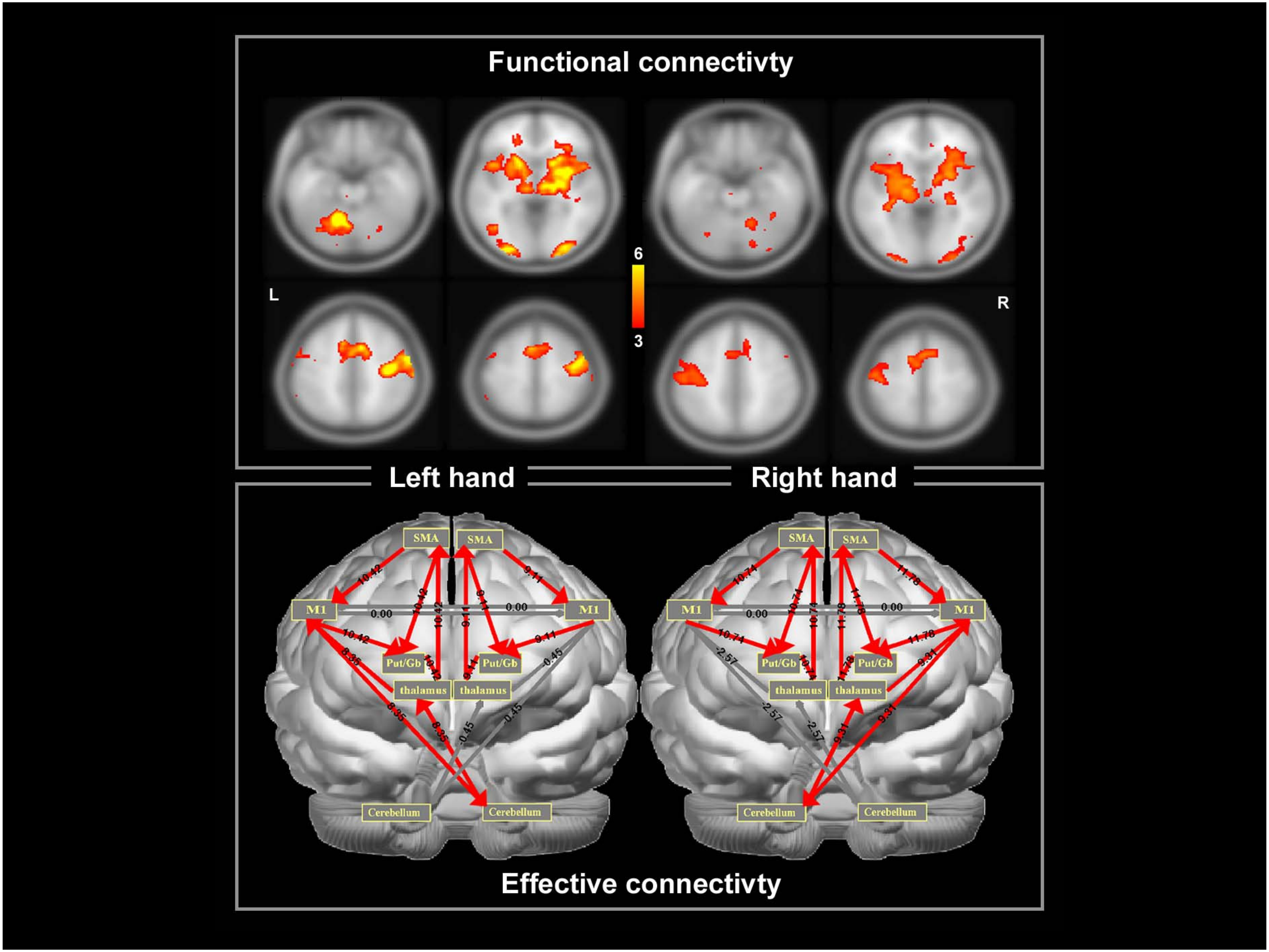
MODEL-DEPENDENT

Confirmatory

Hypothesis driven

Causal

Reduced set of regions



Functional connectivty
L
R
6
3
Left hand
Right hand
SMA
SMA
M1
M1
0.00
0.00
Put/Gb
Put/Gb
thalamus
thalamus
Cerebellum
Cerebellum
10.42
9.11
8.35
-0.45
10.74
11.78
-2.57
9.31
SMA
SMA
M1
M1
Put/Gb
Put/Gb
thalamus
thalamus
Cerebellum
Cerebellum
Effective connectivty

Regional Integration Modeling

- Functional connectivity
  - Bivariate correlation
  - Multivariate modeling (PCA, ICA, PLS)
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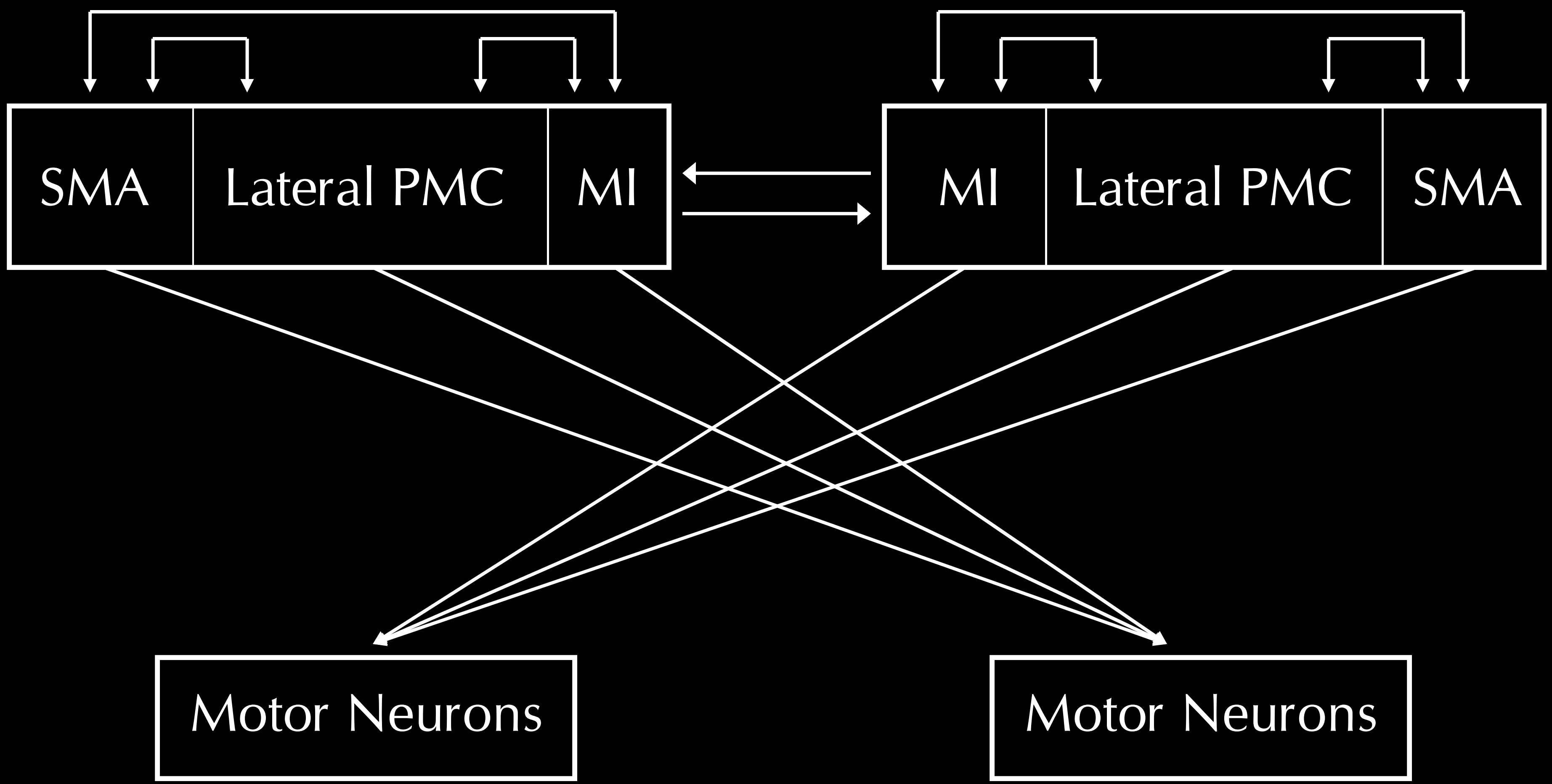
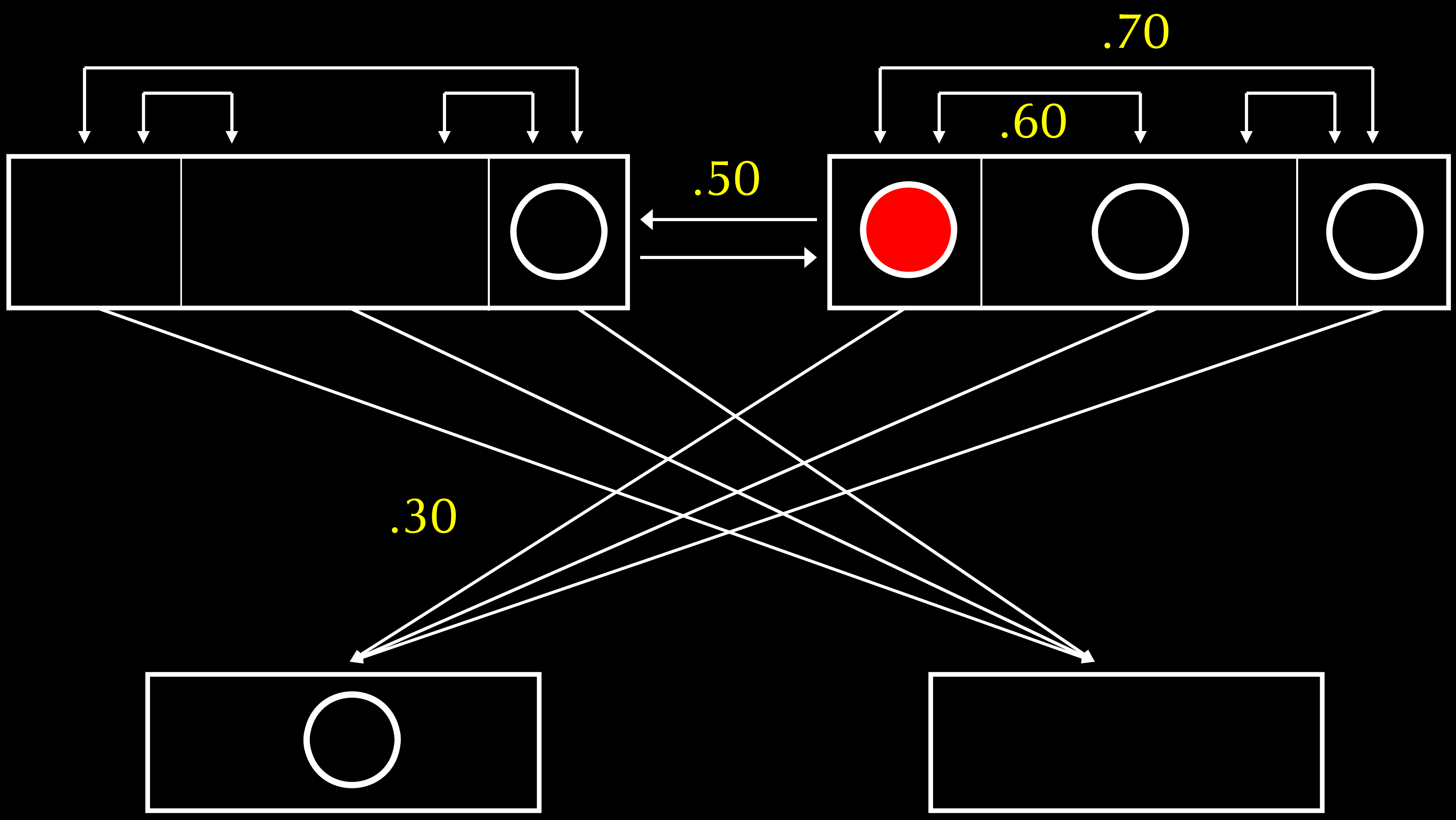
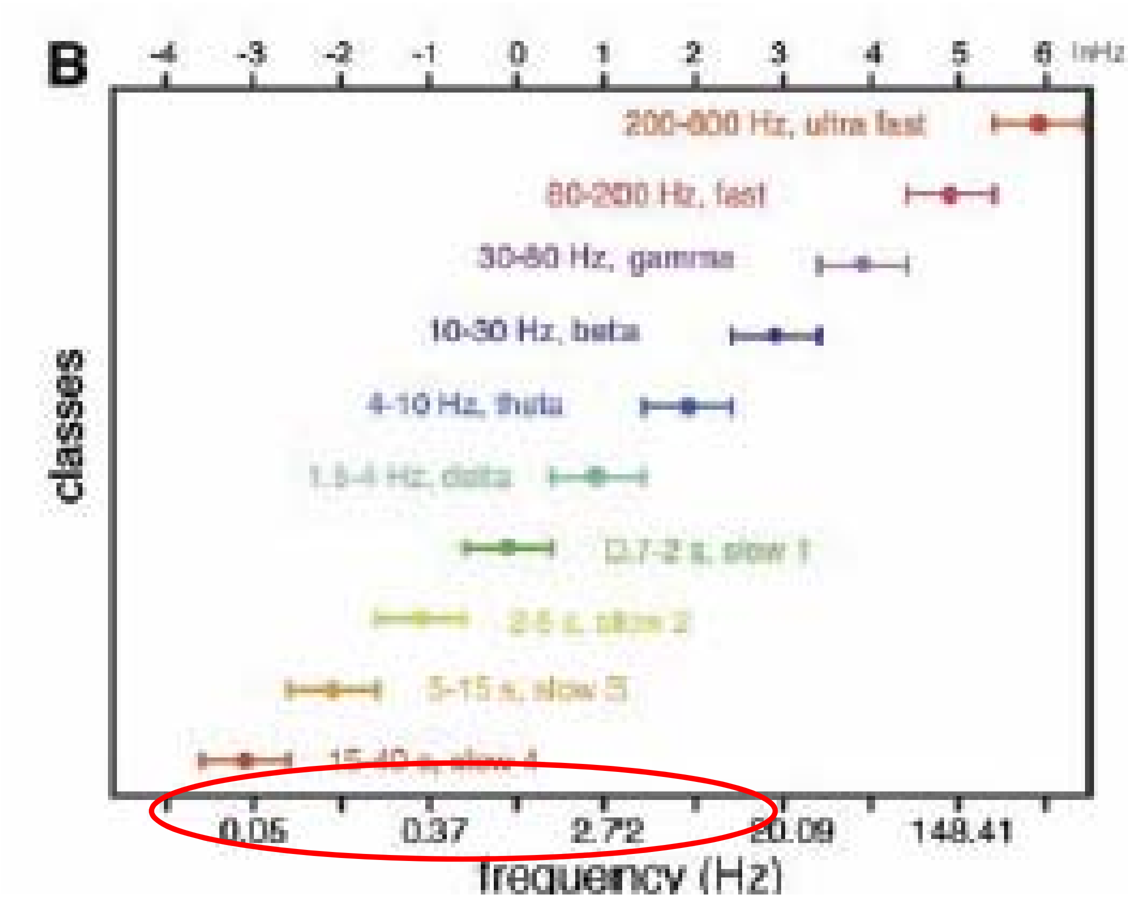
Motor System Horizontal Organization



Bivariate correlation



Information Frequency Bands



[.025 .06], toolbox cutoff [.009 .08]

Buzsaki , Science 2004

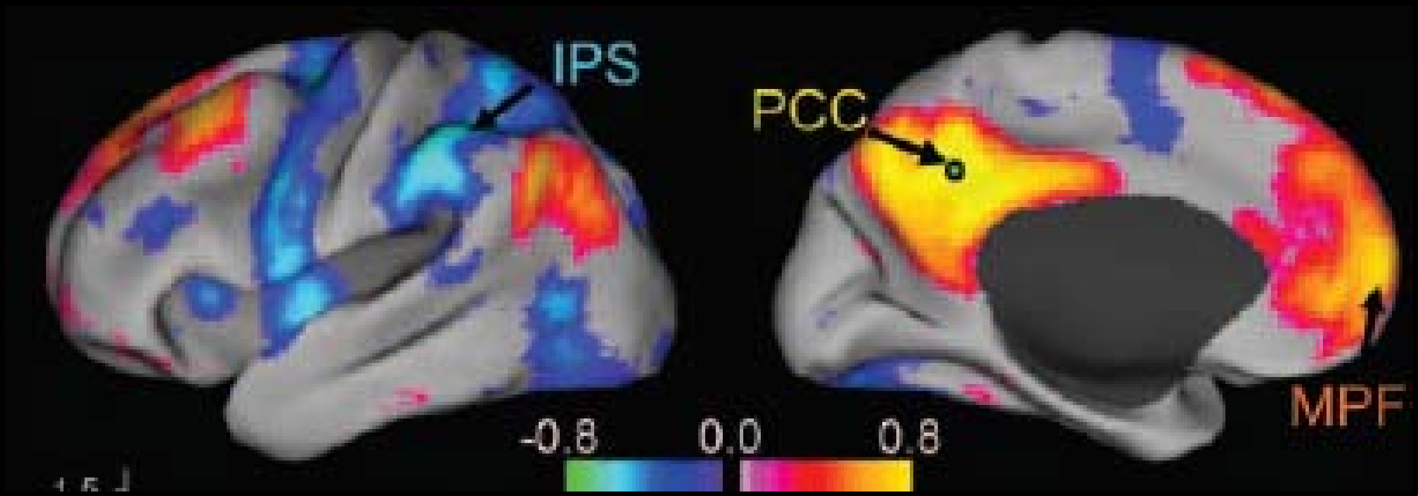
Resting State Networks

Spontaneous, low-frequency fluctuations in fMRI BOLD-contrast that form specific networks of the human brain in the absence of an overt task.

(Biswal 1995, Lowe 2000, ,Greicius 2003, Fox 2005)

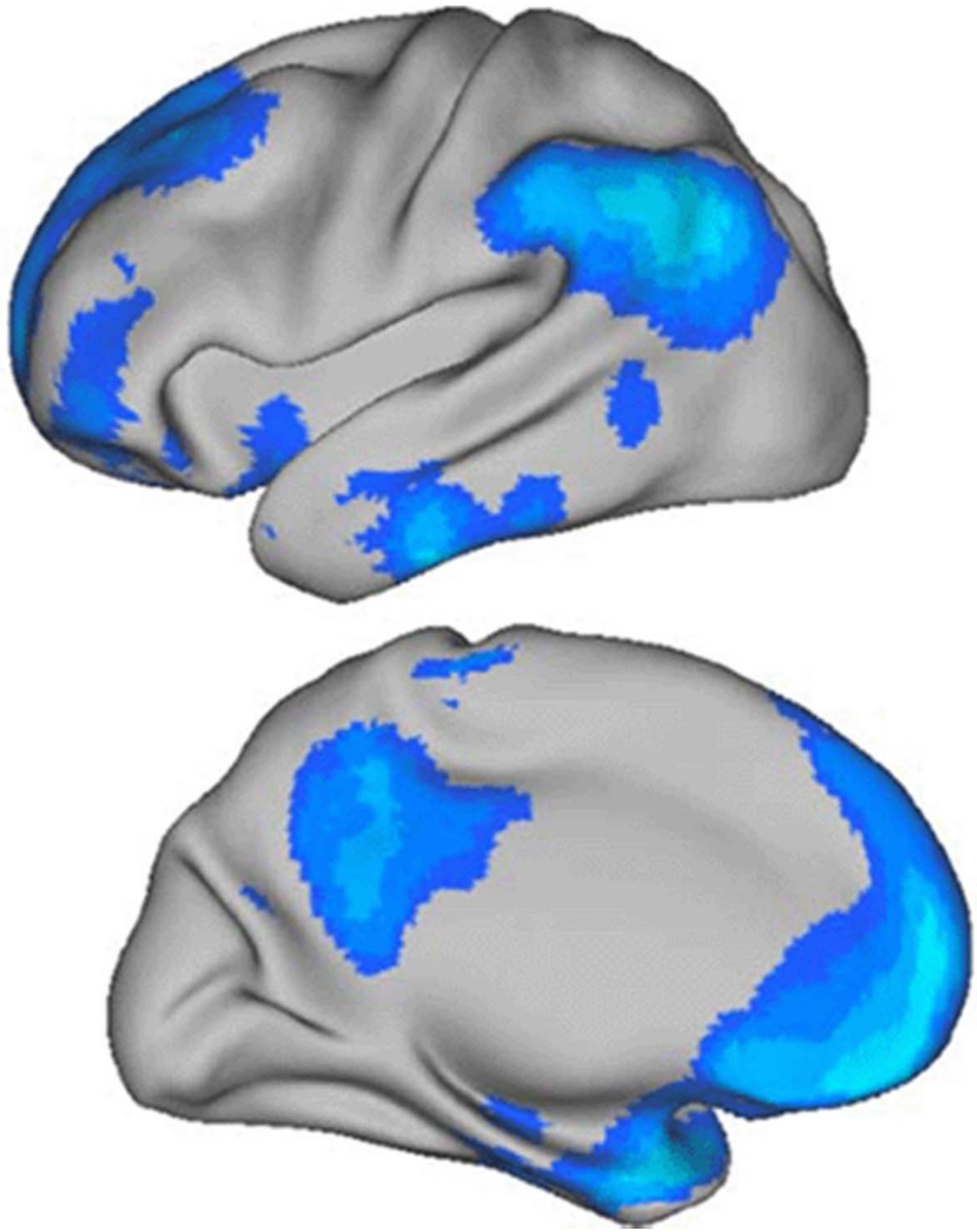
Seed-driven functional connectivity

Estimate maps showing temporal correlations between the BOLD-contrast signal from a given seed and every other brain voxel

