(Functional Connectivity &) PPI

NeuroImaging Training Program

UCLA

July 25, 2014

Agatha Lenartowicz, Ph.D.

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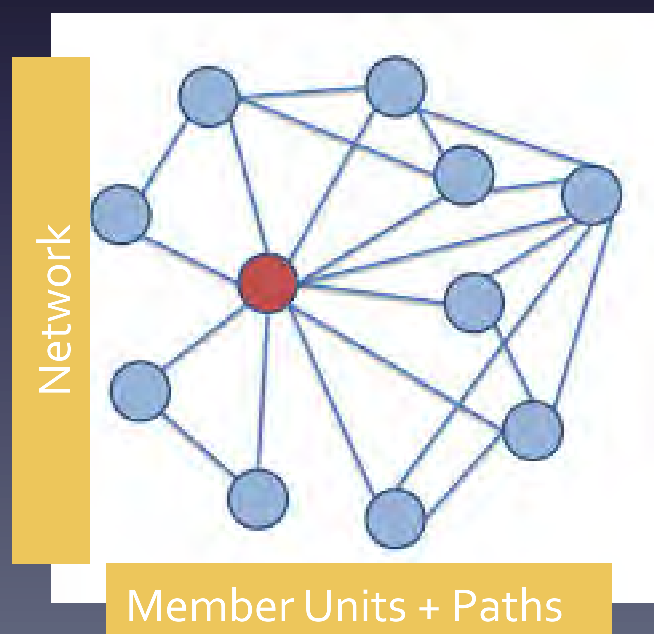
"Connectivity"

- Being joined together
- Ability to communicate (transfer of information)



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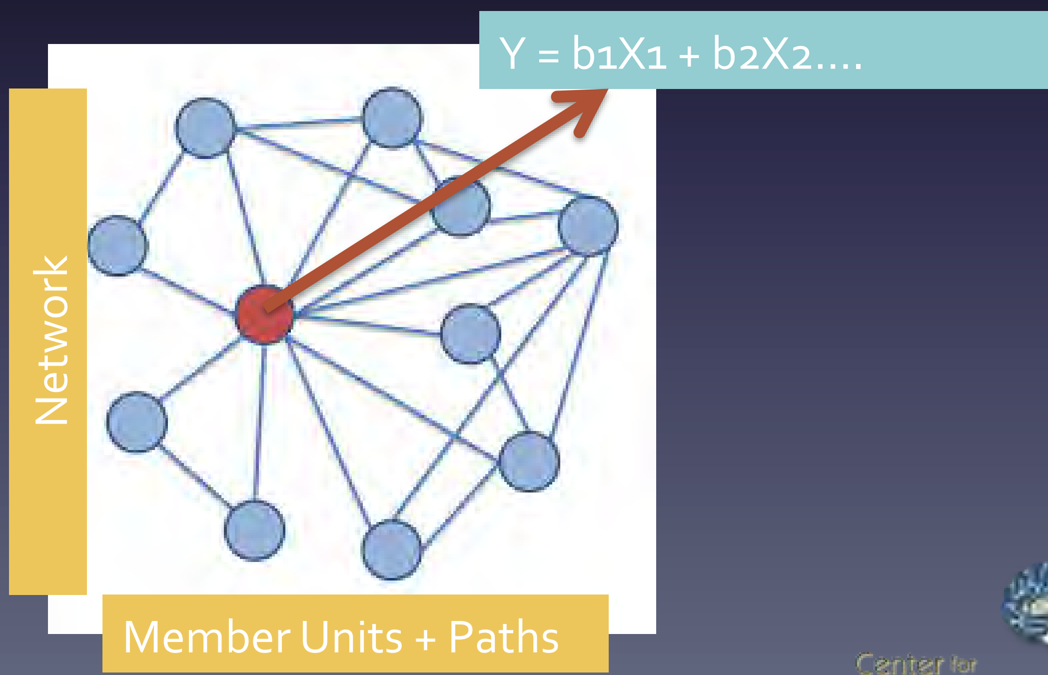