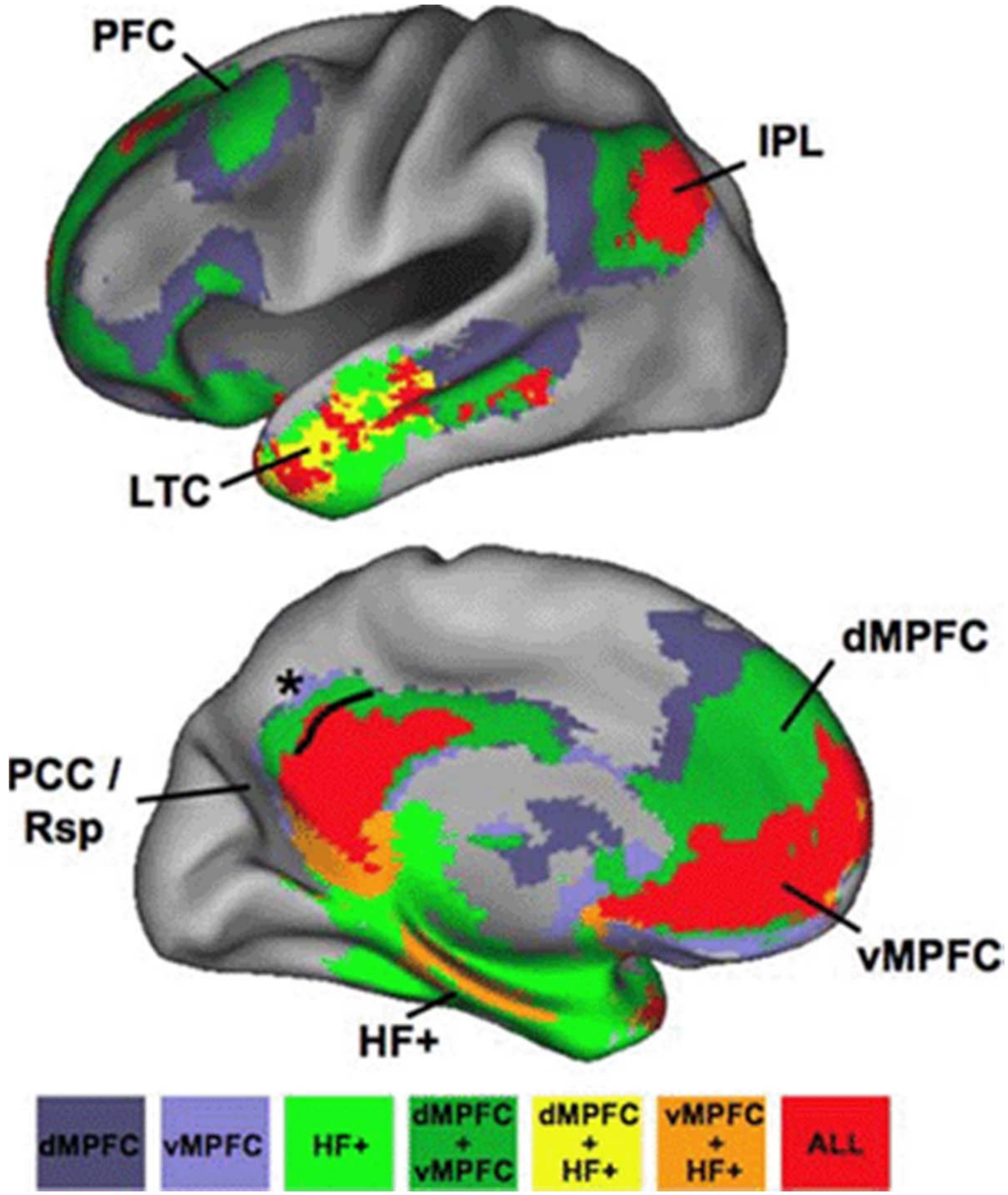


Fox PNAS 2005

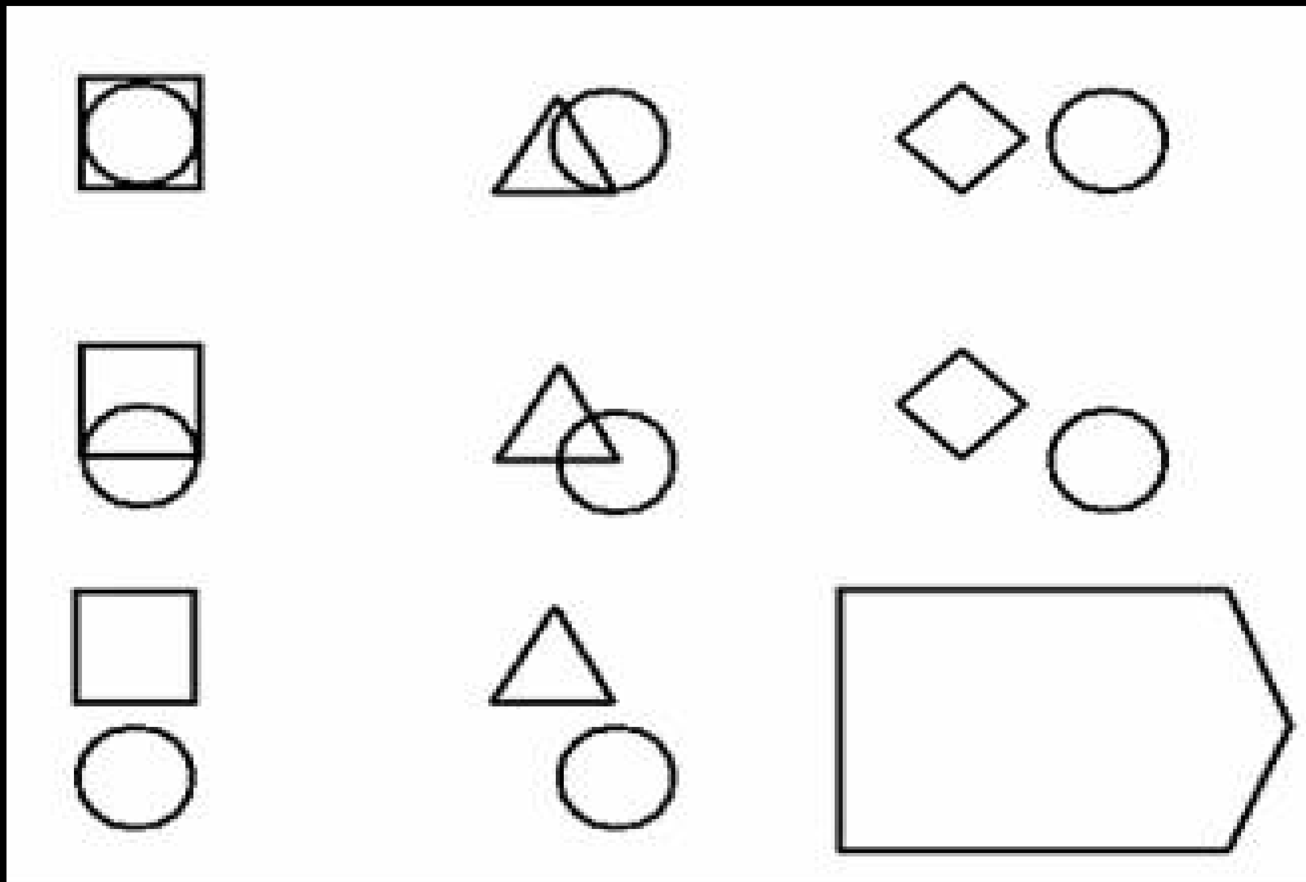
Fox et al., 2005. Proc. Natl. Acad. Sci. 102:9673–9678
Vincent et al, 2006 J Neurophysiol 96:3517–3531
Whitfield-Gabrieli et al, 2009, Proc. Natl. Acad. Sci. 102:9673–9678



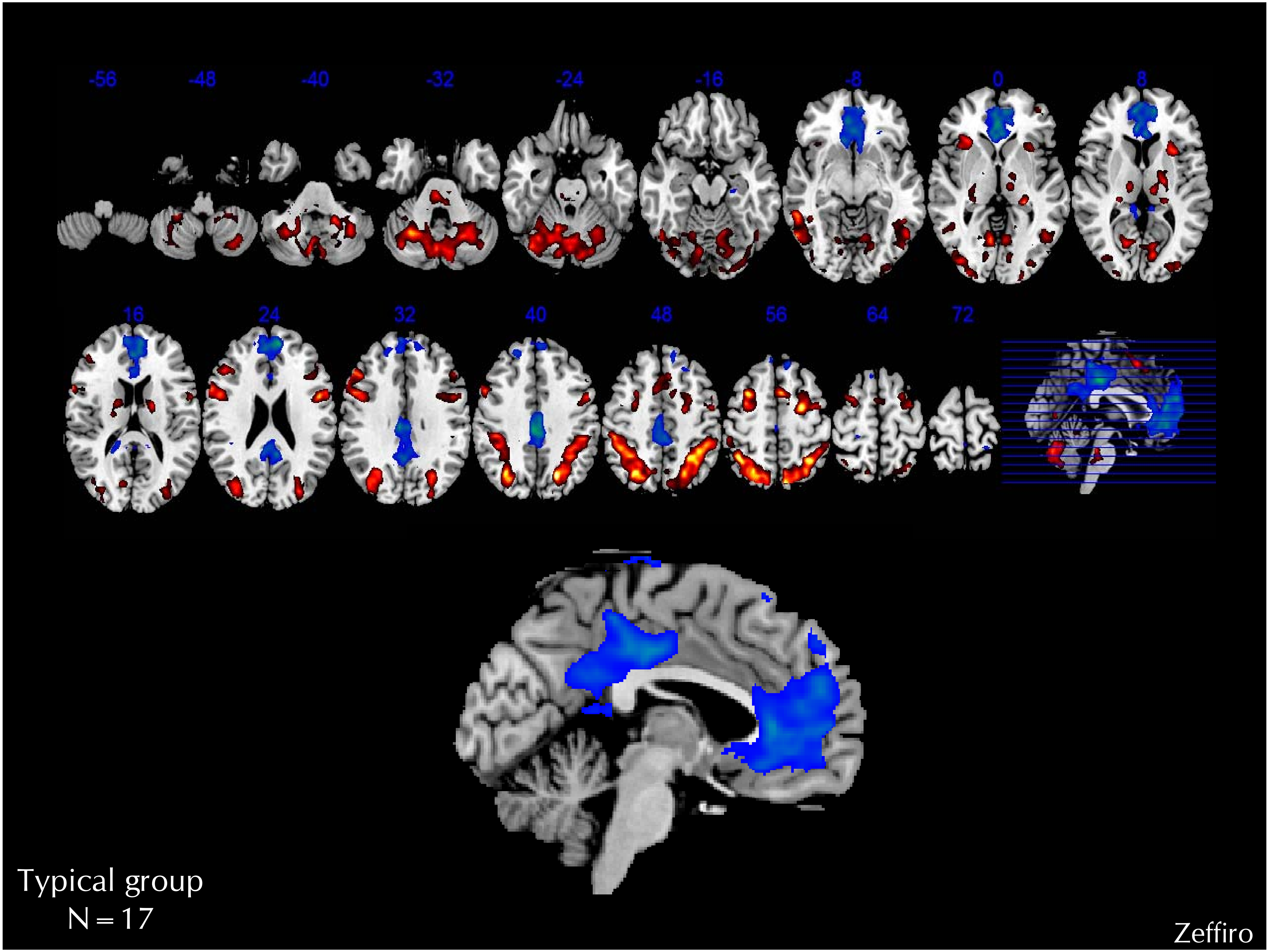
Buckner NYAS 2008



Buckner NYAS 2008



Zeffiro


-56
-48
-40
-32
-24
-16
-8
0
8
16
24
32
40
48
56
64
72
Typical group
N = 17
Zeffiro

Noise in connectivity analyses

Non-neuronal contributions to the BOLD-contrast signal

Noise sources

- Physiological noise
- Scanner drift
- Subject motion

<u>In "activation" studies</u>

Nuisance effects

Usually degrade power (lower statistical significance of the results)

<u>In "connectivity" studies</u>

Confounding effects

Introduce bias in results (show apparent connectivity between unrelated areas)

Need to appropriately characterize and remove noise effects to improve the validity of connectivity analyses

Regional Integration Modeling

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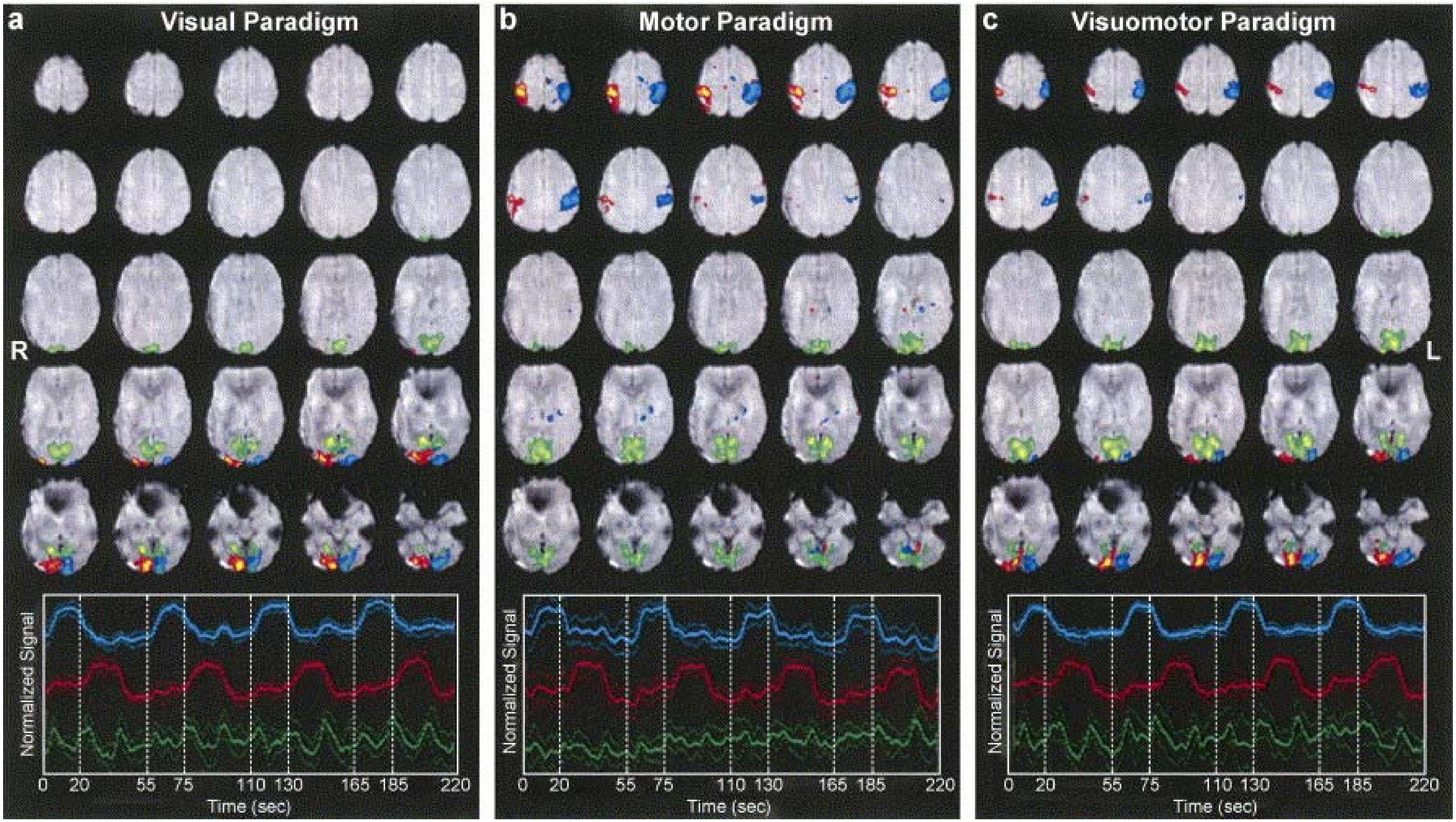


Calhoun MRI 2004

Independent Component Analysis

- A blind source separation (BSS) method
- Goal: separate sources from a linear mixture
- Model: **X=AS**

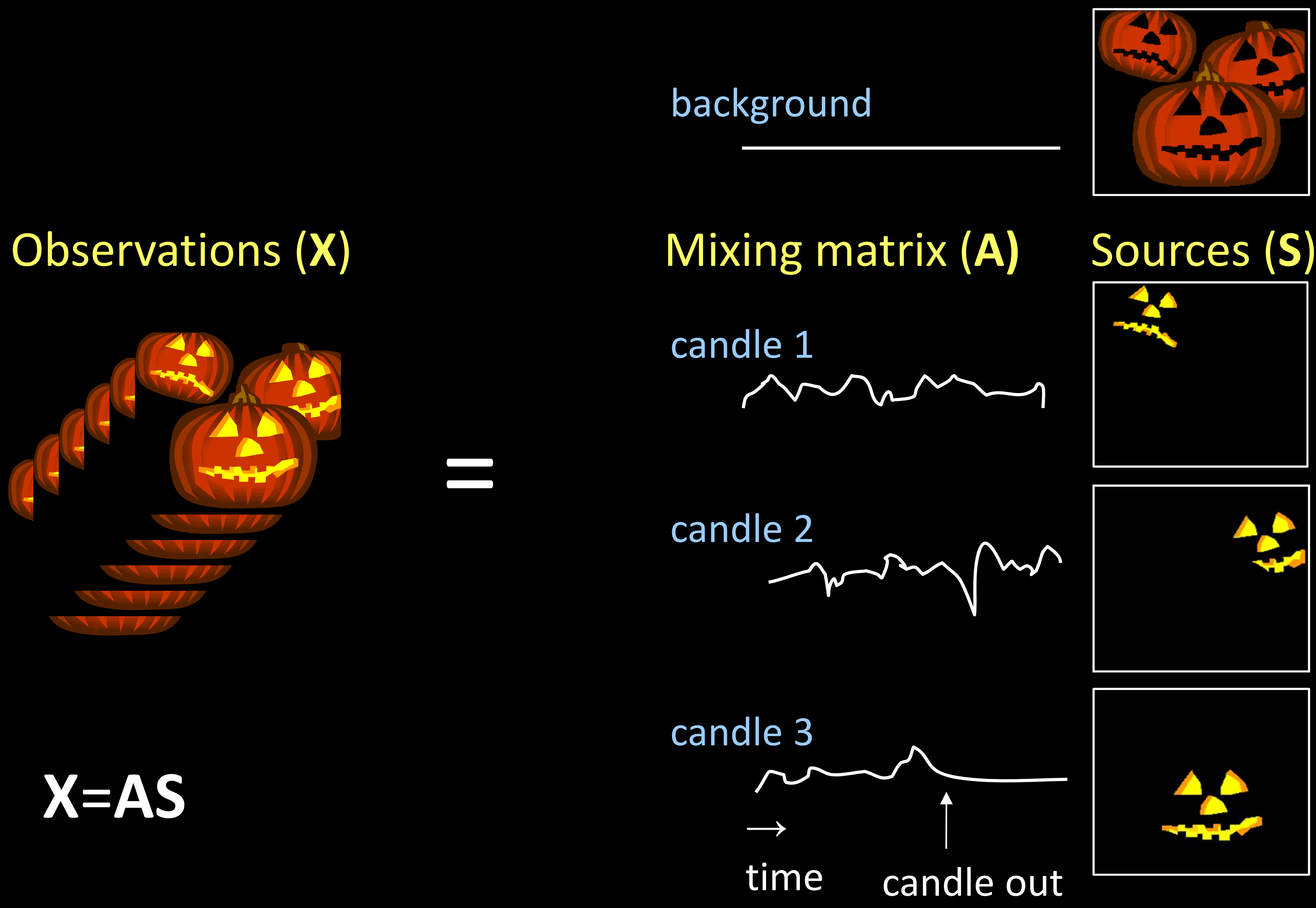
  X: Mixture (observed data)

  A: Mixing coefficients (estimated)

  S: Sources (estimated)

- Estimate: $\hat{\mathbf{S}} = \mathbf{WX}$, $\mathbf{W} = \mathbf{A}^{-1}$, based on maximizing statistical independence of $\hat{\mathbf{S}}$
- Assumptions
  - Linear mixing
  - Independence of sources
  - Non-Gaussian sources

a (not so scary) example

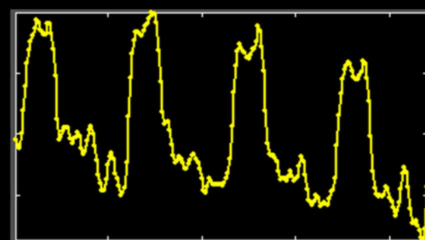


ICA applied to fMRI

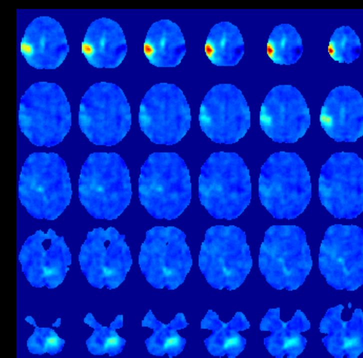
- We typically perform spatial ICA:
  - the sources are maps that are maximally spatially independent (i.e., non-overlapping)
  - the mixing matrix represents activation time courses of the sources.

fMRI task data =

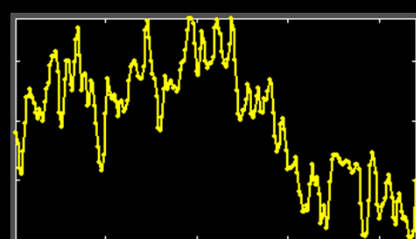
A_1



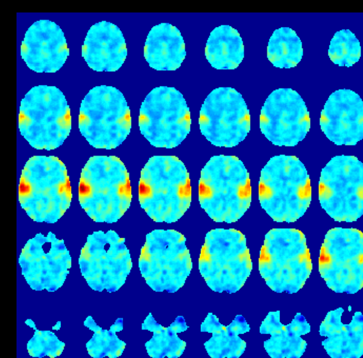
$\hat{S}_1$



A_2



$\hat{S}_2$

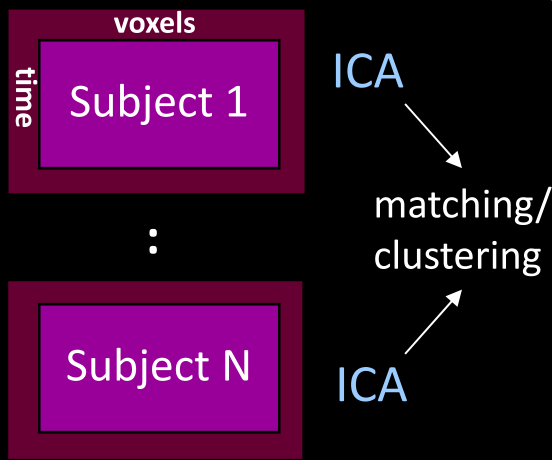


⋮

X=AS

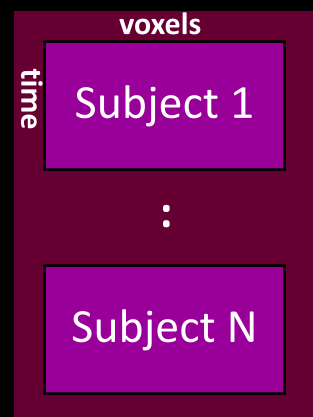
multi-subject ICA frameworks

combine single subject ICAs



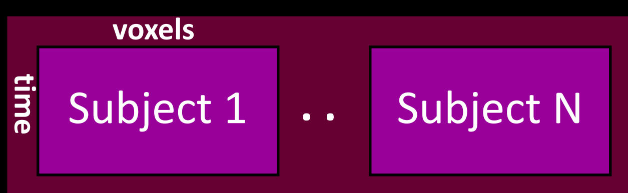
assumptions: variable

group ICA with temporal concatenation



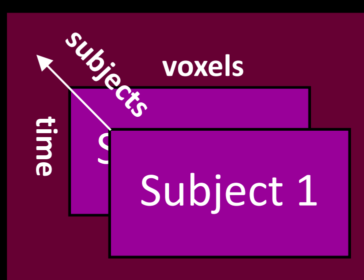
assumptions:
spatial consistency

group ICA with spatial concatenation



assumptions: temporal consistency

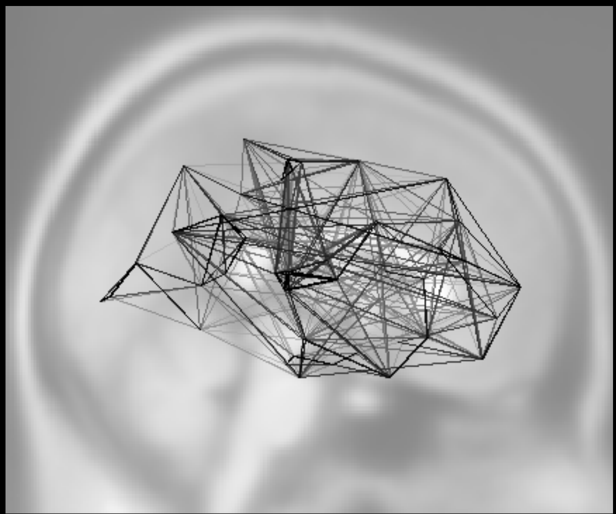
tensor ICA

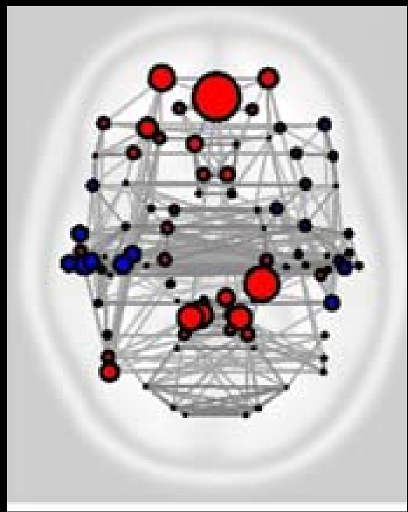


assumptions:
spatial consistency
temporal consistency

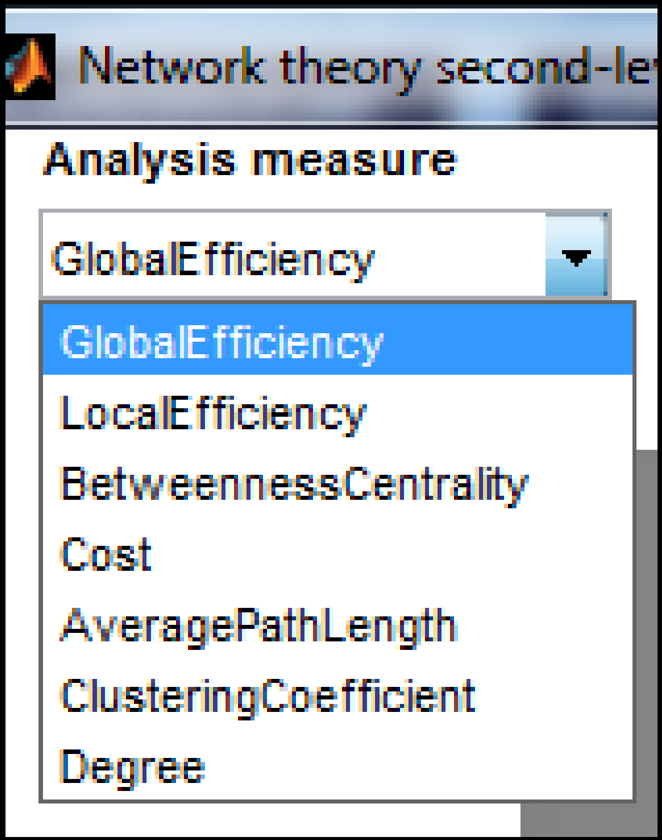
Graph-theory analyses

- **ROI-to-ROI connectivity matrices provide a framework to investigate functional architecture and network topology with graph theoretic analyses.**





Graph-theory analyses

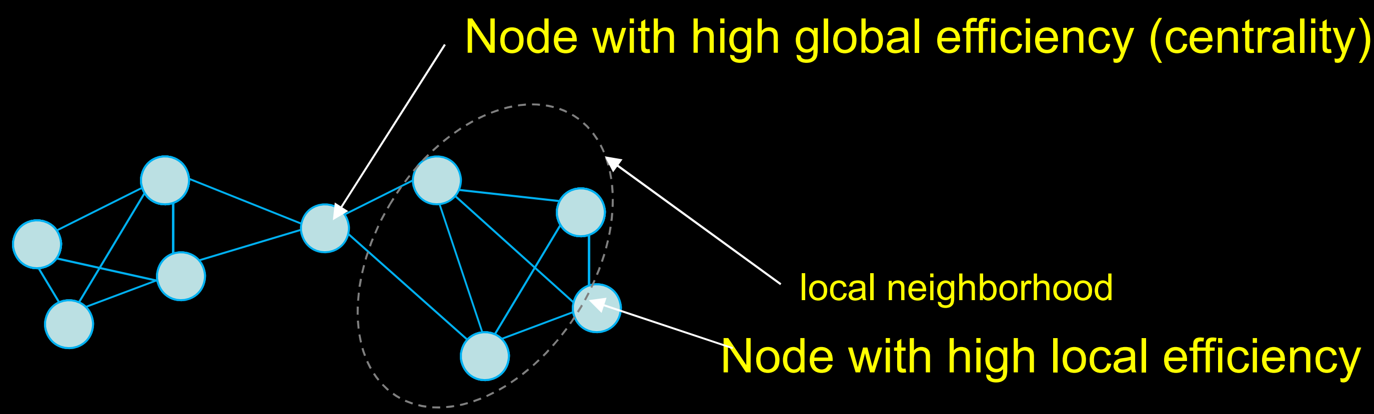


Graph theory

- Properties of each ROI’s contribution to the network:

Global efficiency: Average inverse distance (number of steps) in the shortest-path between one region and each of the other regions.

Measures the relative importance / centrality of a node in a network.



Local efficiency: Average inverse distance among all of the regions connected to a given region (dotted line in the example above).

Measures the ‘locality’ on an ROI (strength of the local network of connected ROIs)

Node: Global & Local Effficiency

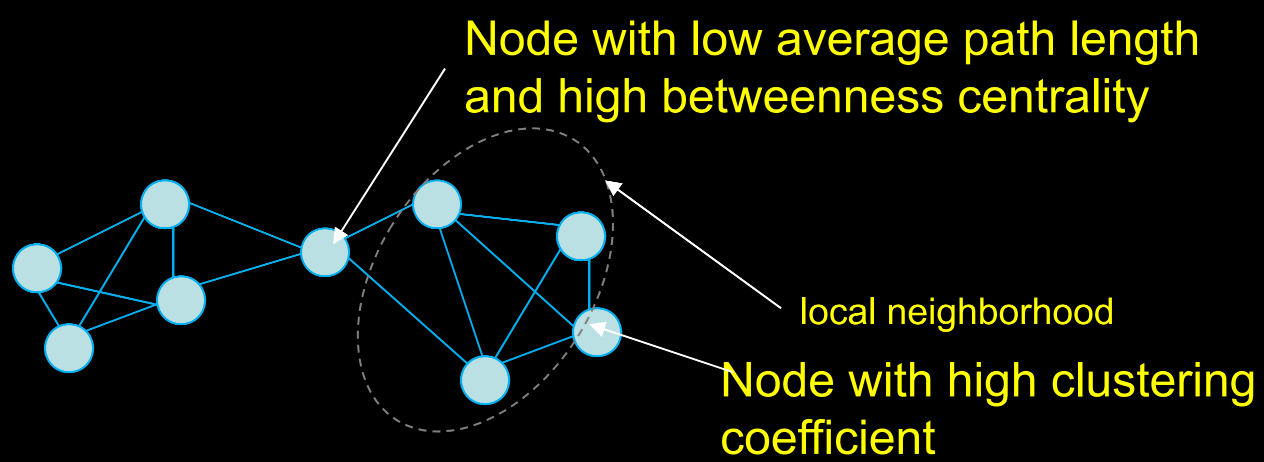
- High '*global efficiency*' for a node means that this node is 'closer' to all of the other nodes (it is also interpreted as a measure of 'centrality')

- High '*local efficiency*' for a node means that its neighbors are well connected to each other

Graph theory

Average path length: *Average distance between a node and the rest of the nodes (inversely related to global efficiency)*

Betweenness centrality: *Proportion of all shortest-paths in the network (between all pairs of nodes) containing a given node*



Cluster coefficient: *Proportion of connected nodes in the local graph containing only the neighbors of each node (related to local efficiency)*

Cost/degree: *Proportion/number of regions connected to a given region*

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Psycho-physiological Interaction (PPI)

- Measure of functional connectivity, and how it is affected by psychological variables

- Looks at how brain activity can be explained by the interaction between 2 variables
  - an experimental variable (e.g. level of attention)
  - activity in a particular brain area (source area)
- This is done voxel-by-voxel across the entire brain

PPIs vs typical interactions

		Task: Attend eyes	Task: Attend mouth
Stimulus	Upright face	$T_1 S_1$	$T_2 S_1$
Stimulus	Inverted face	$T_1 S_2$	$T_2 S_2$

PPIs vs typical interactions

- A typical interaction
  - Use General Linear Model:

$$Y = (T_1 - T_2)\,\beta_1 + (S_1 - S_2)\,\beta_2 + (T_1 - T_2)(S_1 - S_2)\,\beta_3 + e$$

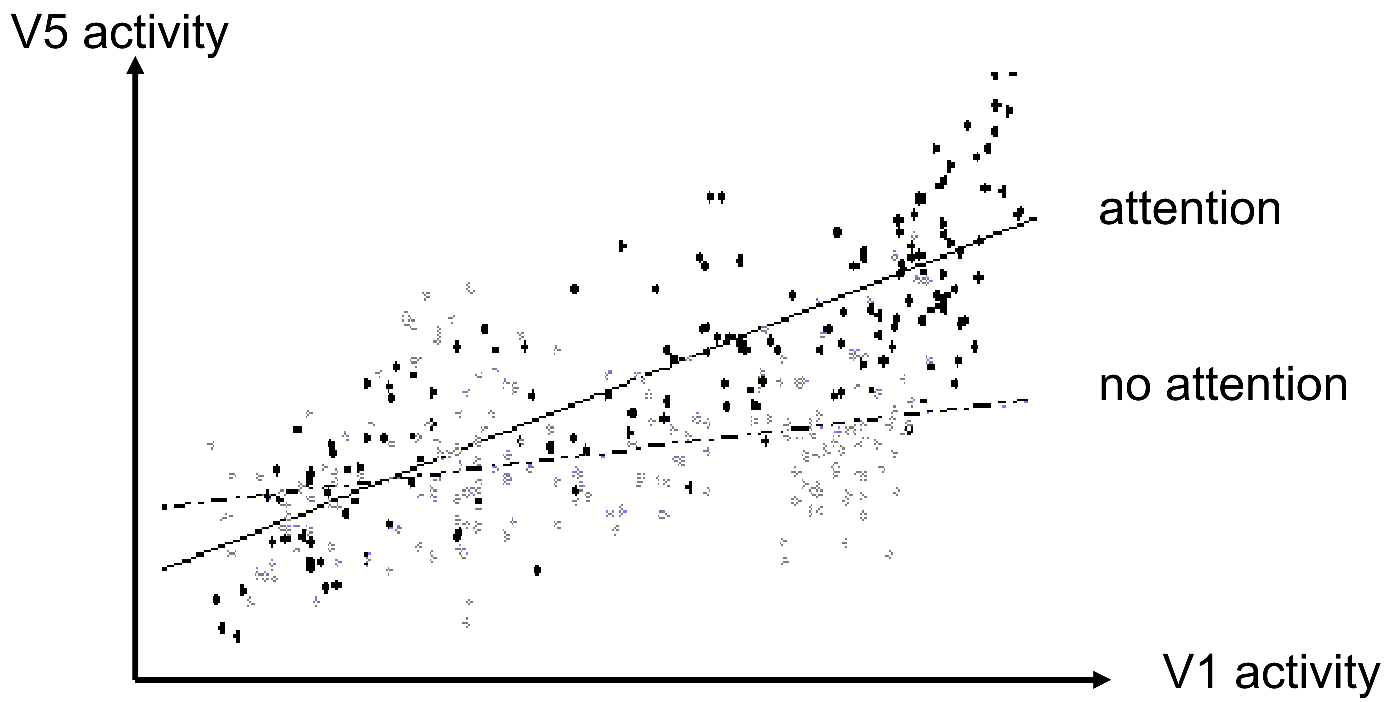
- A PPI
  - Replace one of the variables with activity in source region
    - Eg for source region V1:

$$Y = (T_1 - T_2)\,\beta_1 + \mathbf{V1}\,\beta_2 + (T_1 - T_2)\mathbf{V1}\beta_3 + e$$

PPI – an example

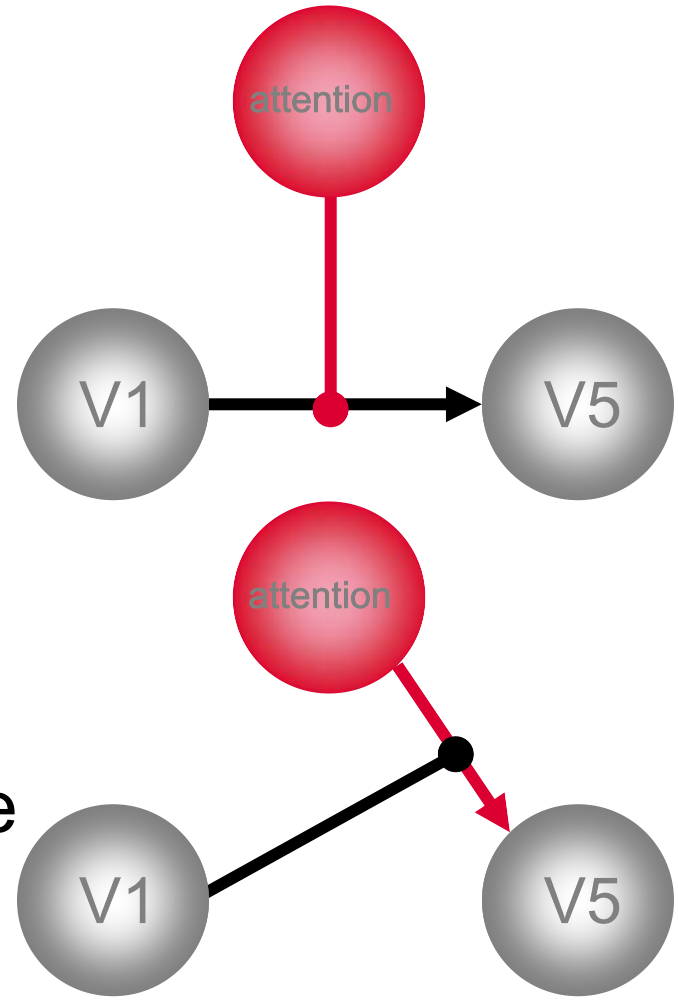
- Investigating influence of 2 factors:
  - V1 activity
  - Attention

  On activity in region V5
- Measure brain activity under 2 conditions of attention



Interpreting PPI

- 2 possible ways:
  - Contribution of source area to target area (ie the effective connectivity) depends on experimental context
  - Response of target area to experimental variable depends on activity of source area
- Mathematically, both are equivalent, but one may be more neurologically plausible



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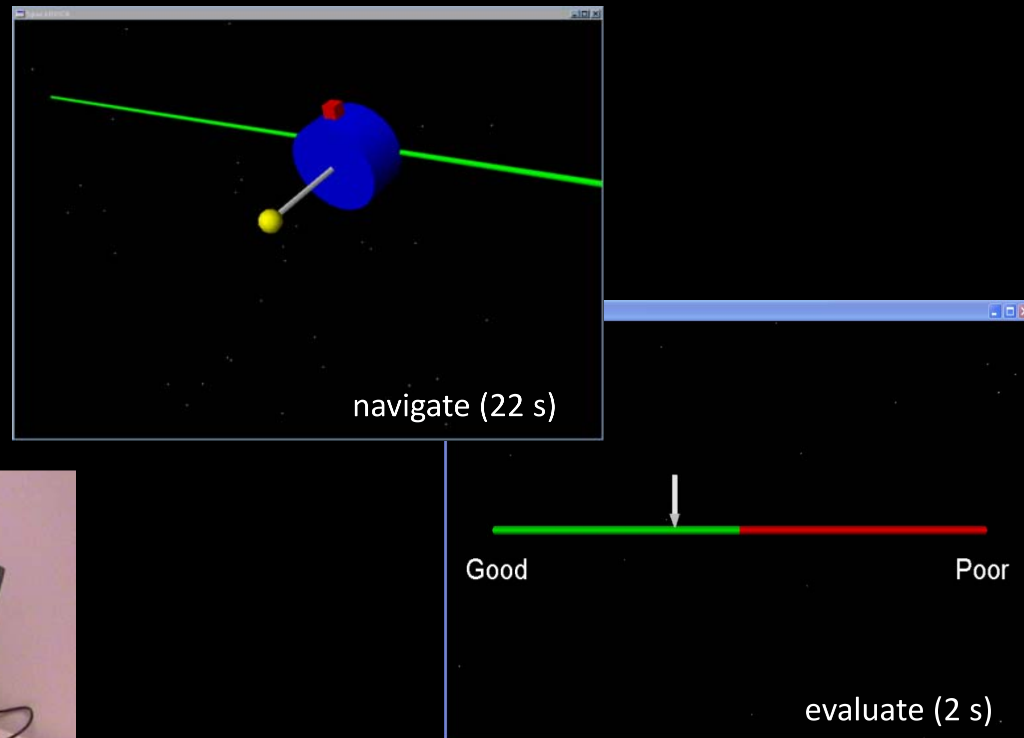
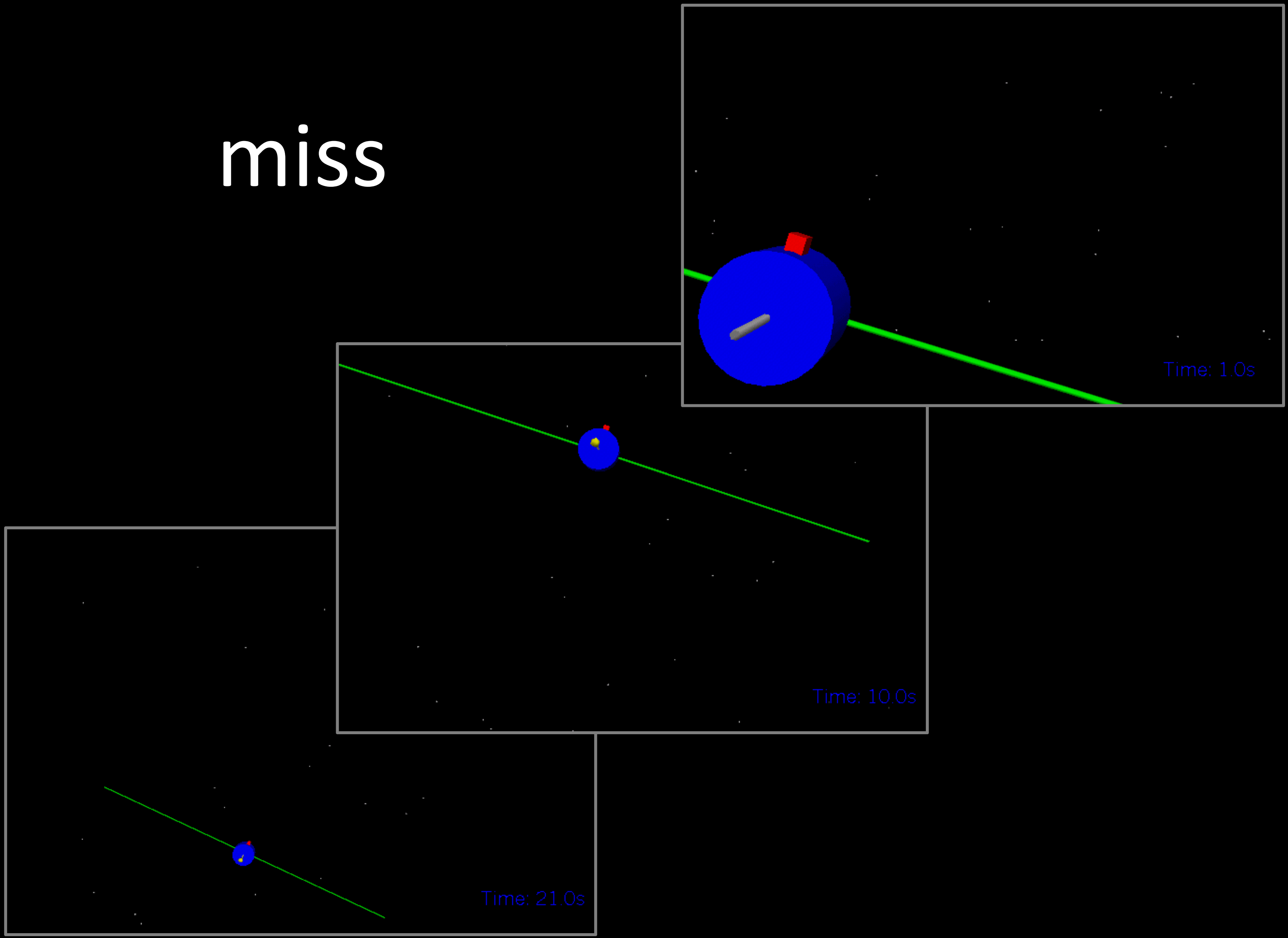
VIEWIMAGES™