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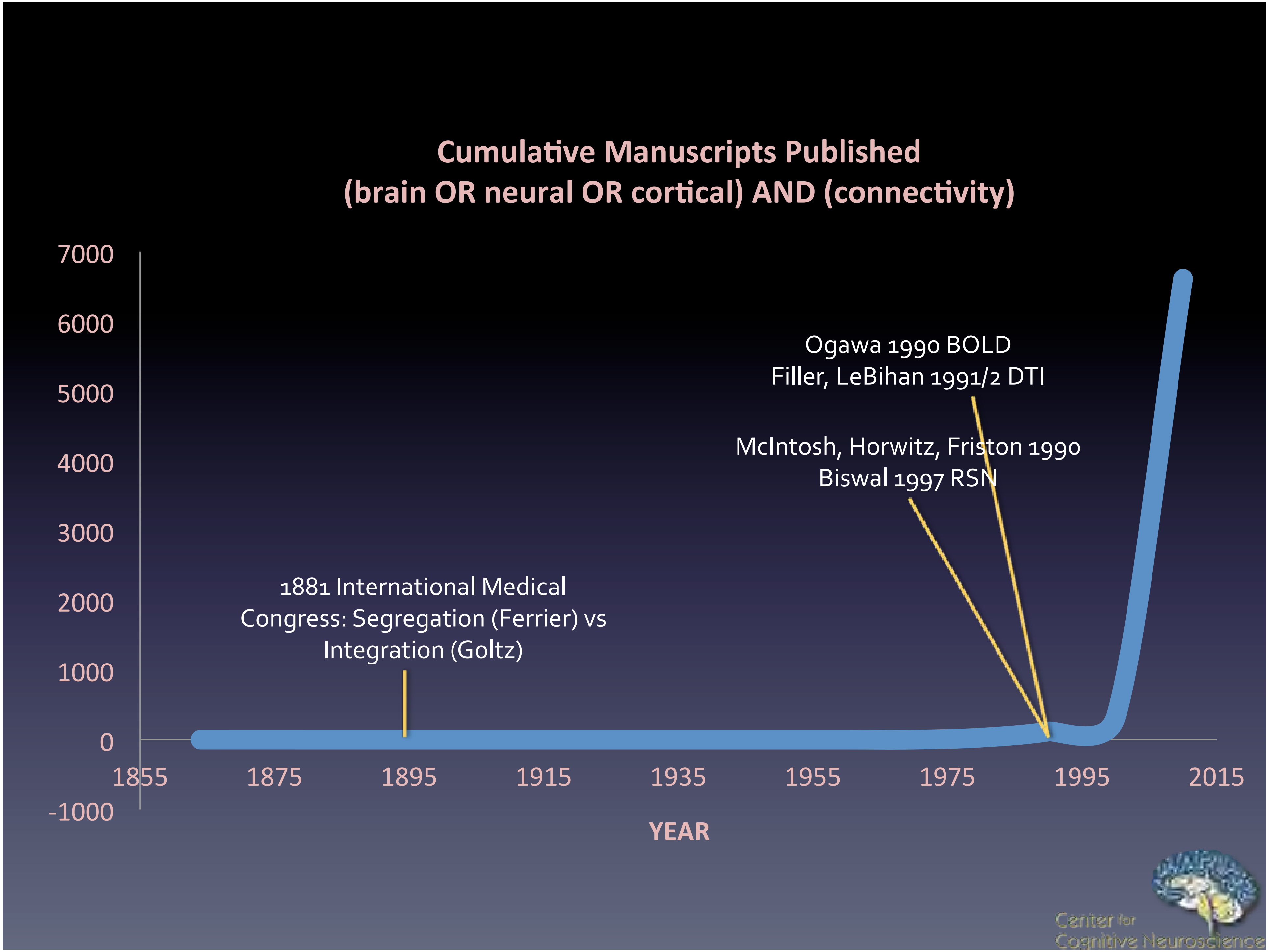
Cumulative Manuscripts Published
(brain OR neural OR cortical) AND (connectivity)
7000
6000
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4000
3000
2000
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0
-1000
1855
1875
1895
1915
1935
1955
1975
1995
2015
YEAR
1881 International Medical Congress: Segregation (Ferrier) vs Integration (Goltz)
Ogawa 1990 BOLD
Filler, LeBihan 1991/2 DTI
McIntosh, Horwitz, Friston 1990
Biswal 1997 RSN
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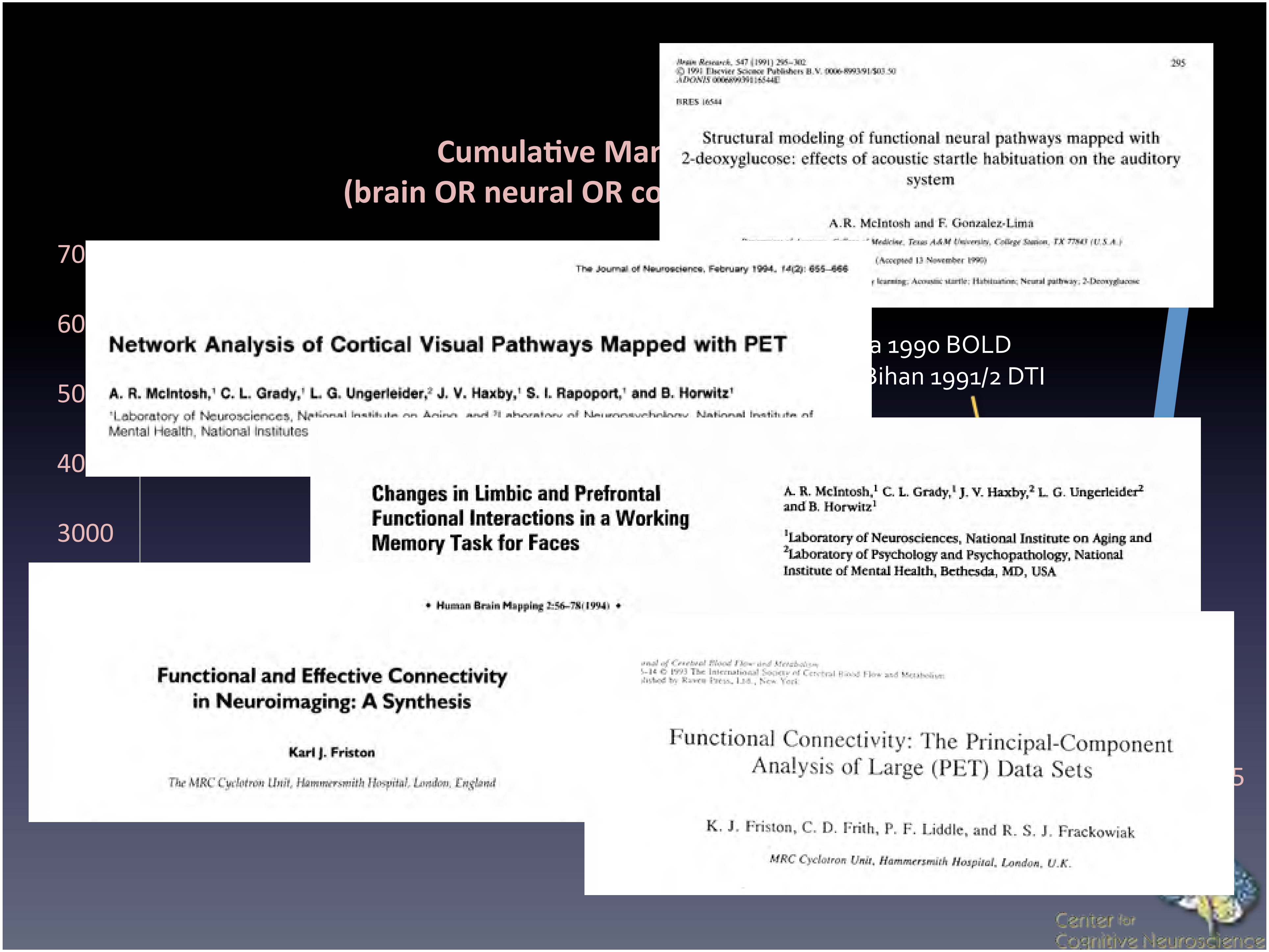
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Brain Research, 547 (1991) 295–302
© 1991 Elsevier Science Publishers B.V. 0006-8993/91/$03.50
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295
Structural modeling of functional neural pathways mapped with 2-deoxyglucose: effects of acoustic startle habituation on the auditory system
A.R. McIntosh and F. Gonzalez-Lima
(Accepted 13 November 1990)
The Journal of Neuroscience, February 1994, 14(2): 655–666
Network Analysis of Cortical Visual Pathways Mapped with PET
A. R. McIntosh,[1] C. L. Grady,[1] L. G. Ungerleider,[2] J. V. Haxby,[1] S. I. Rapoport,[1] and B. Horwitz[1]
Mental Health, National Institutes
Changes in Limbic and Prefrontal Functional Interactions in a Working Memory Task for Faces
A. R. McIntosh,[1] C. L. Grady,[1] J. V. Haxby,[2] L. G. Ungerleider[2] and B. Horwitz[1]
[1]Laboratory of Neurosciences, National Institute on Aging and [2]Laboratory of Psychology and Psychopathology, National Institute of Mental Health, Bethesda, MD, USA
• Human Brain Mapping 2:56–78(1994) •
Functional and Effective Connectivity in Neuroimaging: A Synthesis
Karl J. Friston
The MRC Cyclotron Unit, Hammersmith Hospital, London, England
Functional Connectivity: The Principal-Component Analysis of Large (PET) Data Sets
K. J. Friston, C. D. Frith, P. F. Liddle, and R. S. J. Frackowiak
MRC Cyclotron Unit, Hammersmith Hospital, London, U.K.
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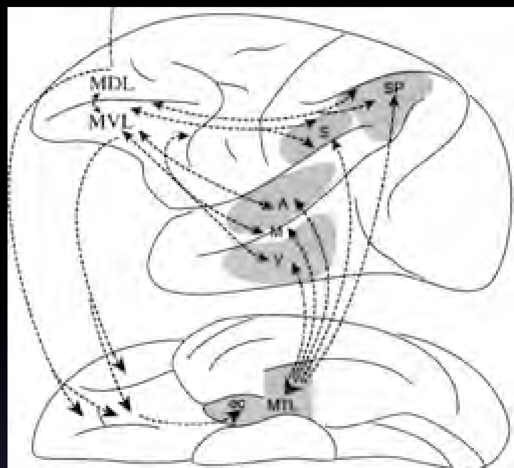
Transition from architectonic analysis and neurophysiological recordings in the animal model to in-vivo human (and non-human) experiments.



Petrides M., (2005) Phil. Trans. R. Soc. B;360:781-795

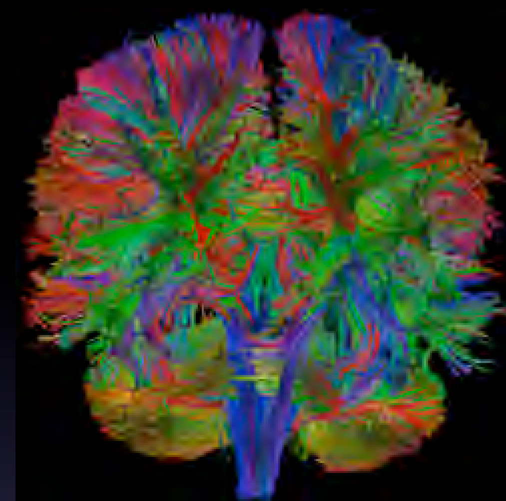
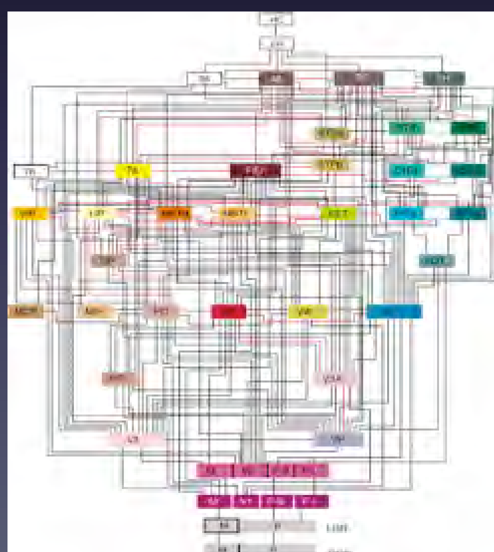
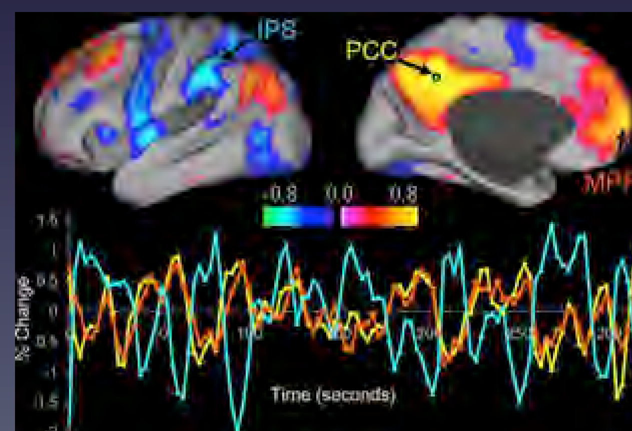


Image Courtesy of Jesse Brown, Ph.D.



Felleman & Van Essen, (1991), Cereb Cortex;1(1);1-47



Fox et al., (2005) Proc. Natl. Acad. Sci. USA. 102; 967-9678

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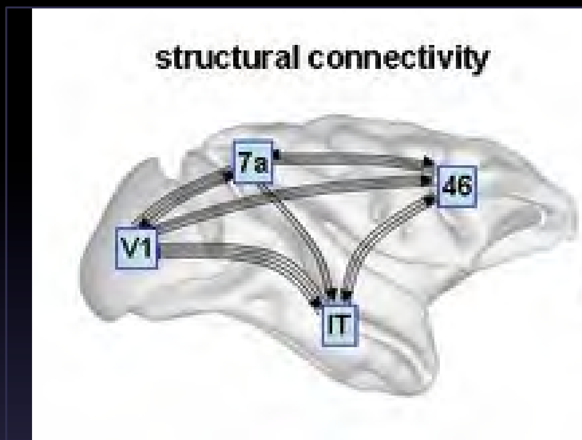
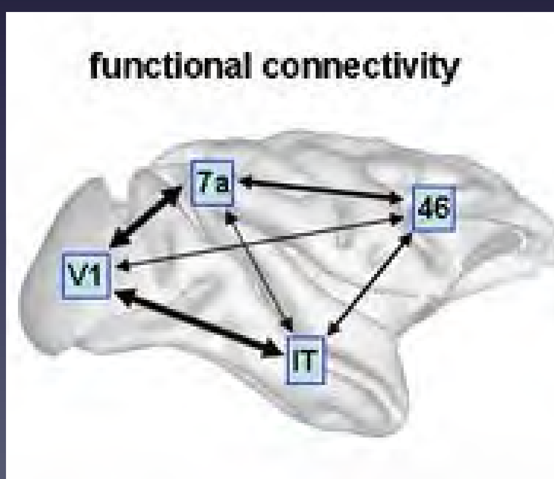
Categories of Connectivity

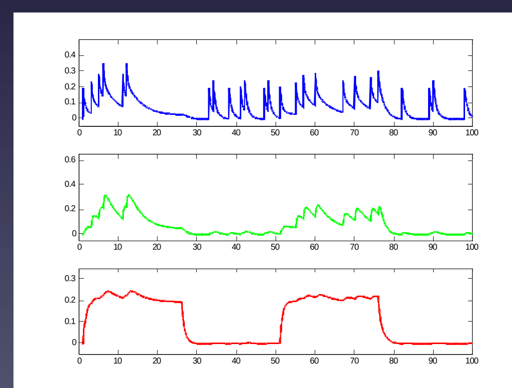


Thanks to SPM group for slide images.

Physical Connections
(tracing, DTI/DWI, dissections)



Sporns 2007 (Scholaropedia, 2 (10):4695)



Statistical Connections
(correlation, coherence, mutual information)

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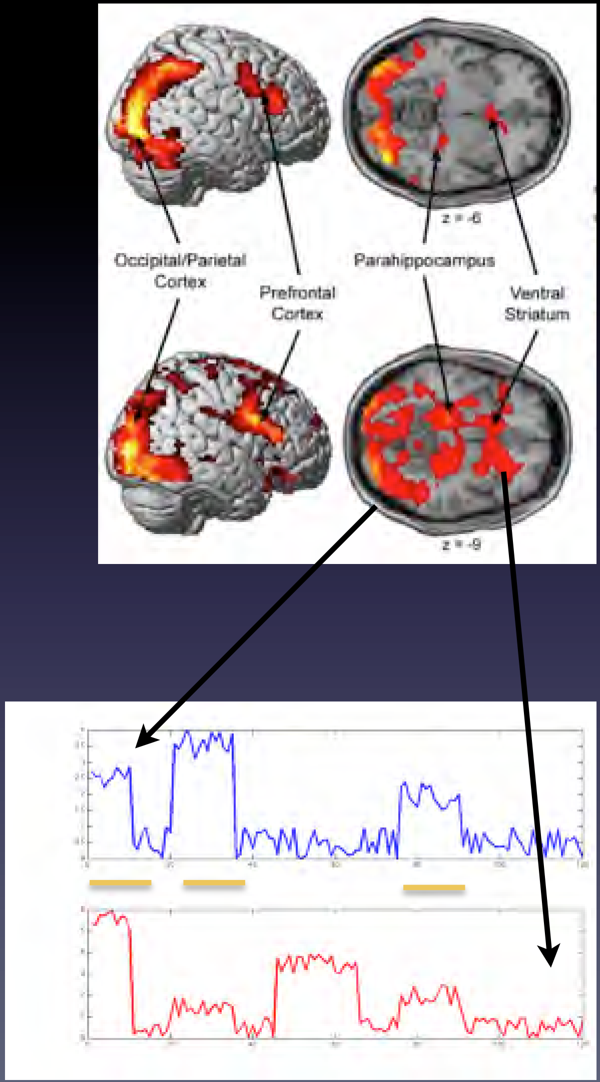
Properties of FC

- typically multivariate (i.e., >1 output variable)
- typically considered independent of external driving stimuli
- typically thought of as incompatible with standard mass univariate (GLM) approach