Simulated target

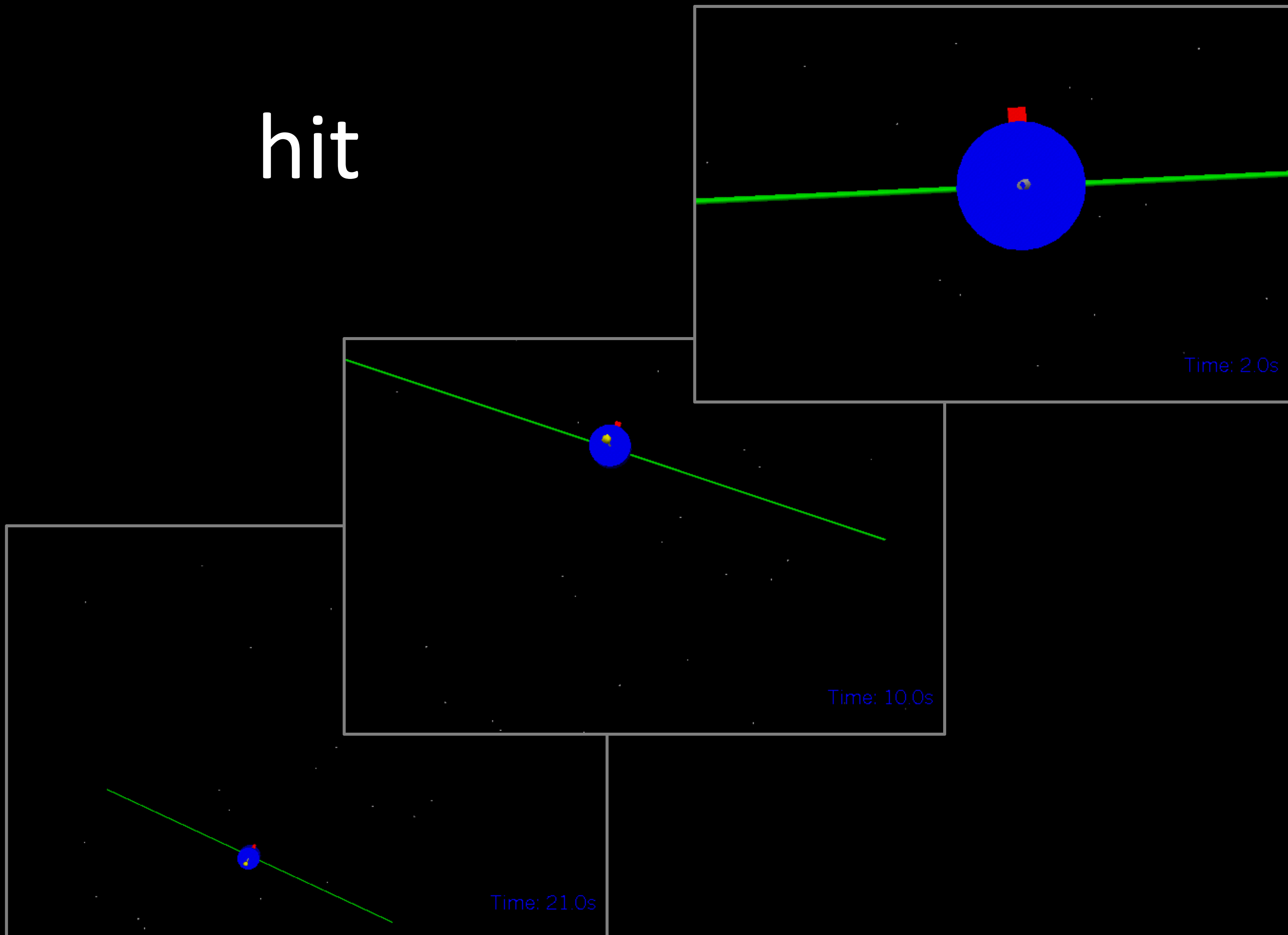


Joystick navigation

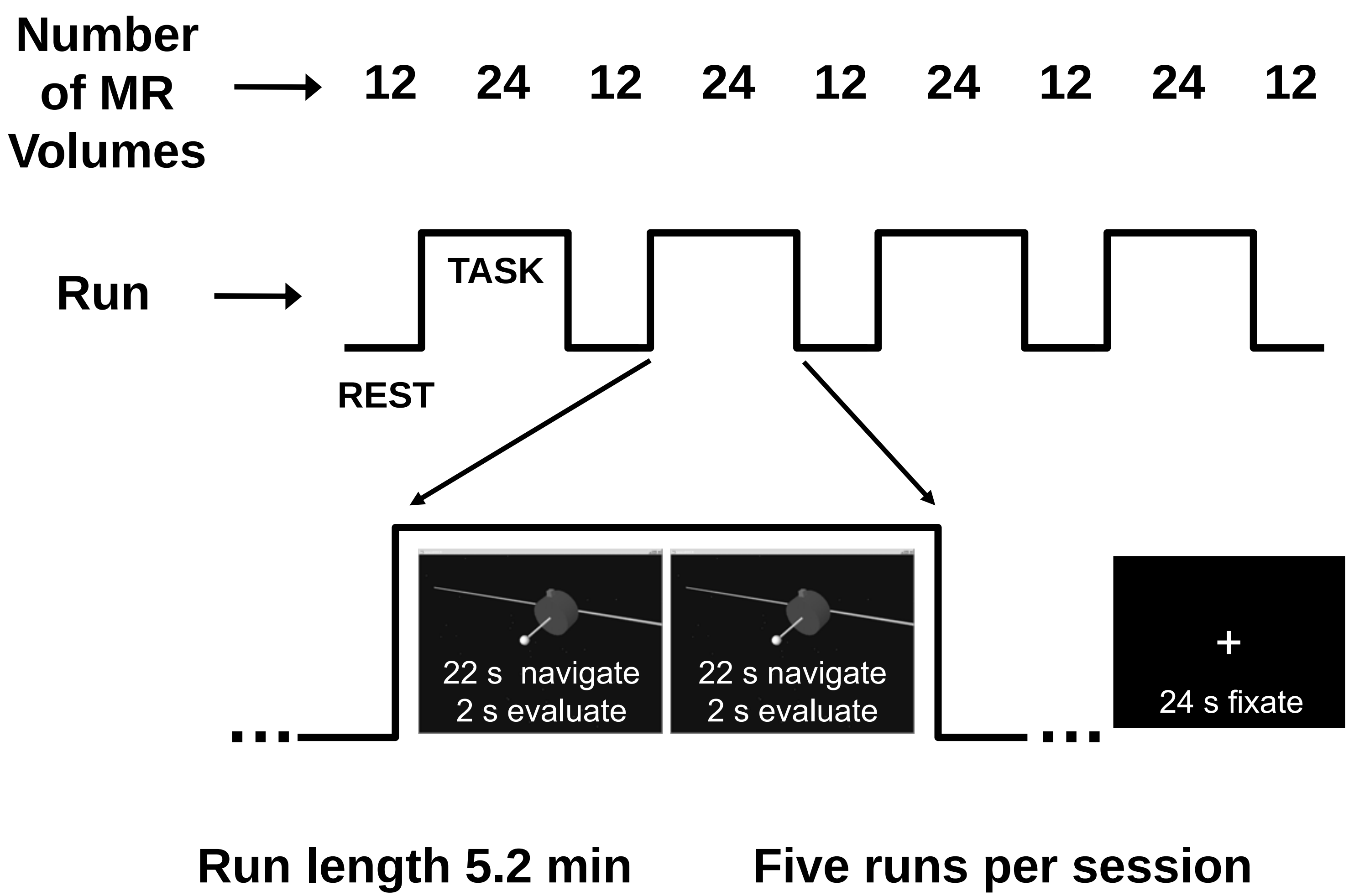
miss



hit



Experiment timing

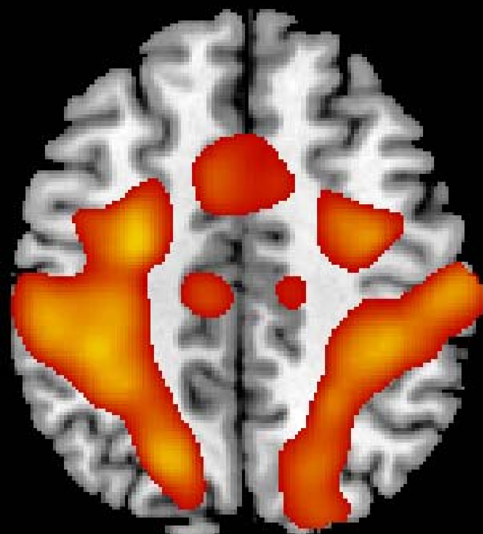


Experiment factorial design

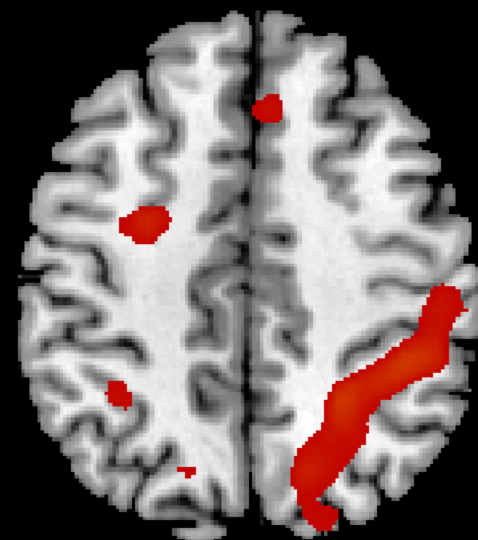
TASK

SLEEP		navigate	evaluate
	normal		
	deprived		

Navigate

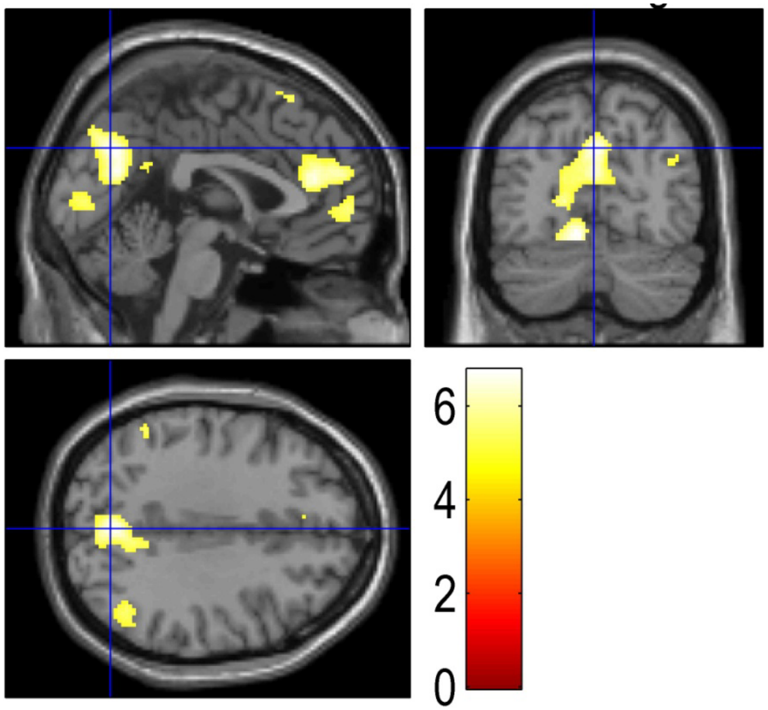


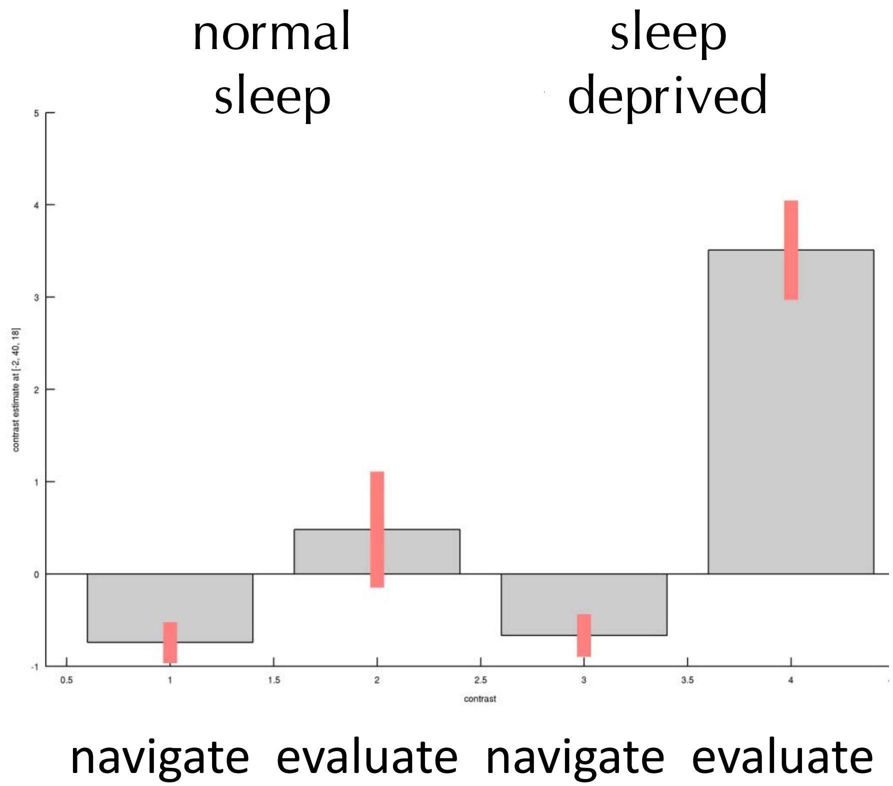
Evaluate



t>4.92 p<0.05 FWE corrected

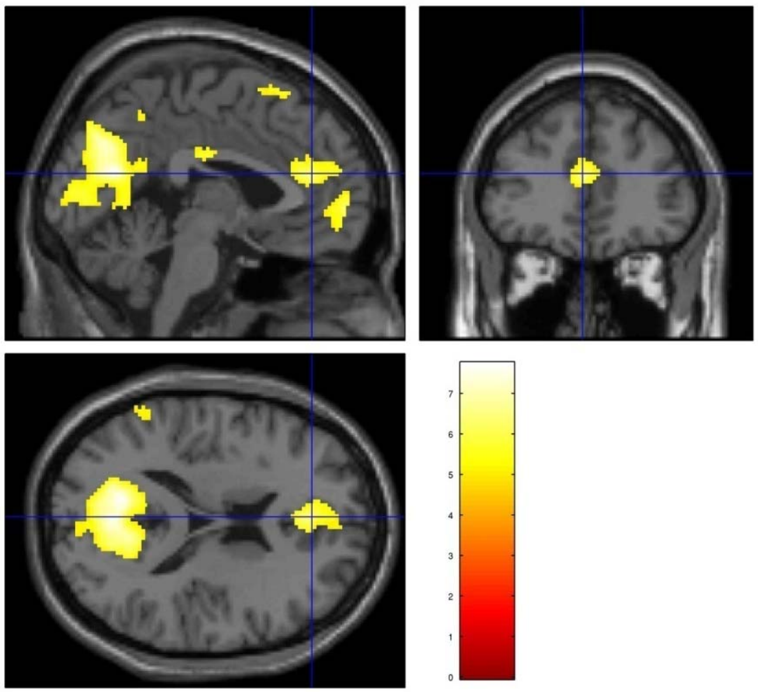
Posterior cingulate cortex



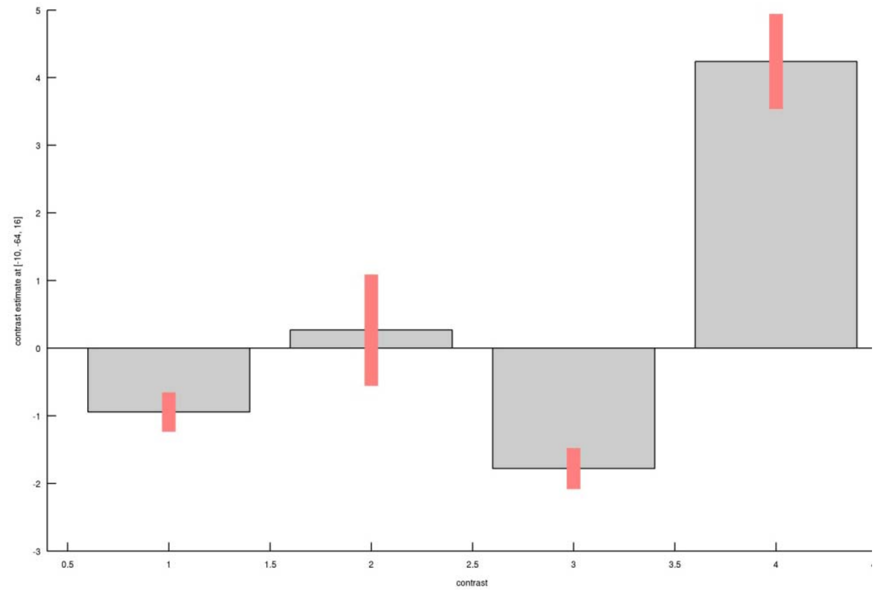


t>4.92 p<0.05 FWE corrected

Medial prefrontal cortex



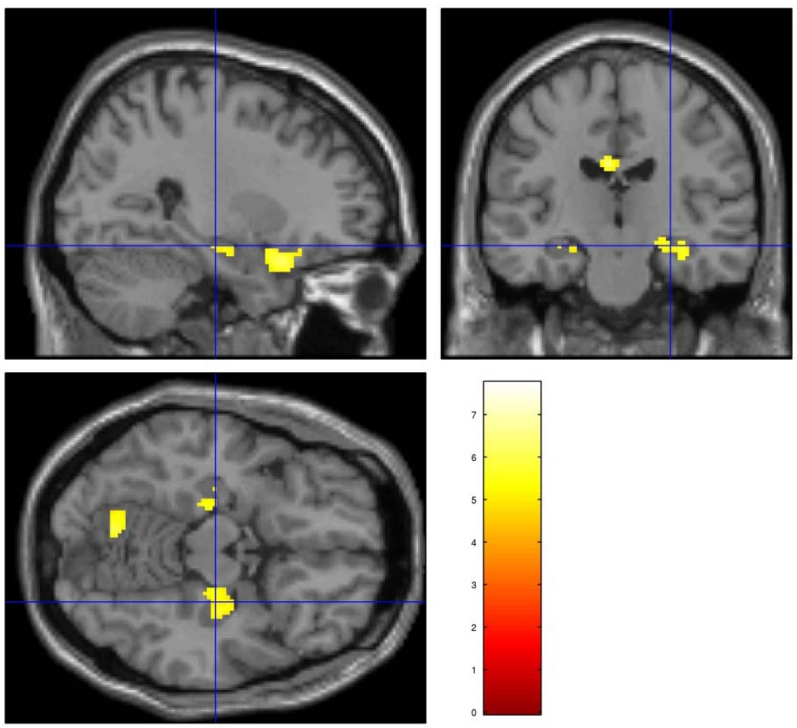
normal sleep | sleep deprived



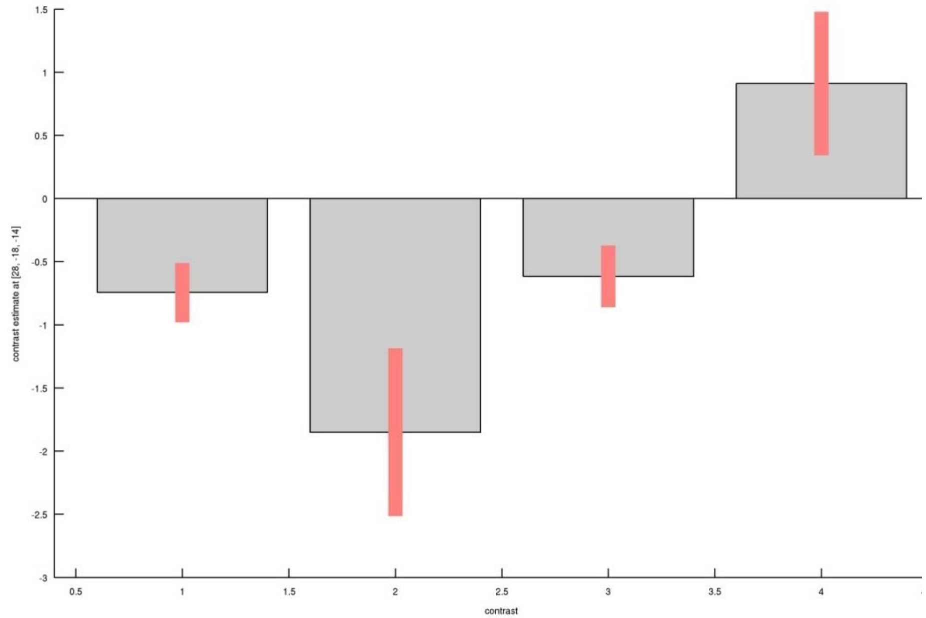
navigate evaluate navigate evaluate

t>4.92 p<0.05 FWE corrected

Right hippocampus

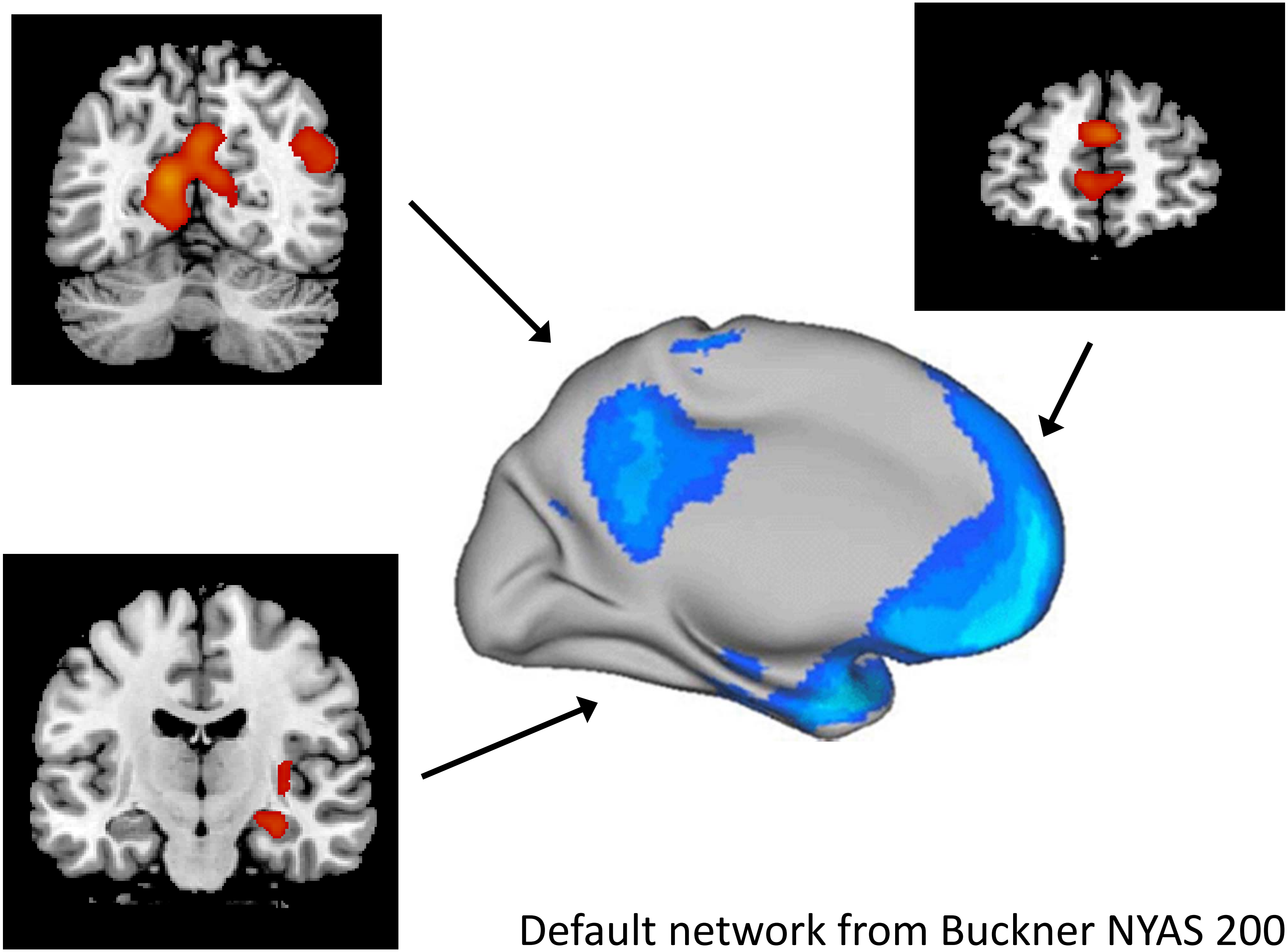


normal sleep | sleep deprived



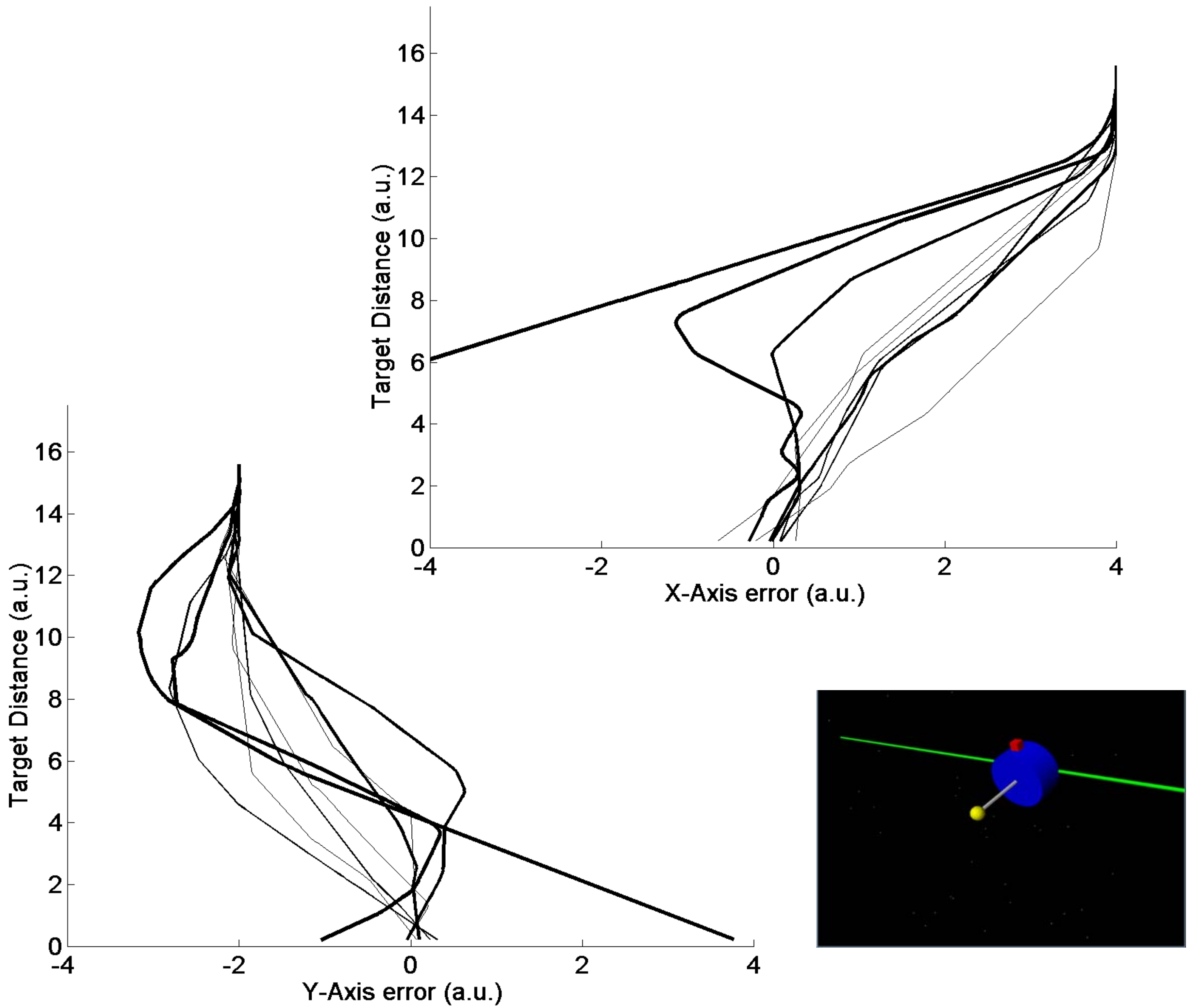
navigate evaluate navigate evaluate