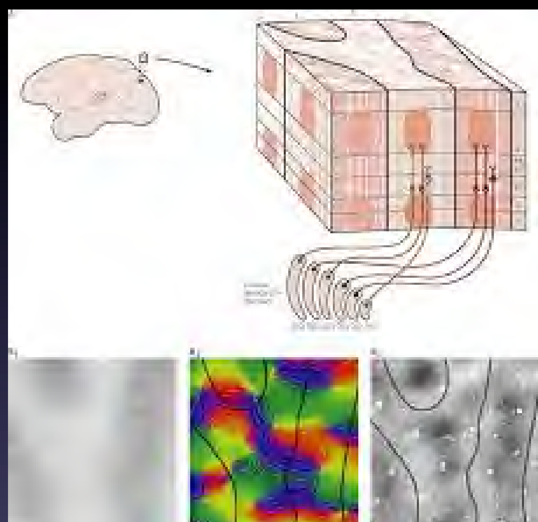


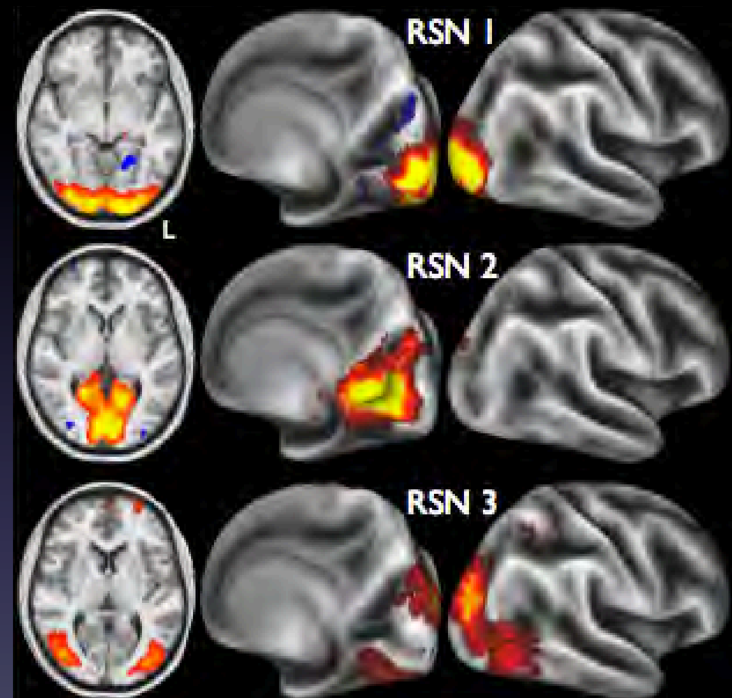
$$Y(1\ \text{voxel}) = b_1X_1 + b_2X_2 \ldots$$

vs.

$$a_1Y_1 + a_2Y_2 \ldots = b_1X_1 + b_2X_2 \ldots$$

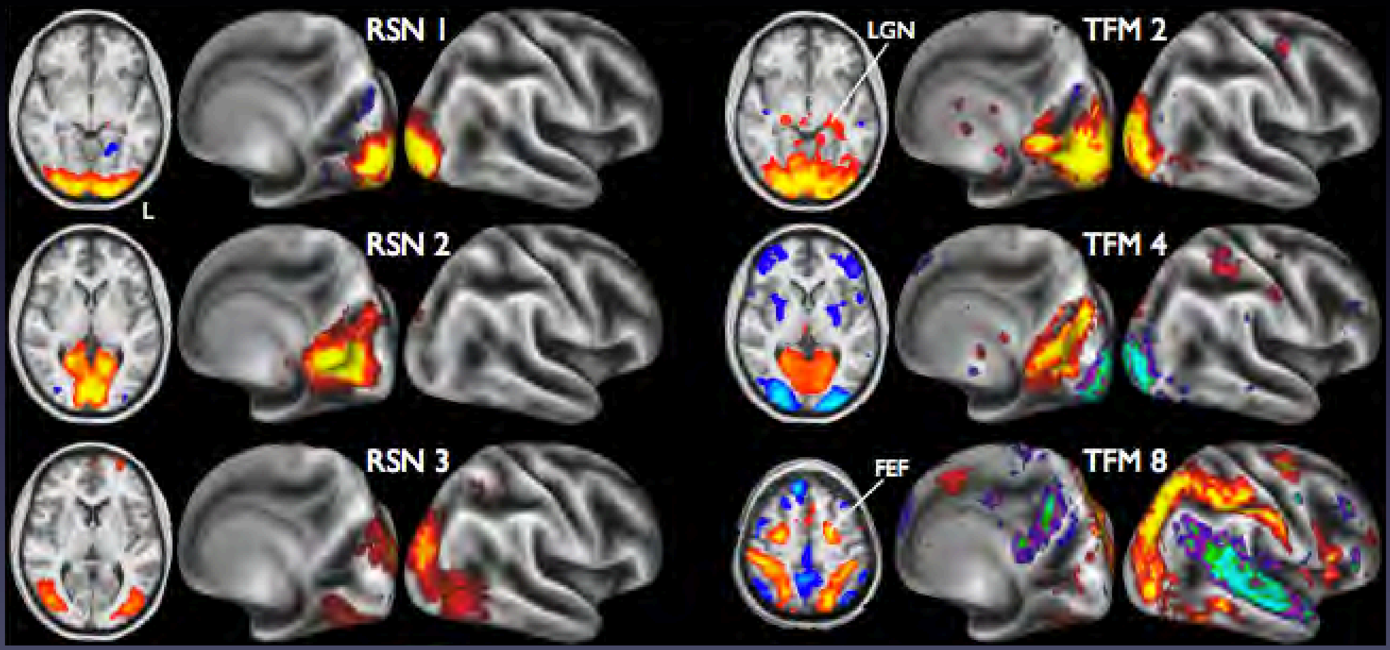
Properties of FC



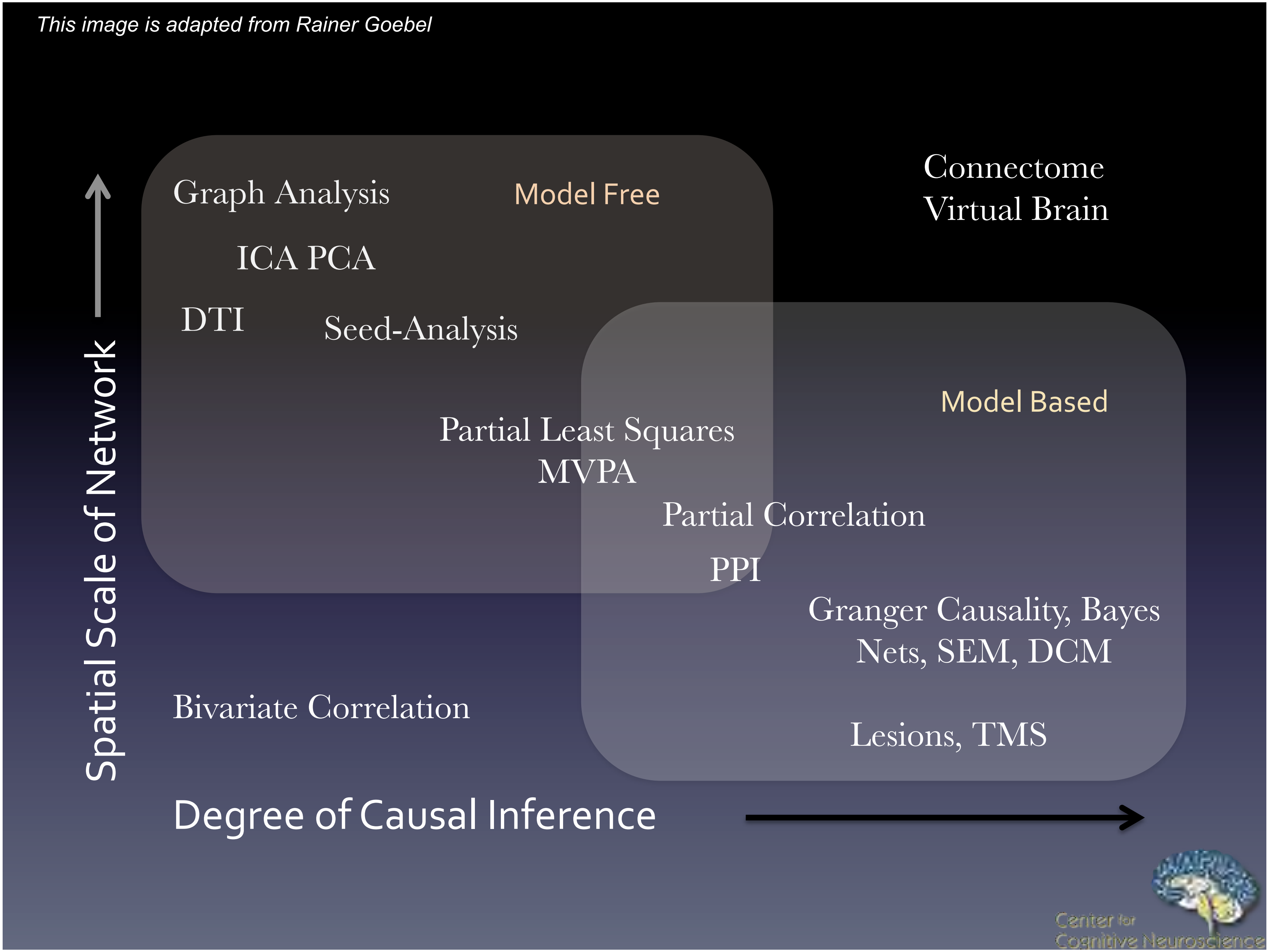


- dependent on level of analysis

Properties of FC



Smith, S., et al., (2012), PNAS, 109(8): 3131-3136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ICA PCA
DTI
Seed-Analysis
Connectome
Virtual Brain
Model Based
Partial Least Squares
MVPA
Partial Correlation
PPI
Granger Causality, Bayes Nets, SEM, DCM
Bivariate Correlation
Lesions, TMS
Spatial Scale of Network
Degree of Causal Inference
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This image is adapted from Rainer Goebel

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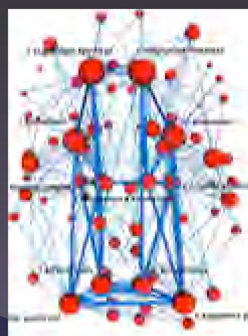

Model Based

Partial Least Squares
MVPA

Partial Correlation

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Granger Causality, Bayes Nets, SEM, DCM