t>4.92 $p<0.05$ FWE corrected



Default network from Buckner NYAS 2008

Can brain activity measured while engaged in a demanding task predict performance better than behavioral measures alone?

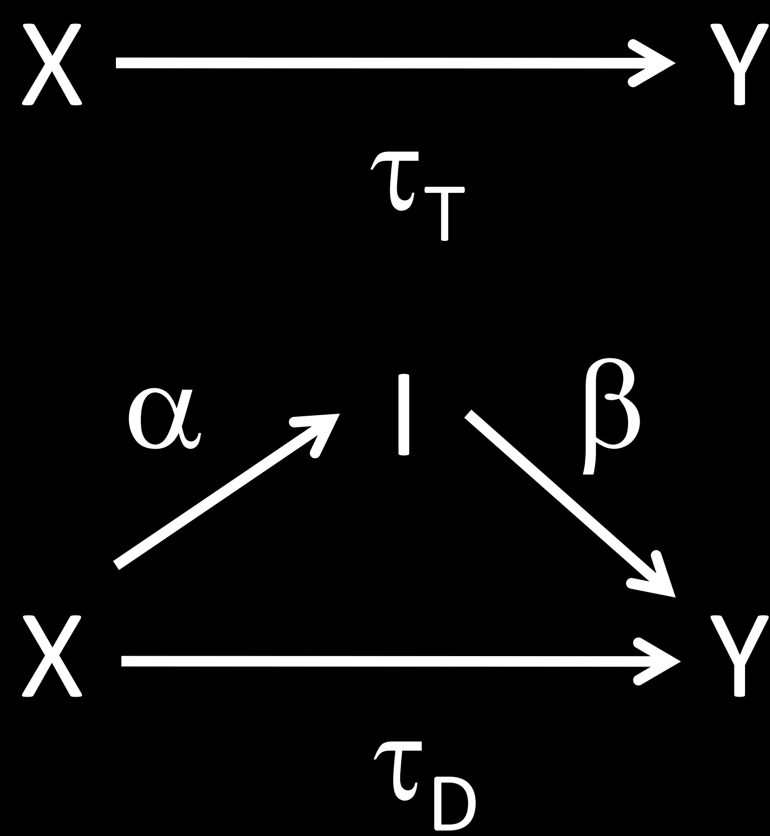

Target Distance (a.u.)
X-Axis error (a.u.)
Target Distance (a.u.)
Y-Axis error (a.u.)

What is mediation?

Total effect

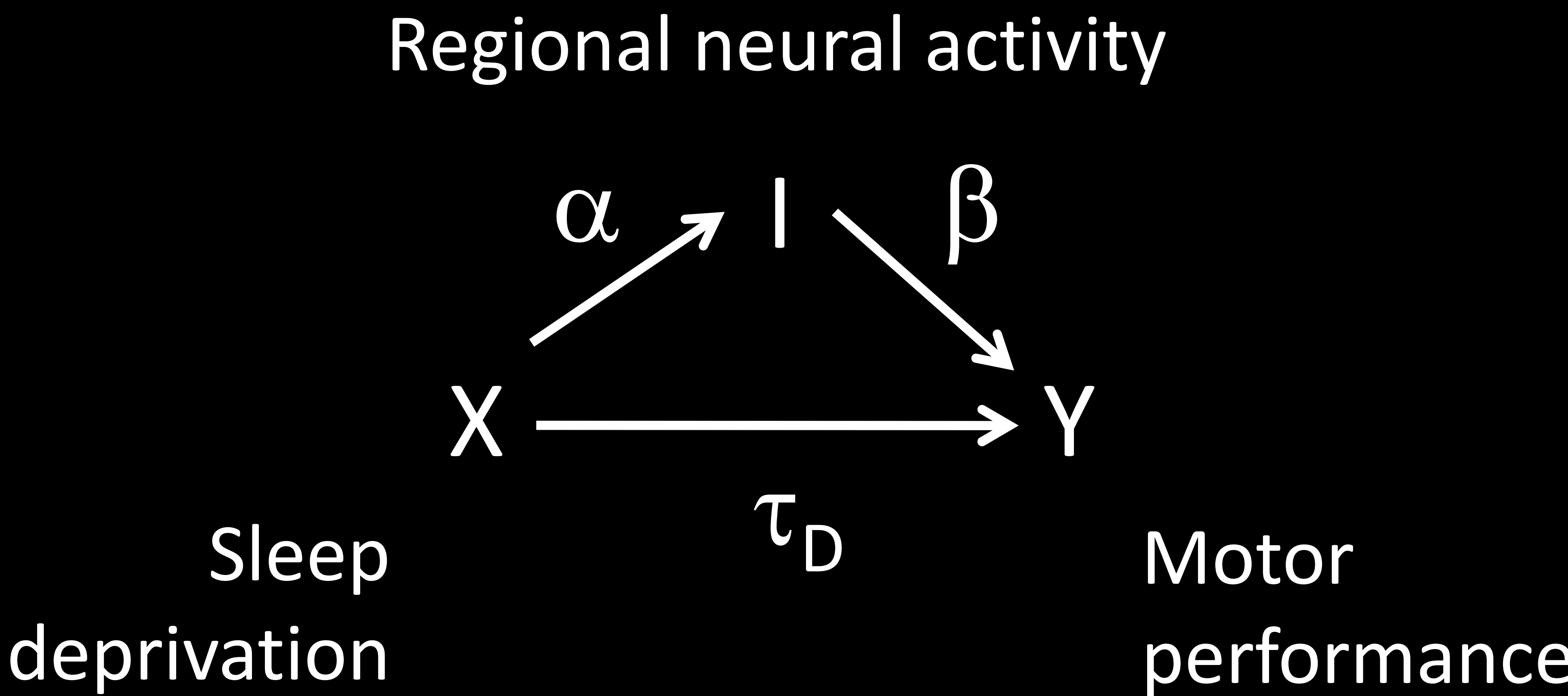
Indirect effect

Direct effect

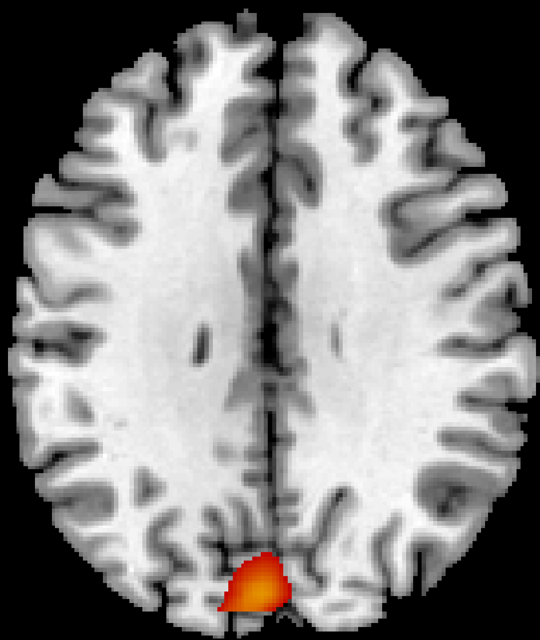


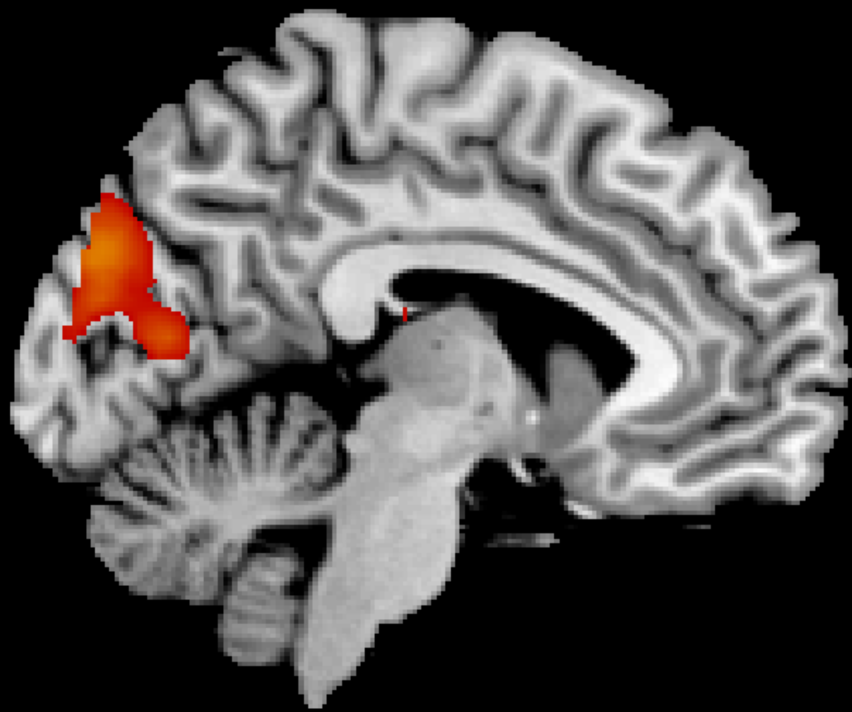
Mediation is a causal model

Can brain activity predict motor performance?



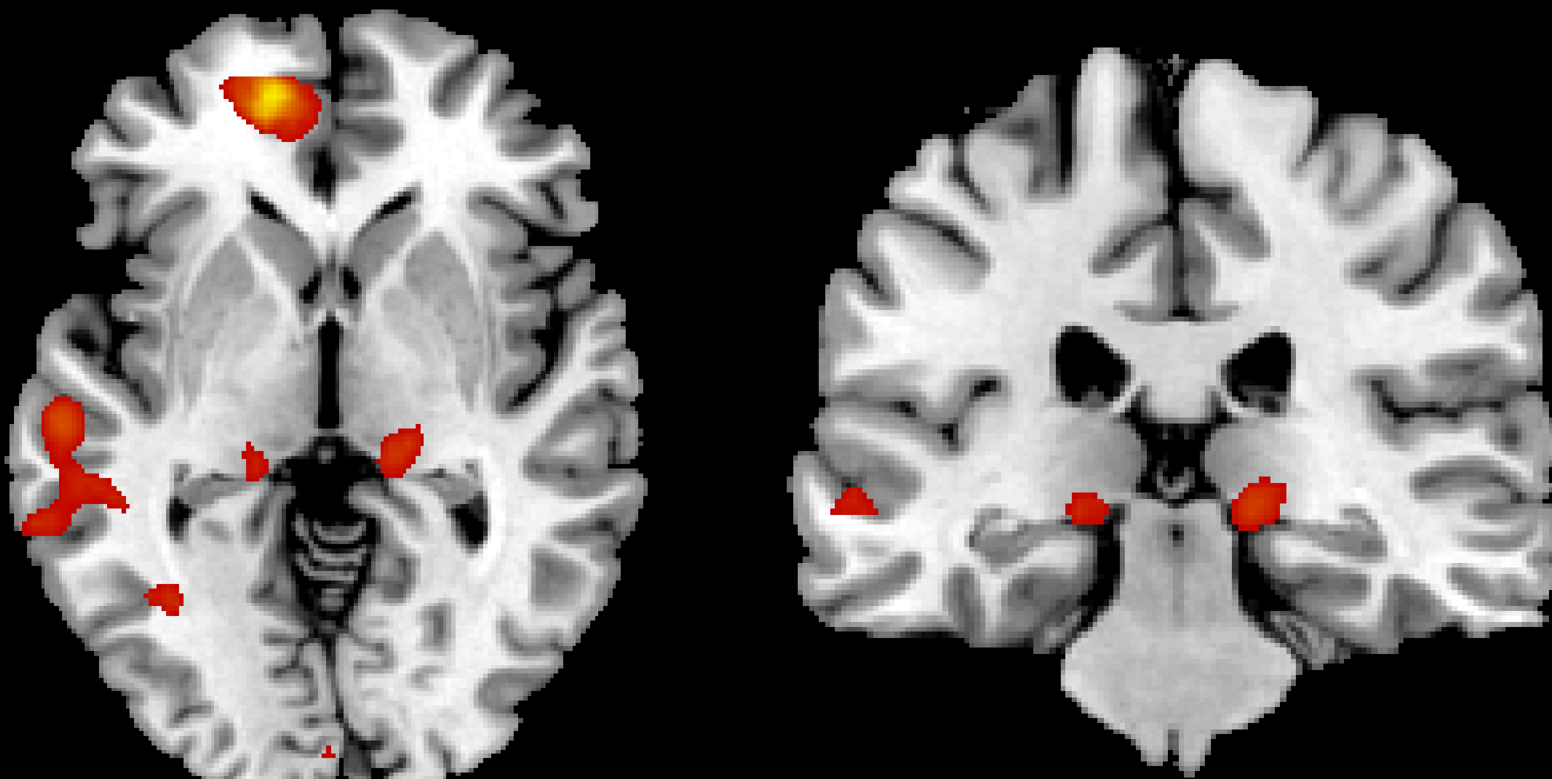
Occipital brain activity during NAVIGATION predicts motor performance better than the degree of sleep deprivation



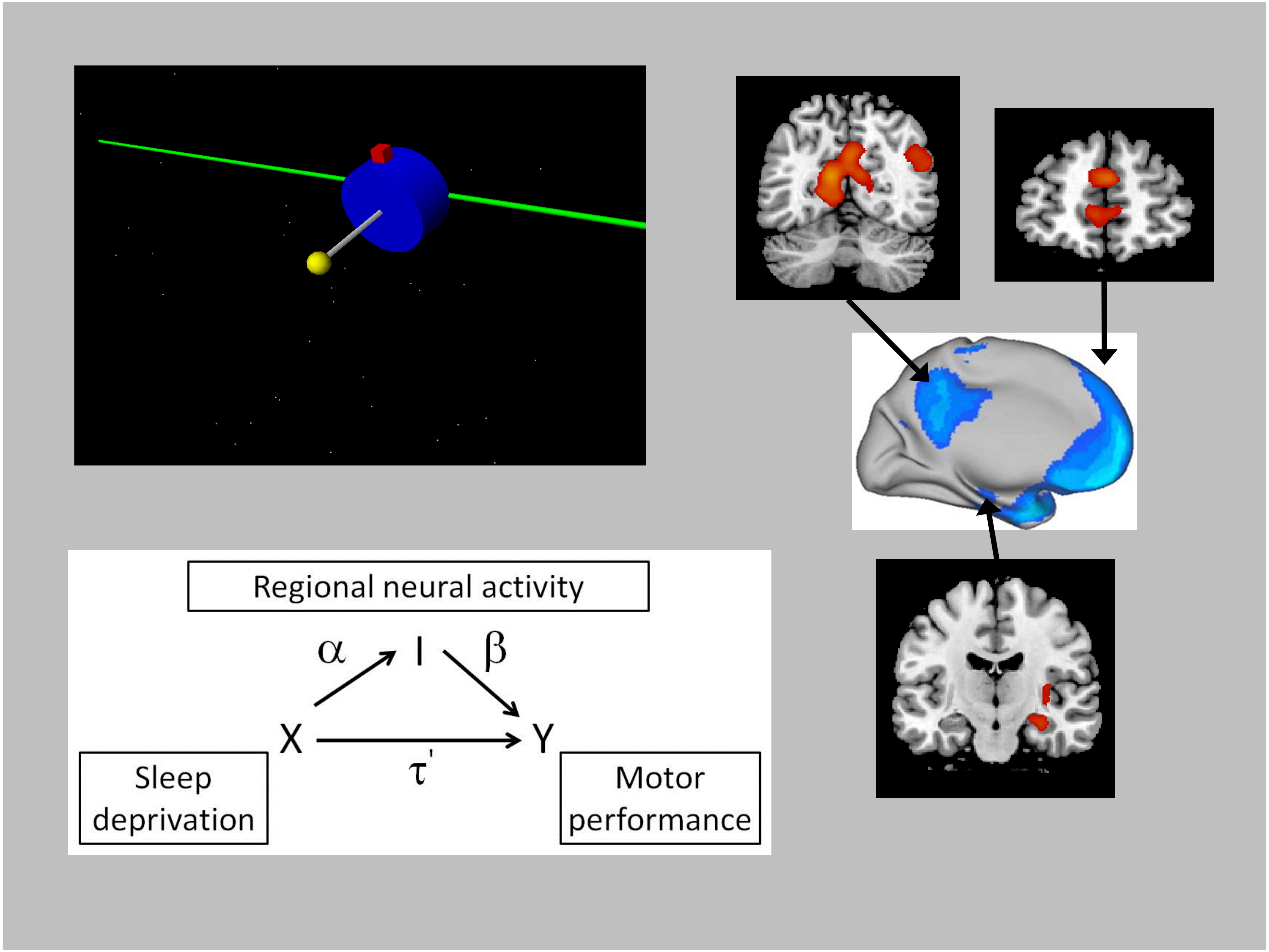


Sobel Test z>1.5

Thalamic and prefrontal activity during EVALUATION predict <u>motor performance</u> better than the degree of <u>sleep deprivation</u>