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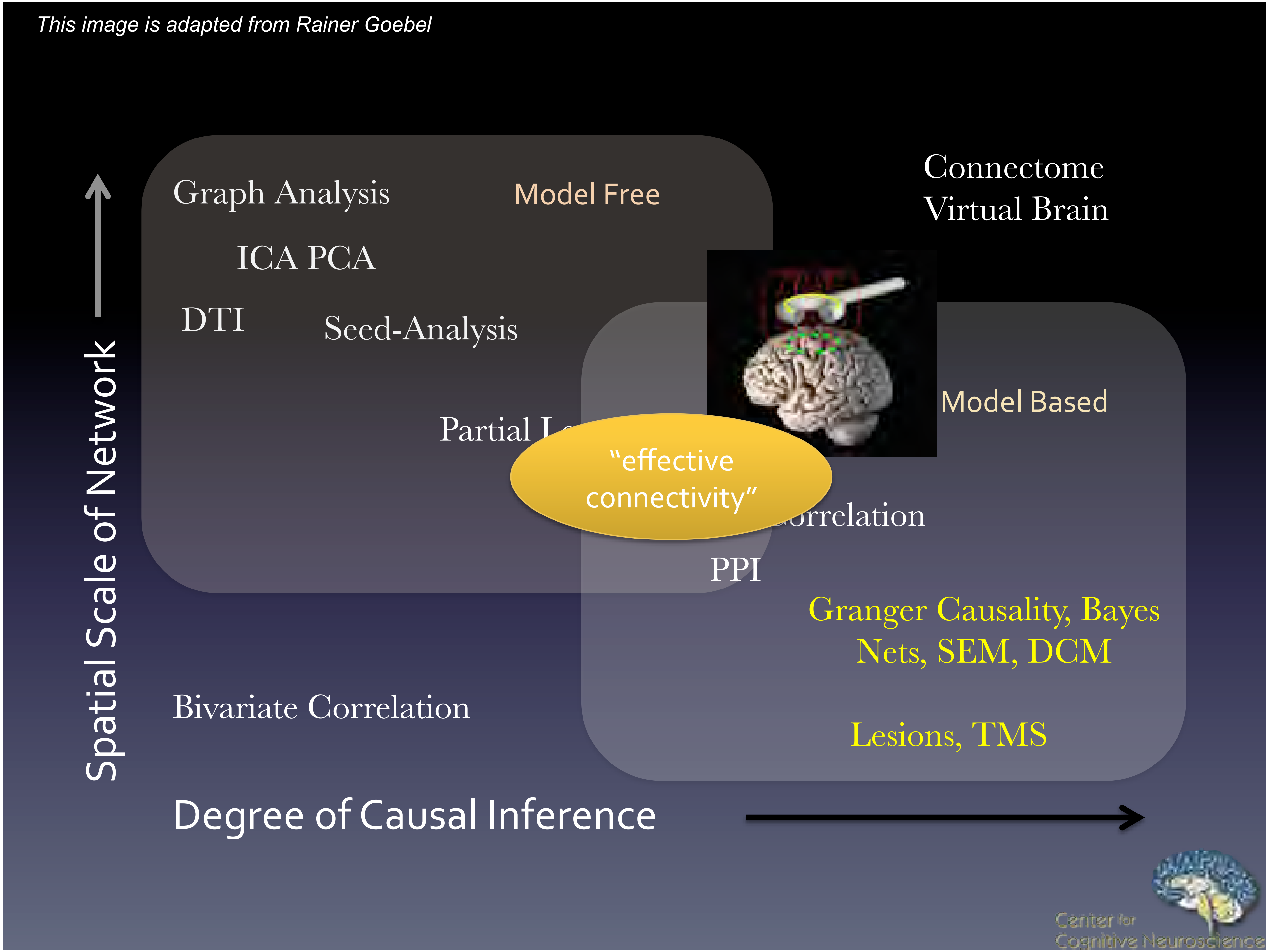
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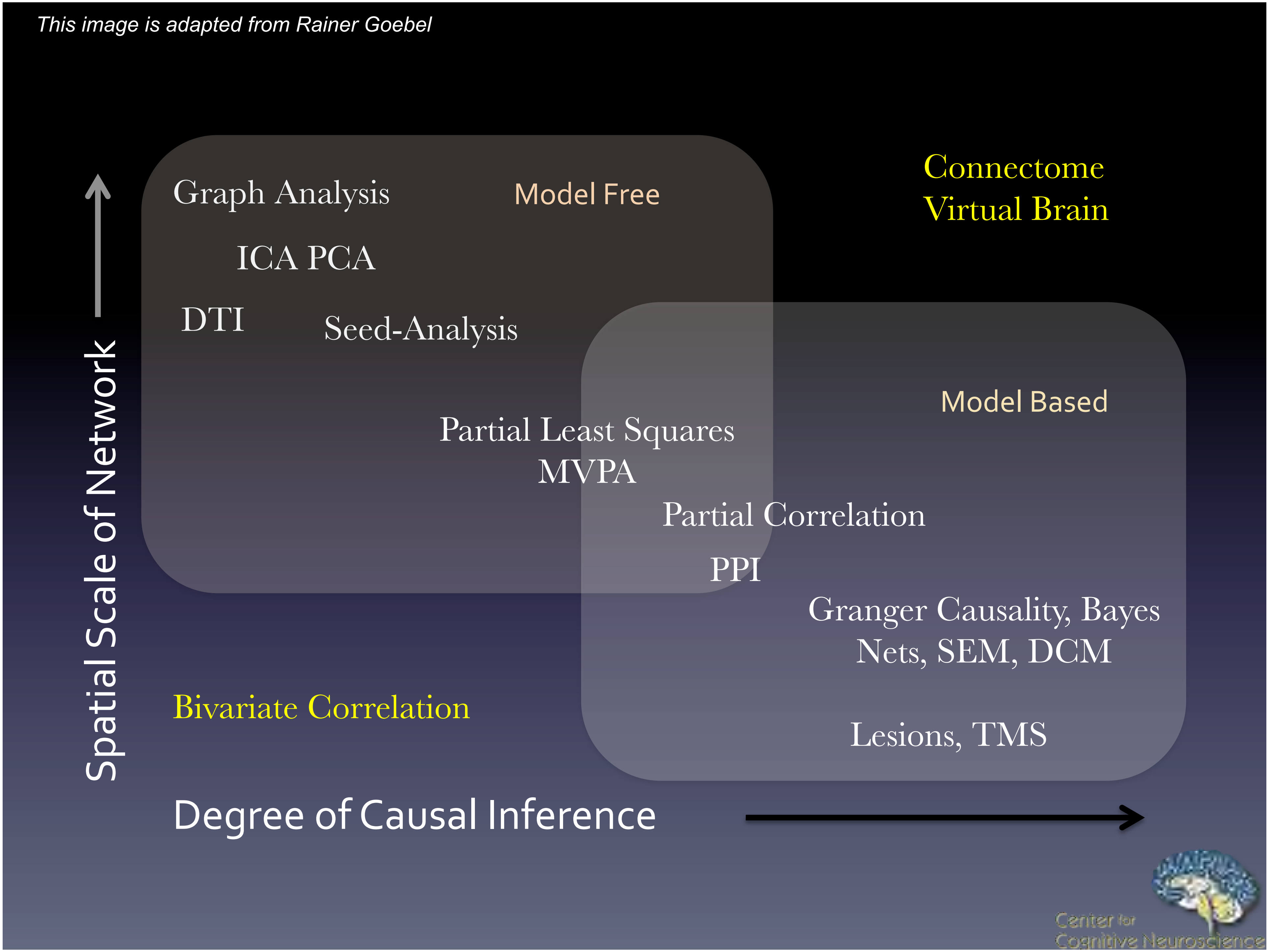
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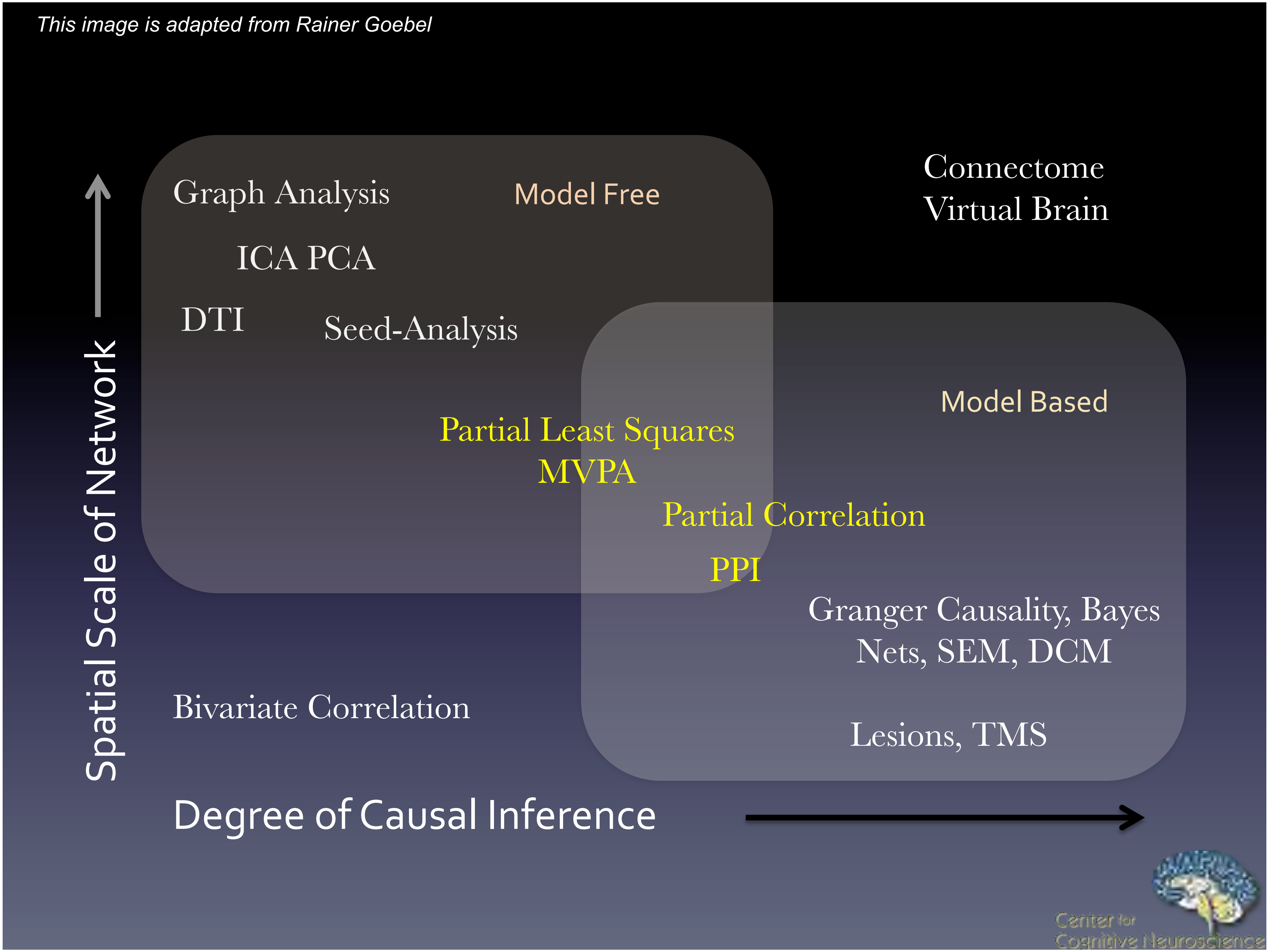
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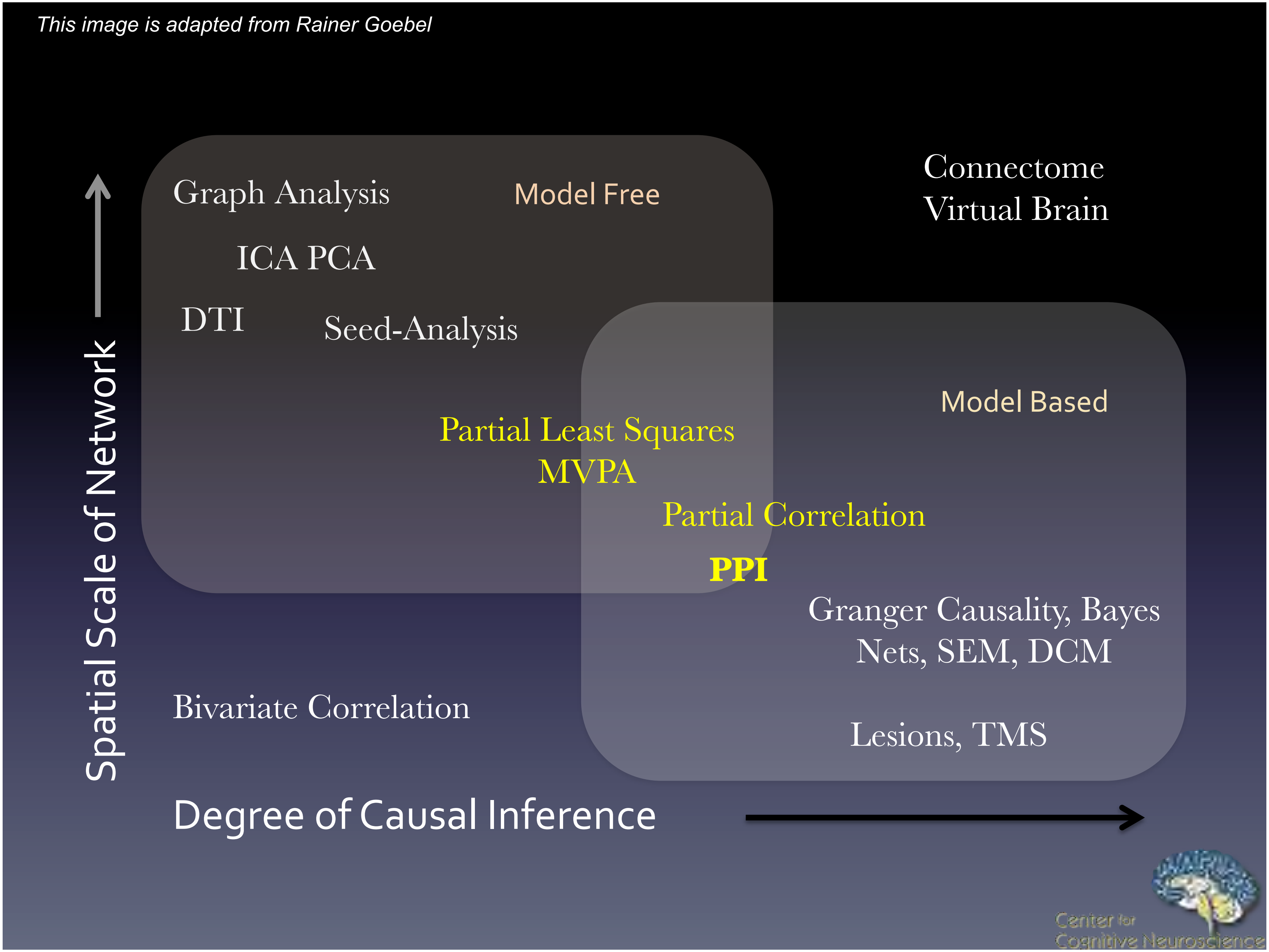
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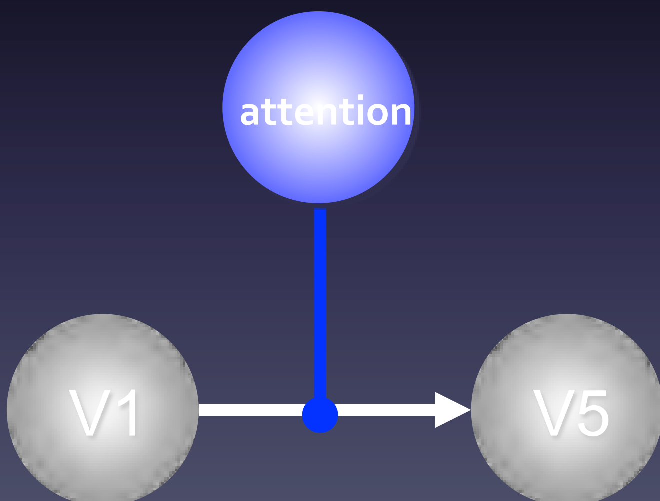
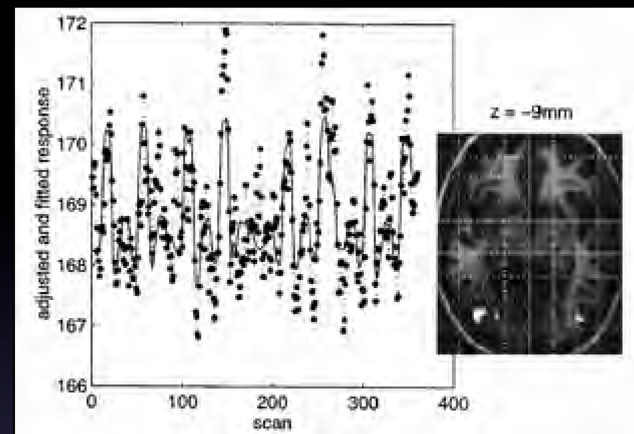
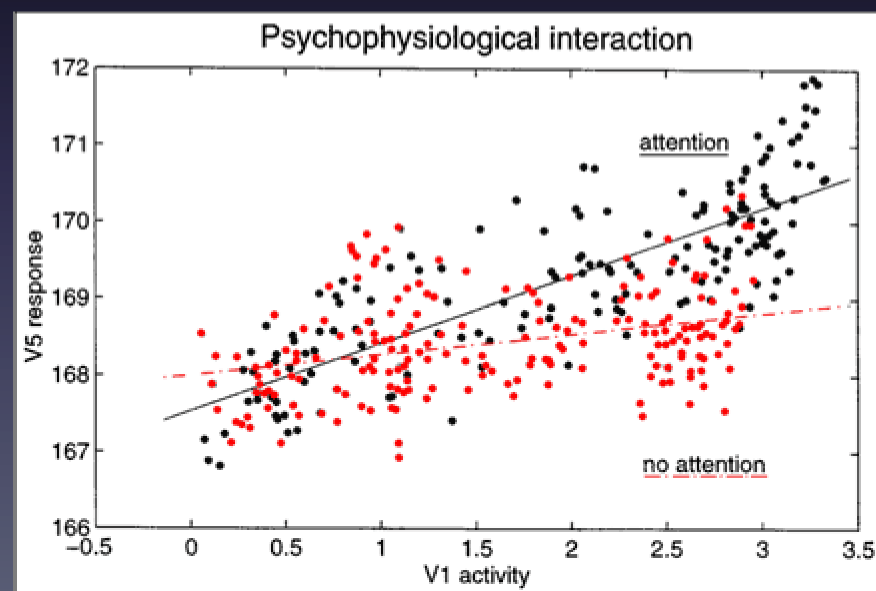
Psychophysiological Interaction







Friston, K.J., et al., (1997), NeuroImage, 6: 218-229

Slide images courtesy of UCL group

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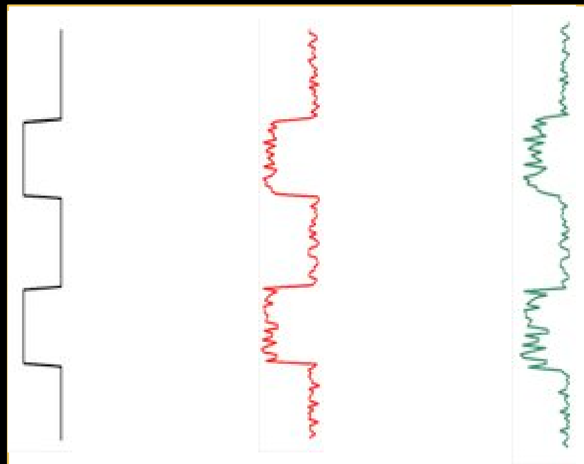
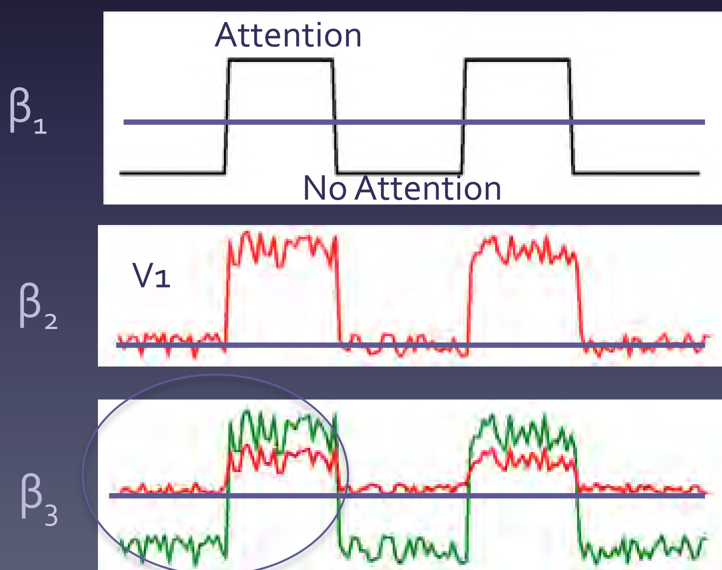
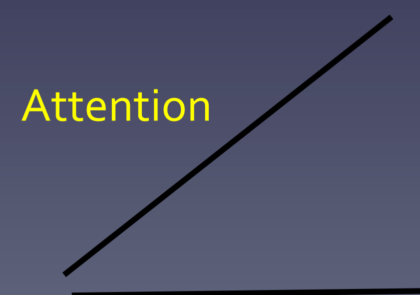


$$Y = \beta_1\, psy + \beta_2\, roi + \beta_3\, psy{*}roi + error$$



- PPI is an interaction term between a task regressor (psy) and a time series from an ROI; test of slopes