Sobel Test z>1.5


Regional neural activity
α
I
β
X
Y
τ'
Sleep deprivation
Motor performance

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Structural Equation Modelling (SEM)

- Another way of measuring effective connectivity
- Like PPI, looks at how effective connectivity is affected by experimental variables
- PET or fMRI

- Looks at covariances in activity between different brain areas (the degree to which their activity is related).
- Combines these data with anatomical model of how the areas are connected to one another
- Connectivity can be compared over time, or across different conditions (eg different levels of attention)

Steps in SEM

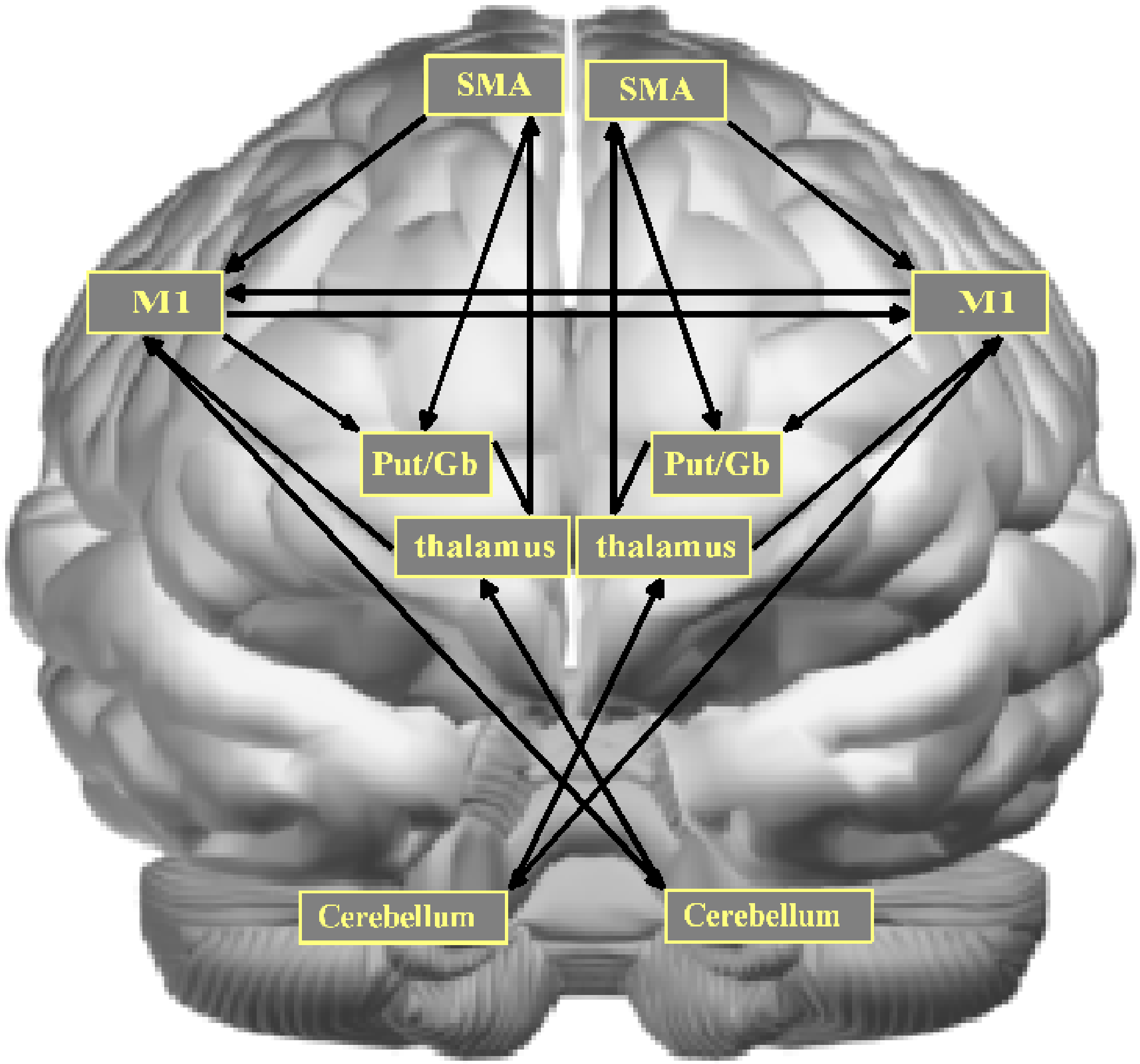
1. Select regions of interest
2. Build model specifying how they are connected to one another. Free parameters of model are ‘path coefficients’ – represent strength of connections
3. See what patterns of covariance this model predicts
4. Compare to observed patterns of covariance
5. ‘goodness of fit’ of model is diff between predicted and observed patterns

Deciding on regions

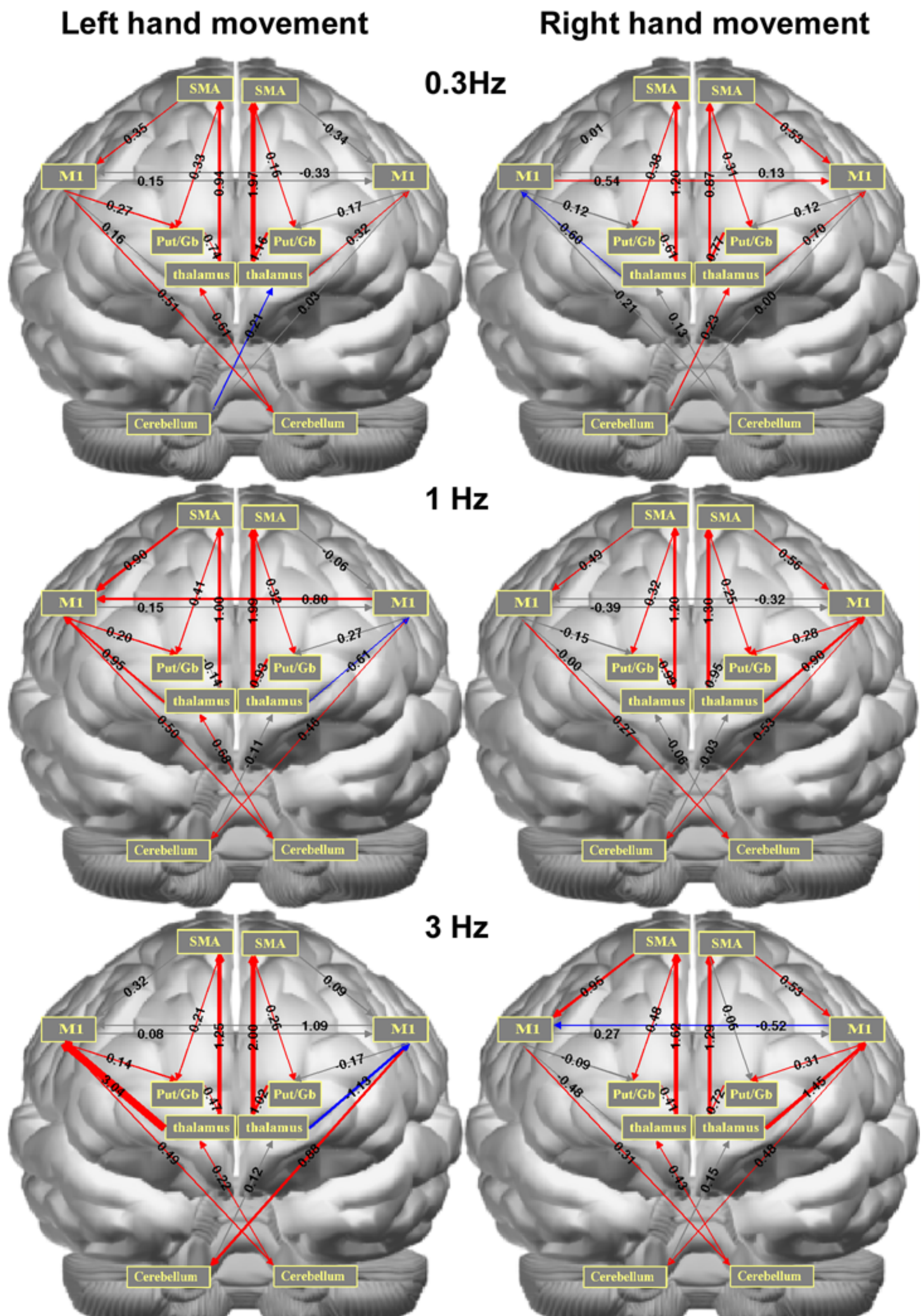
- Use existing fMRI and lesion data to identify likely areas
- We know how these areas are likely to be connected from
  - Tracer studies in animals
  - Diffusion Tensor Imaging (DTI) studies in humans

Advantages and Disadvantages

- Unlike PPI, it is possible to examine the influence of many brain areas simultaneously
- But the models do not allow the strength of a connection to vary over the time series



Lin et al. Human Brain Mapping 2010


Left hand movement
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0.3Hz
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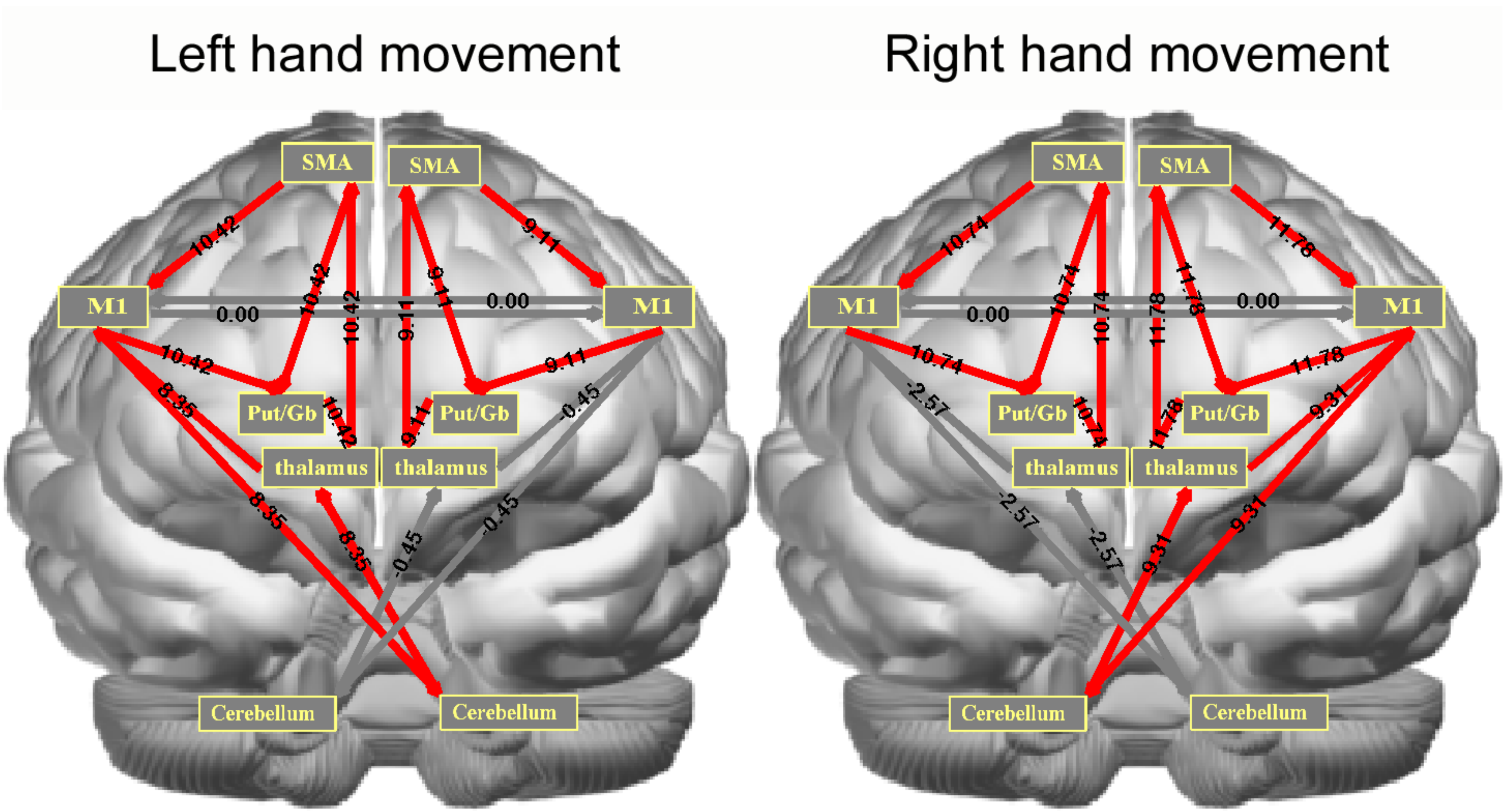

Lin et al. Human Brain Mapping 2010

Regional Integration Modeling

- Functional connectivity
  - Bivariate correlation
  - Multivariate modeling (PCA, ICA, PLS)
- Effective connectivity
  - Psychophysiologic interaction (PPI)
  - Mediation analysis
  - Structural equation modeling (SEM)
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A

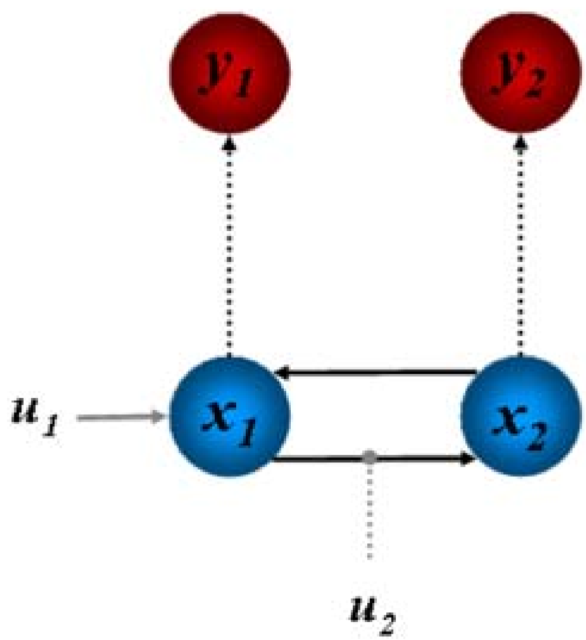
state changes | *fixed connectivity* | *modulation of connectivity* | *input parameters*

General bilinear state equation

$$\dot{x} = (A + \sum_{j=1}^{m} u_j B^j)x + Cu$$

external inputs

B



$$\dot{x}_1 = a_{11}x_1 + a_{12}x_2 + c_{11}u_1$$

$$\dot{x}_2 = a_{21}x_1 + a_{22}x_2 + b_{21}^{(2)}u_2x_1$$

Conceptual overview

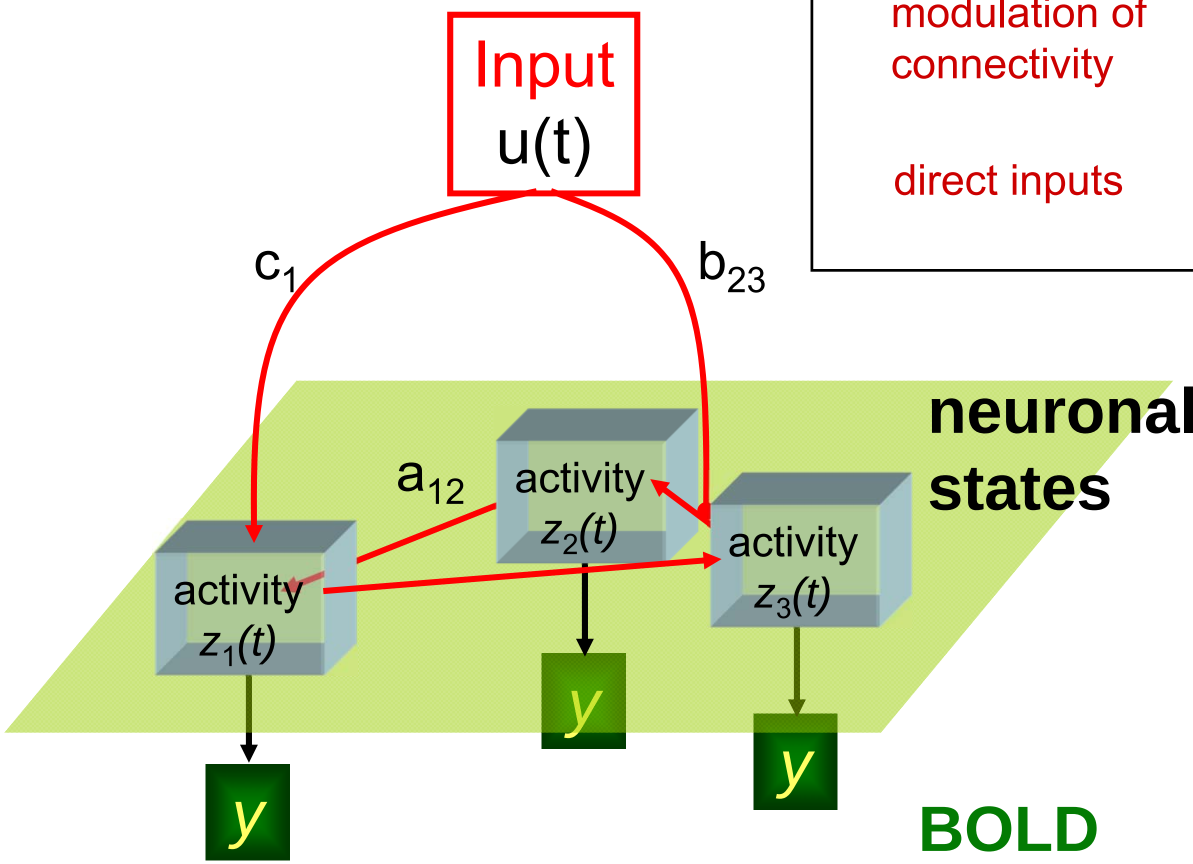
Neuronal state equation $\dot{z} = F(z, u, \theta^n)$

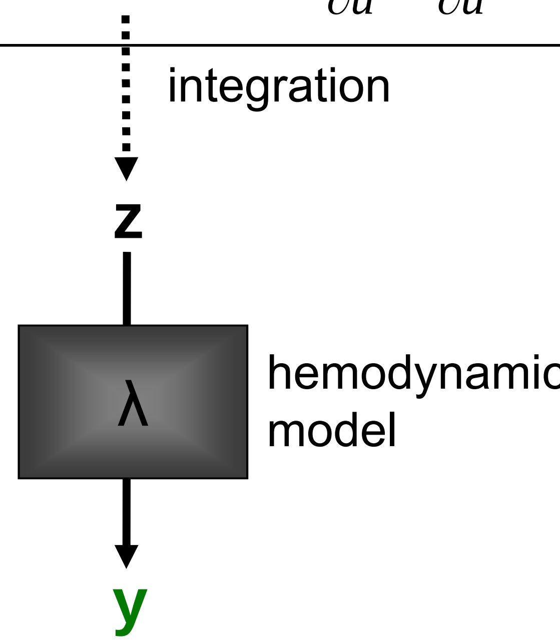
The bilinear model $\dot{z} = (A + \sum u_j B^j) z + Cu$

effective connectivity $$A = \frac{\partial F}{\partial z} = \frac{\partial \dot{z}}{\partial z}$$

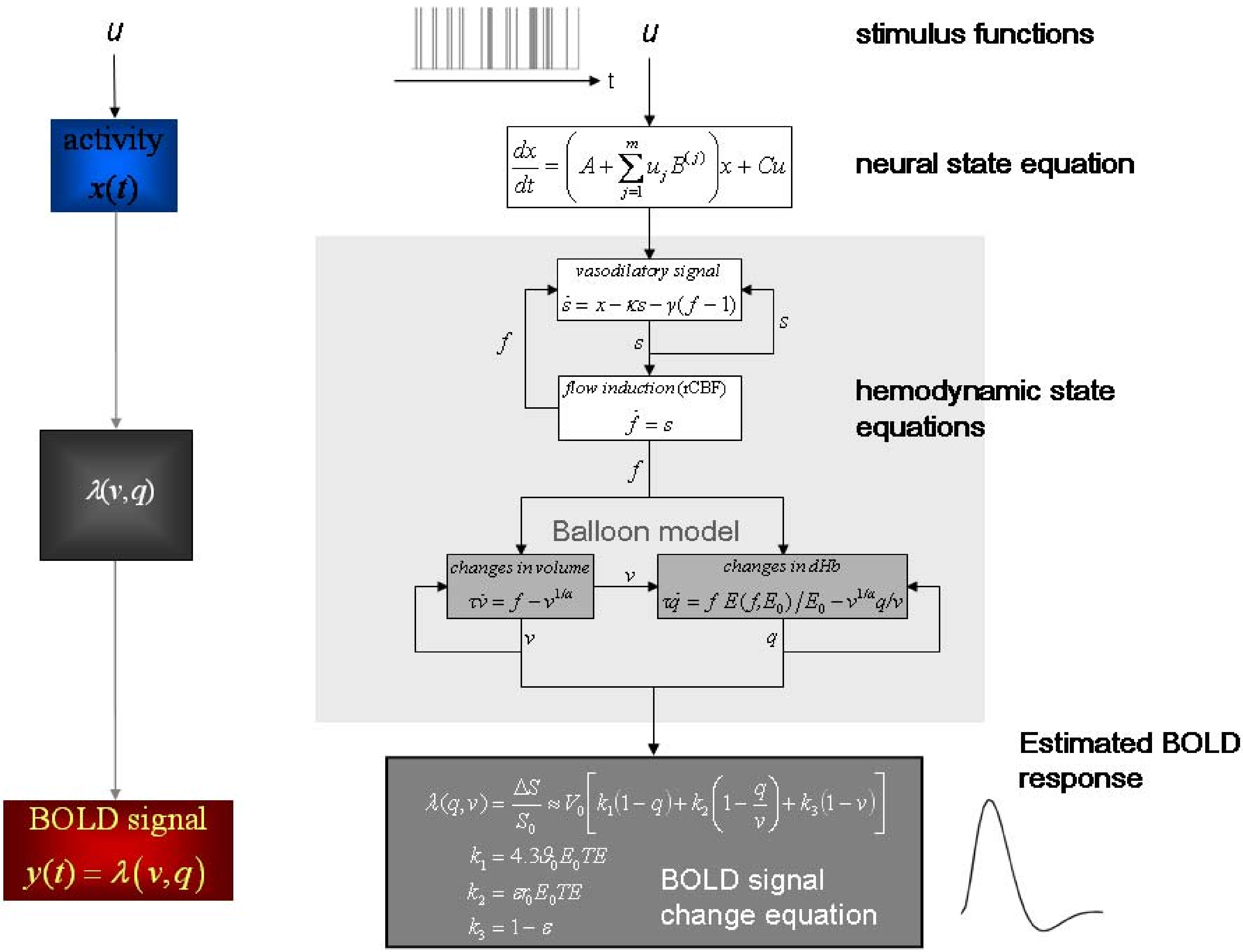
modulation of connectivity $$B^j = \frac{\partial^2 F}{\partial z \partial u_j} = \frac{\partial}{\partial u_j} \frac{\partial \dot{z}}{\partial z}$$

direct inputs $$C = \frac{\partial F}{\partial u} = \frac{\partial \dot{z}}{\partial u}$$



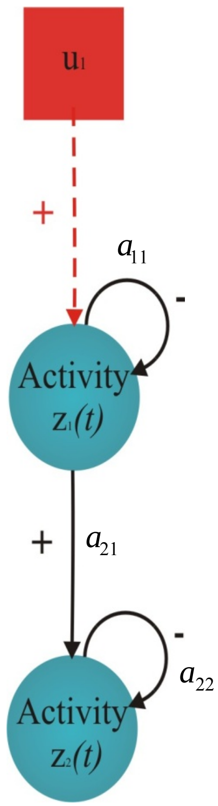


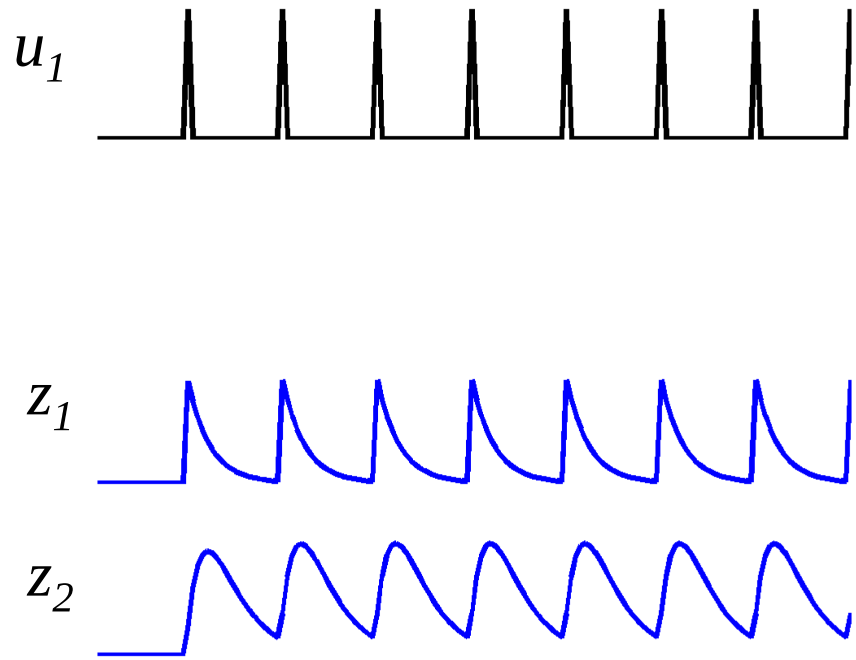
Friston et al. 2003, *NeuroImage*



u
activity
x(t)
λ(v,q)
BOLD signal
y(t) = λ(v,q)
t
u
stimulus functions
neural state equation
vasodilatory signal
flow induction (rCBF)
hemodynamic state equations
Balloon model
changes in volume
changes in dHb
Estimated BOLD response
BOLD signal change equation

Neurodynamics: Two nodes with input

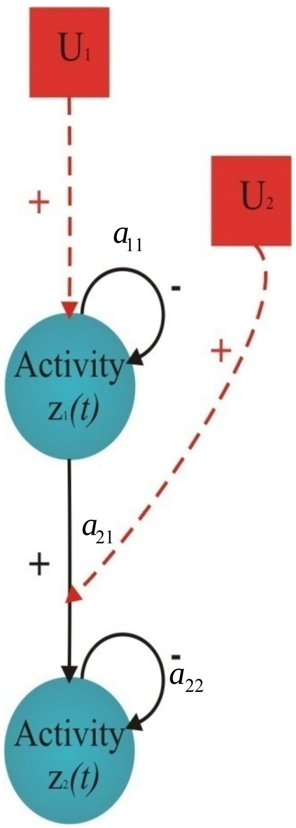


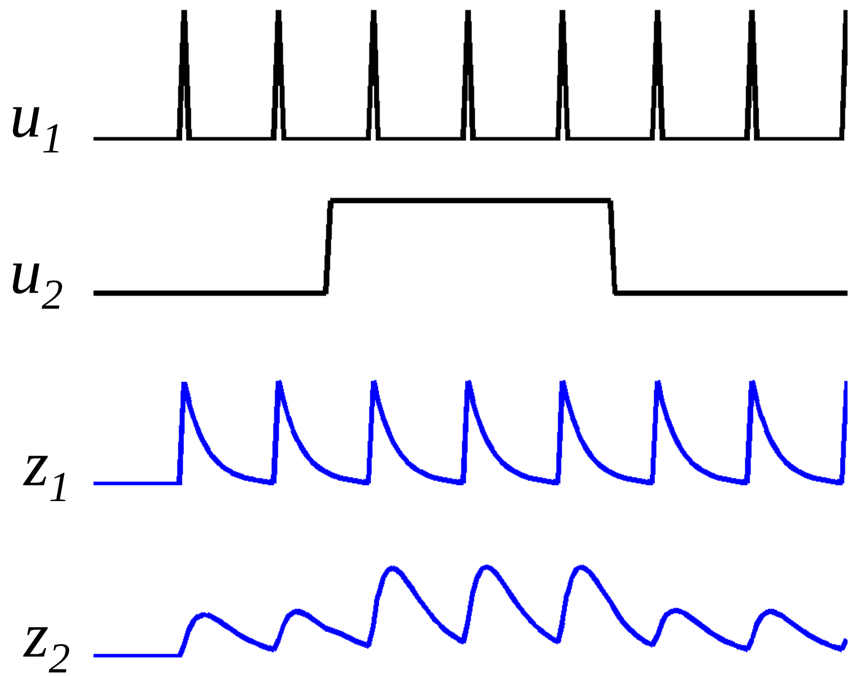


$$\begin{bmatrix}\dot{z}_1\\ \dot{z}_2\end{bmatrix}=\begin{bmatrix}a_{11} & 0\\ a_{21} & a_{22}\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix}+\begin{bmatrix}c\\ 0\end{bmatrix}u_1 \qquad a_{21}>0$$

activity in z_2 is coupled to z_1 via coefficient a_{21}

Neurodynamics: positive modulation



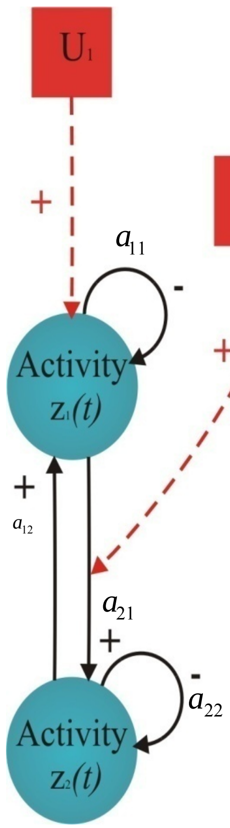


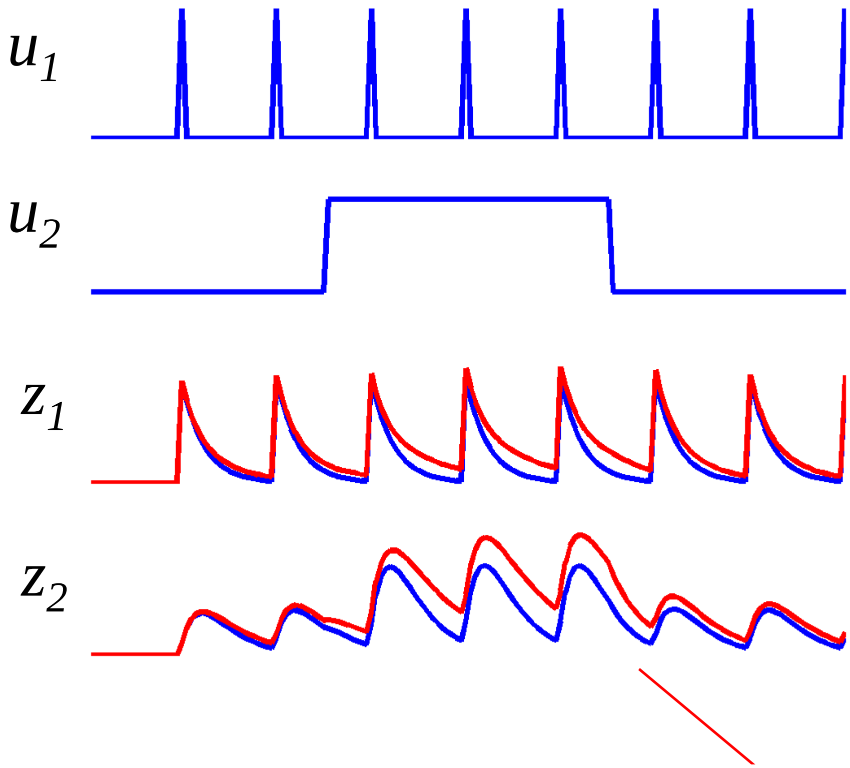
$$\begin{bmatrix}\dot{z}_1\\ \dot{z}_2\end{bmatrix}=\begin{bmatrix}a_{11} & 0\\ a_{21} & a_{22}\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix}+u_2\begin{bmatrix}0 & 0\\ b_{21}^{2} & 0\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix}+\begin{bmatrix}c\\ 0\end{bmatrix}u_1$$

$b_{21}^{2} > 0$

modulatory input ***u2*** activity through the coupling a_{21}

Neurodynamics: reciprocal connections

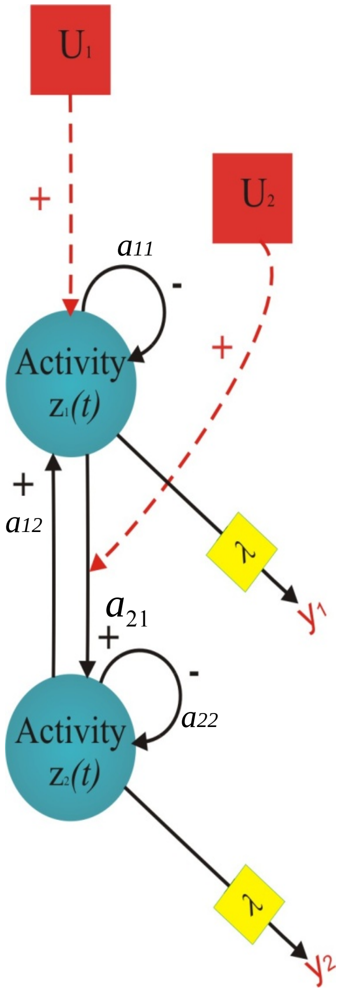




$$\begin{bmatrix}\dot z_1\\ \dot z_2\end{bmatrix}=\begin{bmatrix}a_{11} & a_{12}\\ a_{21} & a_{22}\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix}+u_2\begin{bmatrix}0 & 0\\ b_{21}^2 & 0\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix}+\begin{bmatrix}c\\ 0\end{bmatrix}u_1 \qquad a_{21}>0 \qquad a_{12}>0 \qquad b_{21}^2>0$$

reciprocal connection disclosed by u_2

Hemodynamics: reciprocal connections

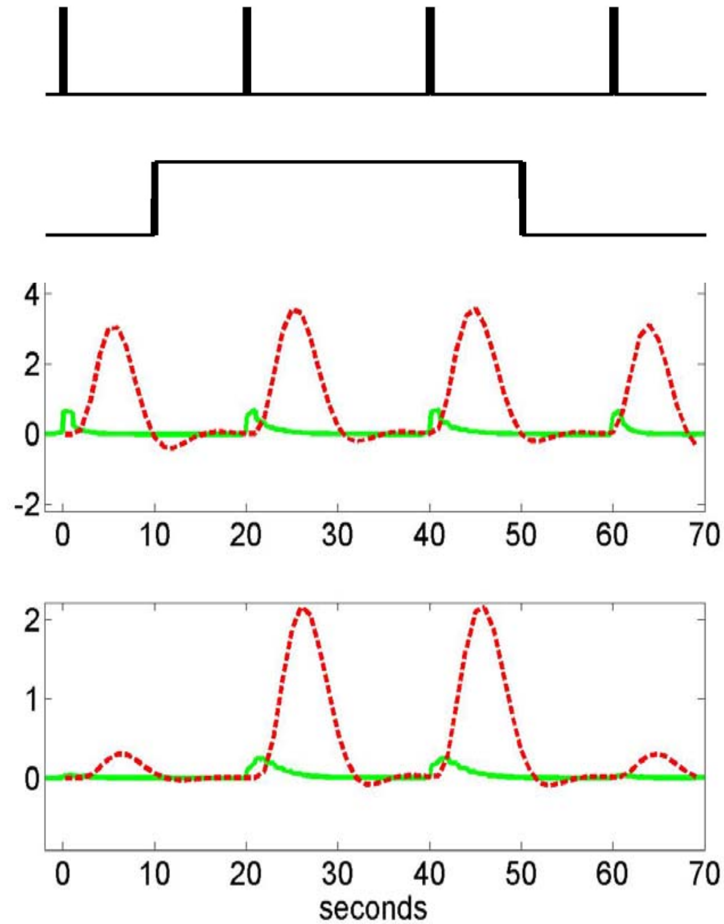


Bold

Response

Bold

Response



$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ b_{21}^2 & 0 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix} u_1 \qquad a_{21} > 0 \qquad a_{12} > 0 \qquad b_{21}^2 > 0$$

green: neuronal activity

red: bold response

Conceptual overview

Neuronal state equation $\dot{z} = F(z, u, \theta^n)$

The bilinear model $\dot{z} = (A + \sum u_j B^j)z + Cu$

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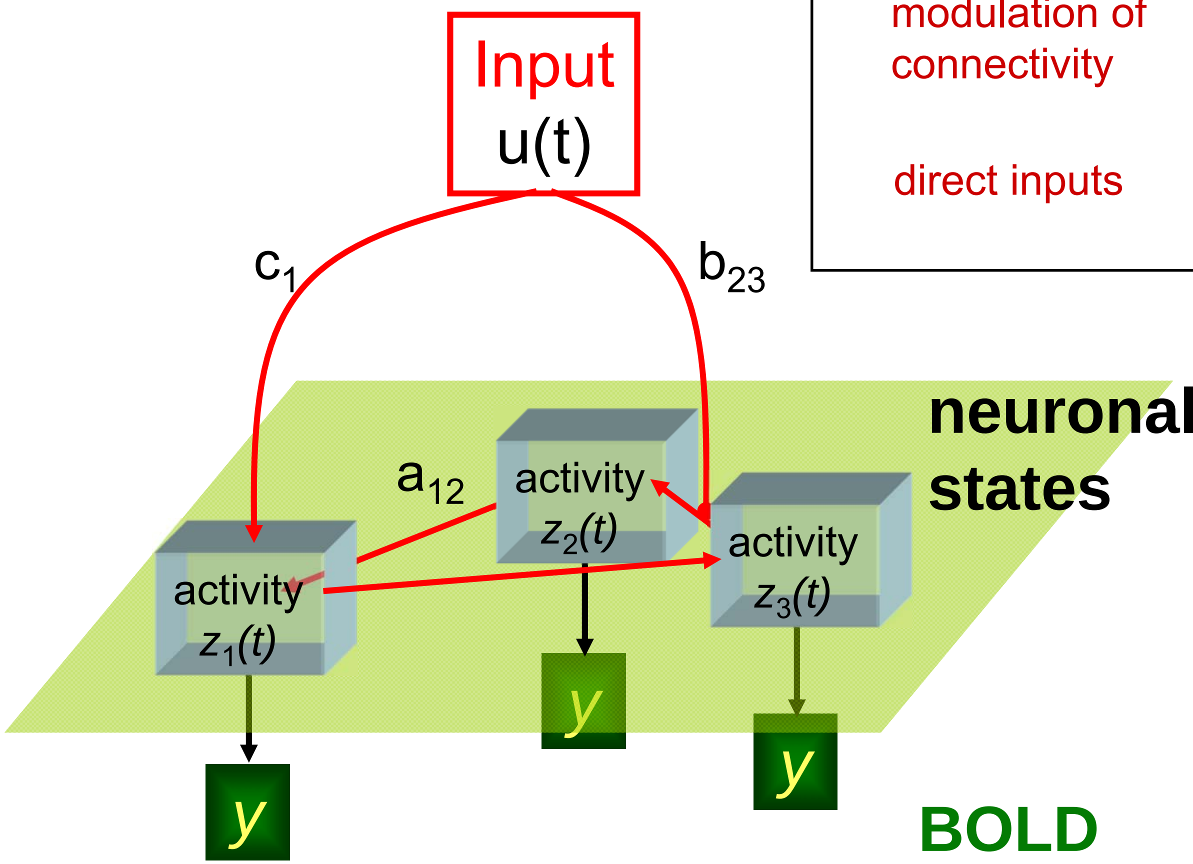

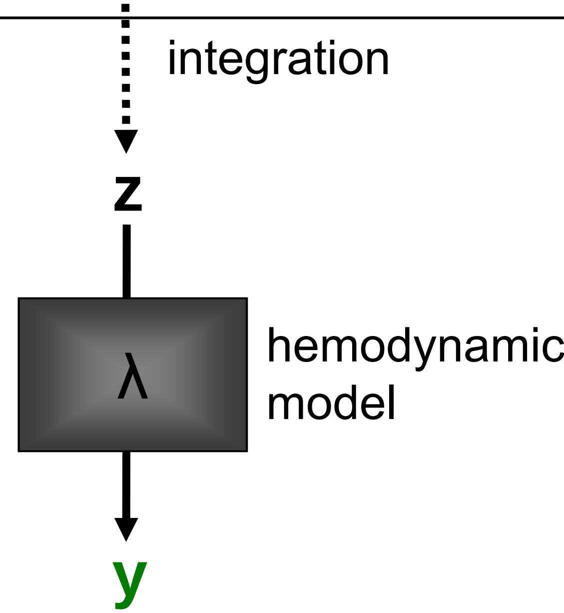

Friston et al. 2003, *NeuroImage*

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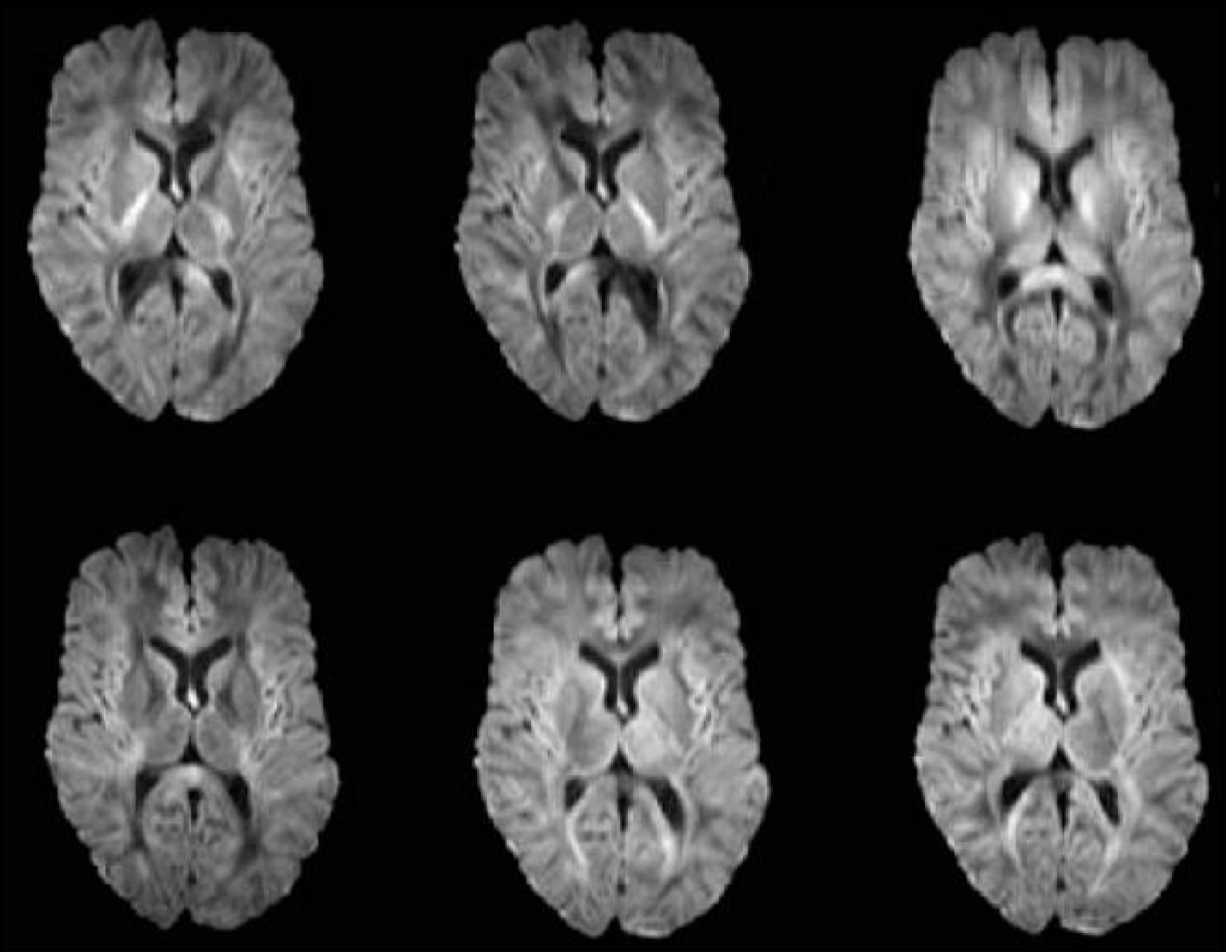
- SPM 8/12
- ART Toolbox
- PPI
- GIFT
- DCM
- Connectivity Toolbox
- Brainwaver

[redacted]

Diffusion Tensor Imaging

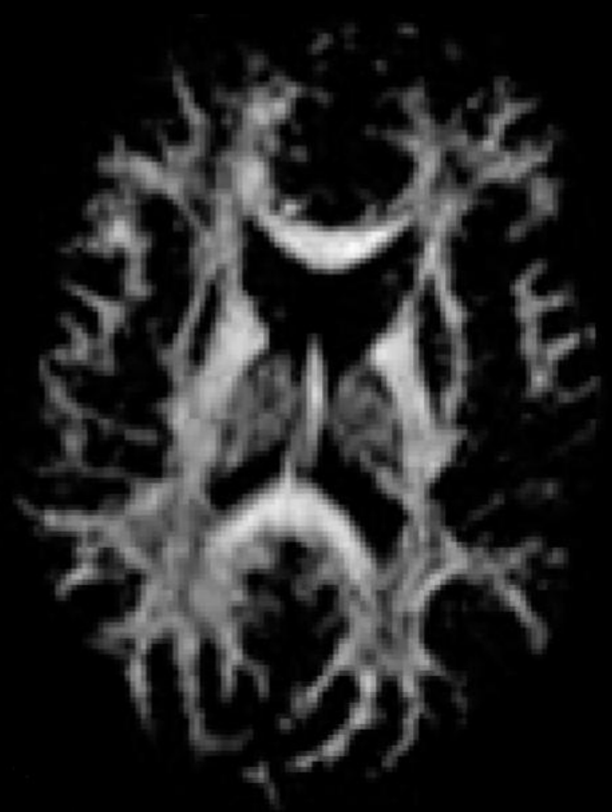
- Diffusion sensitive gradients applied in six directions with b = 800
- Dark areas represent areas with a higher diffusion



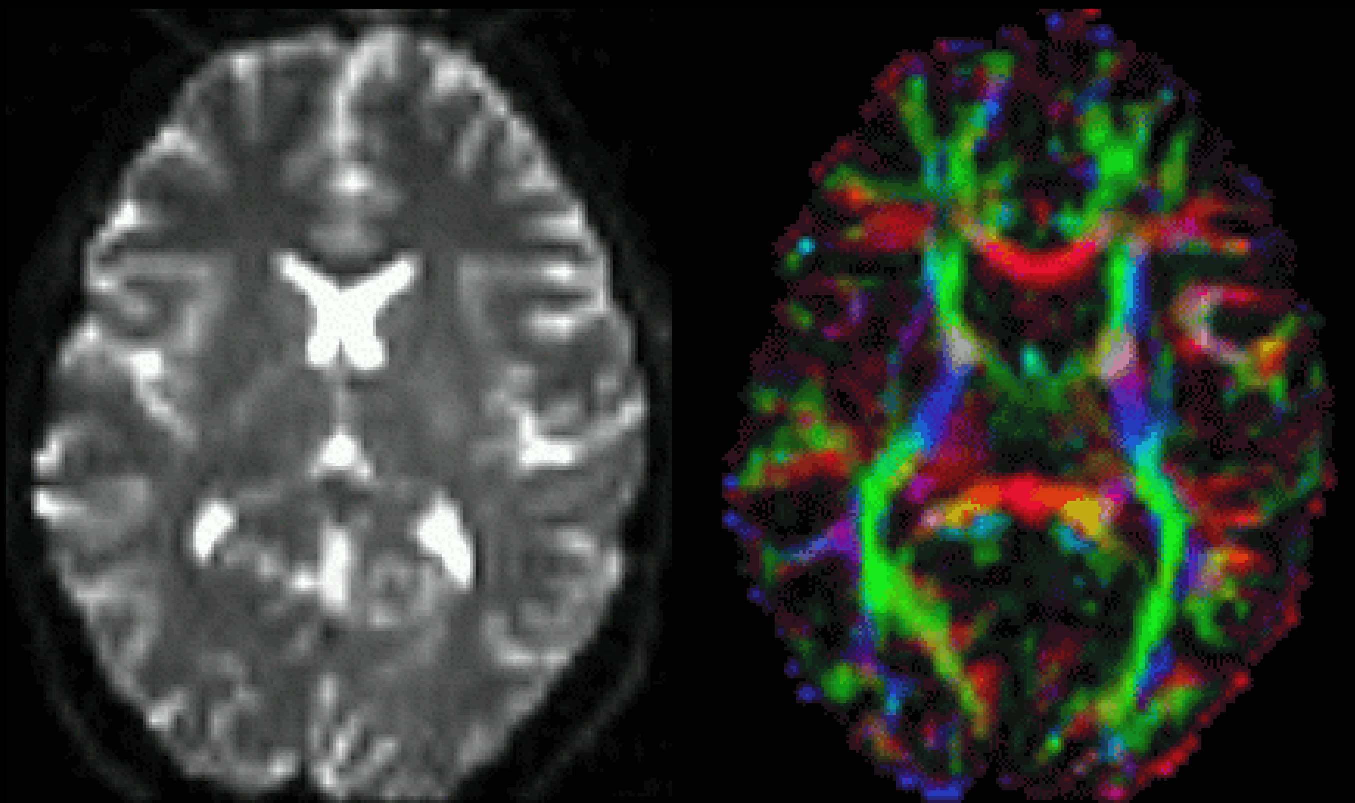
Fractional Anisotropy (FA)

- Measure of degree of anisotropy regardless of direction
- Brighter areas correspond to areas with higher FA

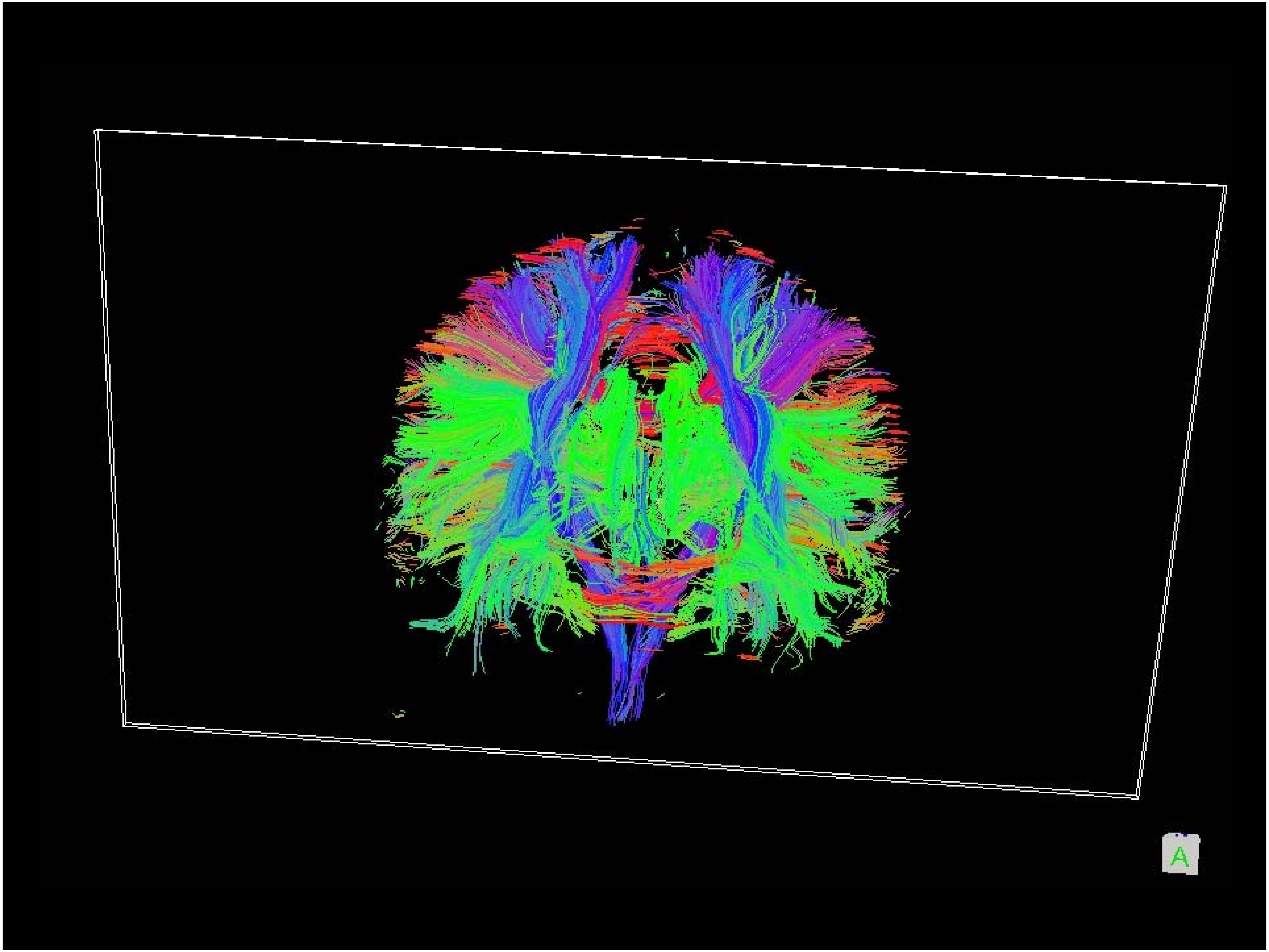
$$FA^2 = \frac{(I_x - I_y)^2 + (I_x - I_z)^2 + (I_y - I_z)^2}{2(I_x^2 + I_y^2 + I_z^2)}$$

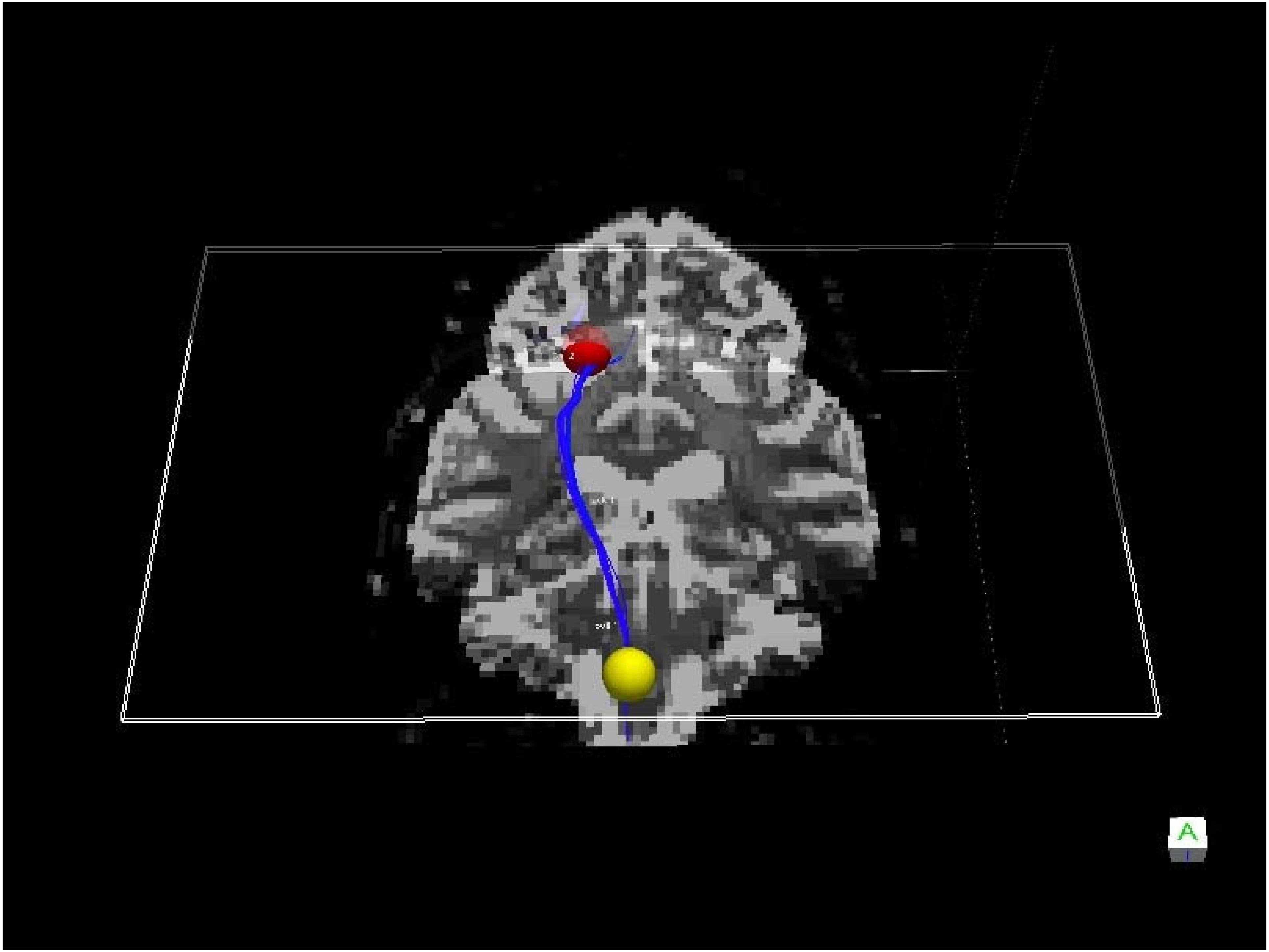


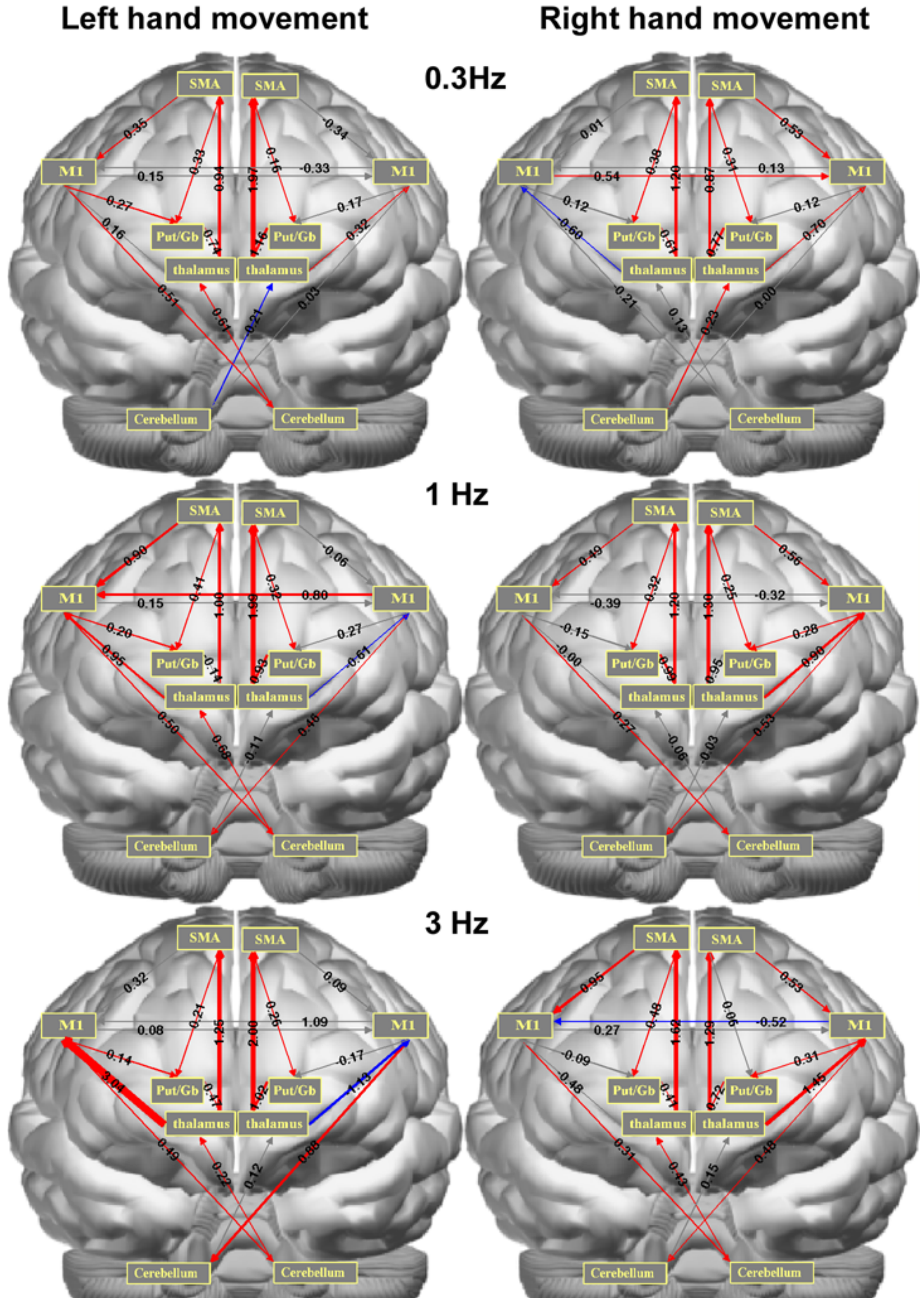
Diffusion Directions



Red = Left-Right
Green = Anterior-Posterior
Blue = Superior-Inferior


A


A



Left hand movement
Right hand movement
0.3Hz
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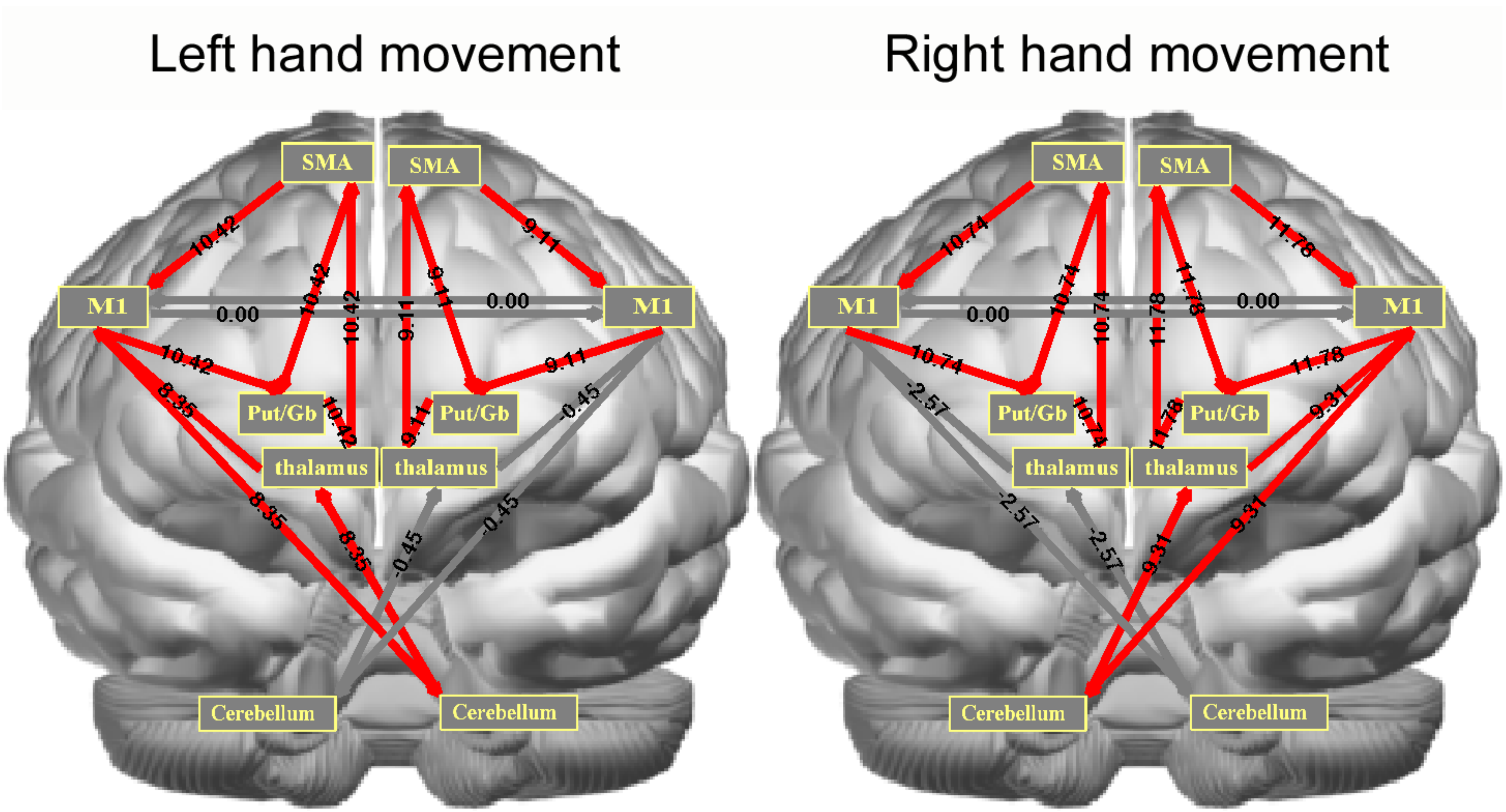
Left hand movement
Right hand movement
SMA
SMA
M1
M1
Put/Gb
Put/Gb
thalamus
thalamus
Cerebellum
Cerebellum
10.42
9.11
0.00
0.00
8.35
-0.45
10.74
11.78
-2.57
9.31