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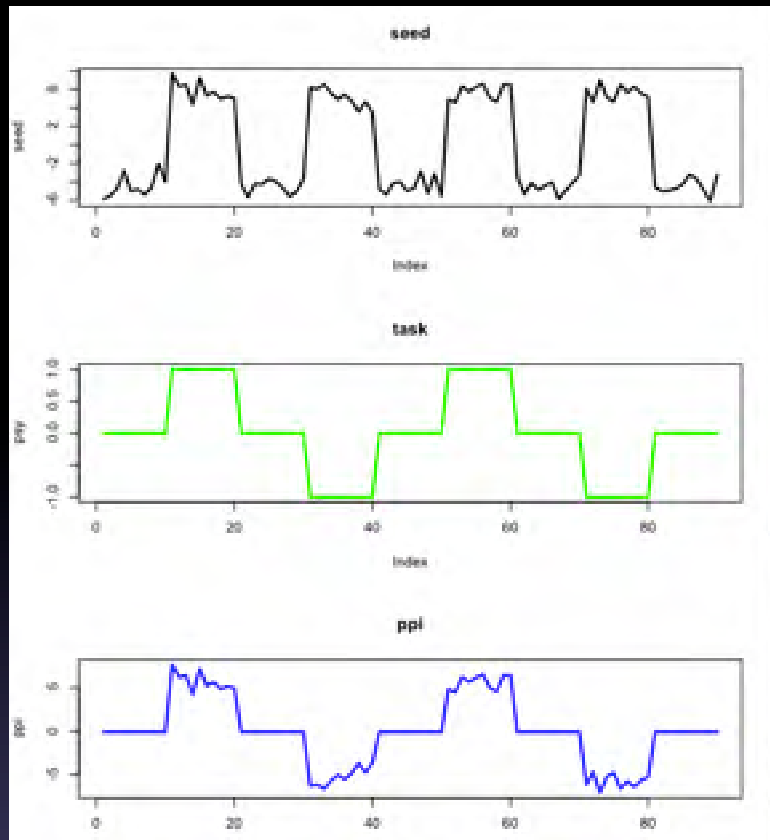
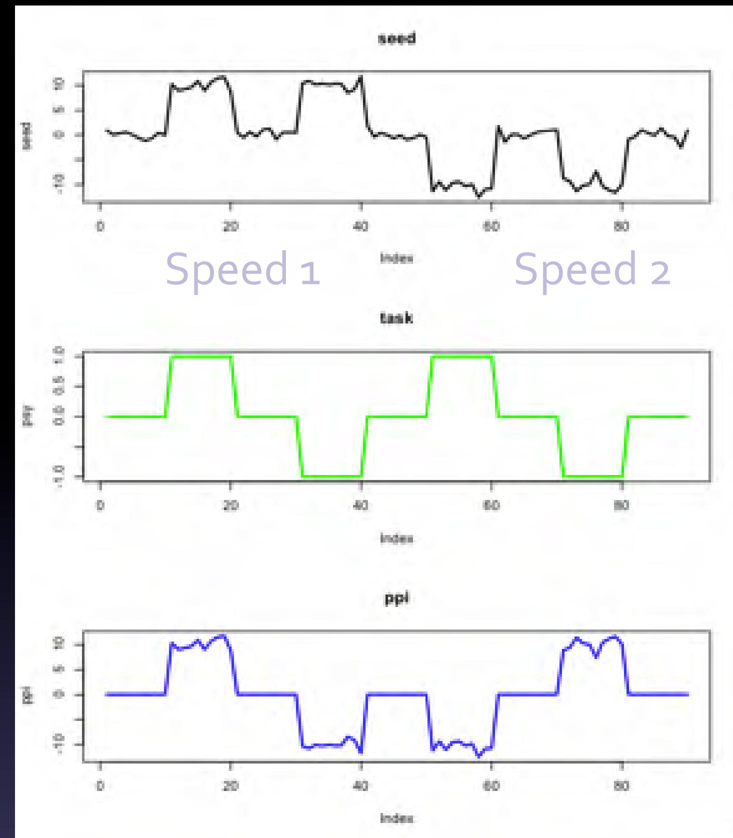
ROI:V1

PSY: Att vs NoAtt

PPI: Interaction





Corr(V1,PPI) = .05

Corr(PSY,PPI) = .97

Corr(V1,PSY) = .03

Corr(V1,PPI) = .02

Corr(PSY,PPI) = .01

Corr(V1,PSY) = .02

Non-Factorial

Factorial

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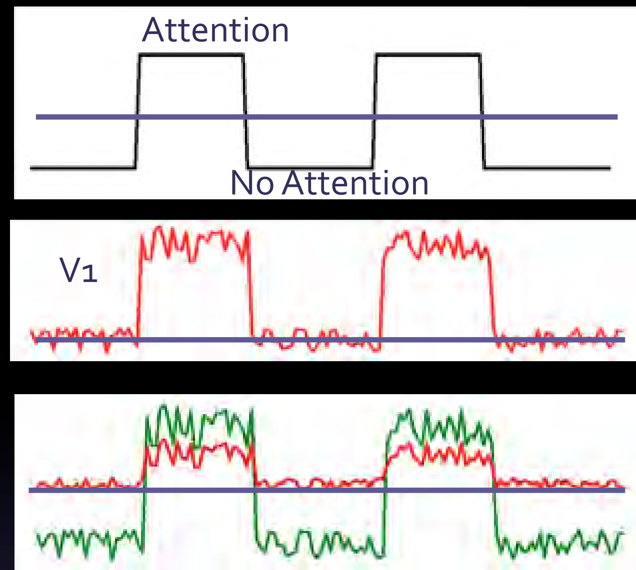
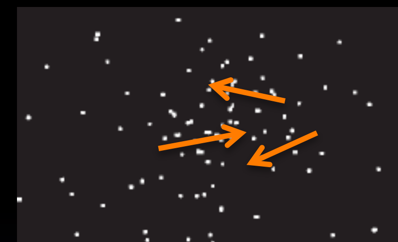
β_1

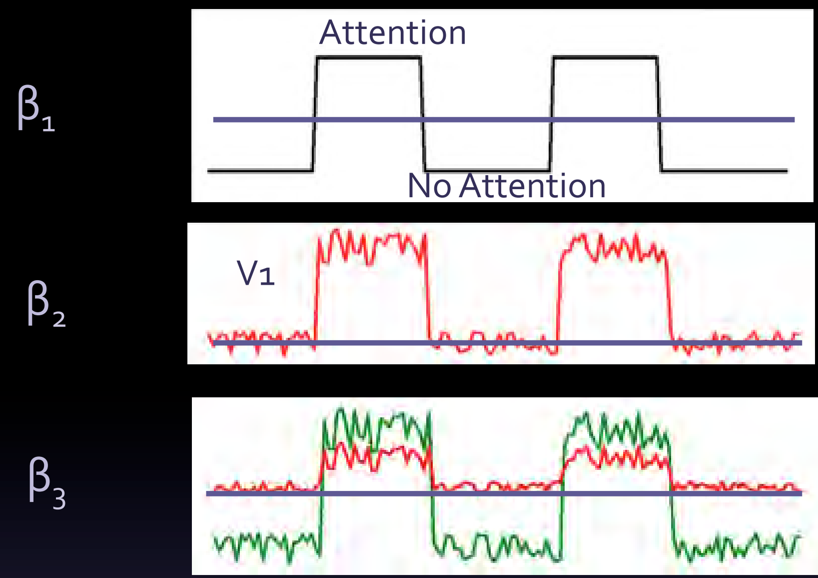
β_2

β_3



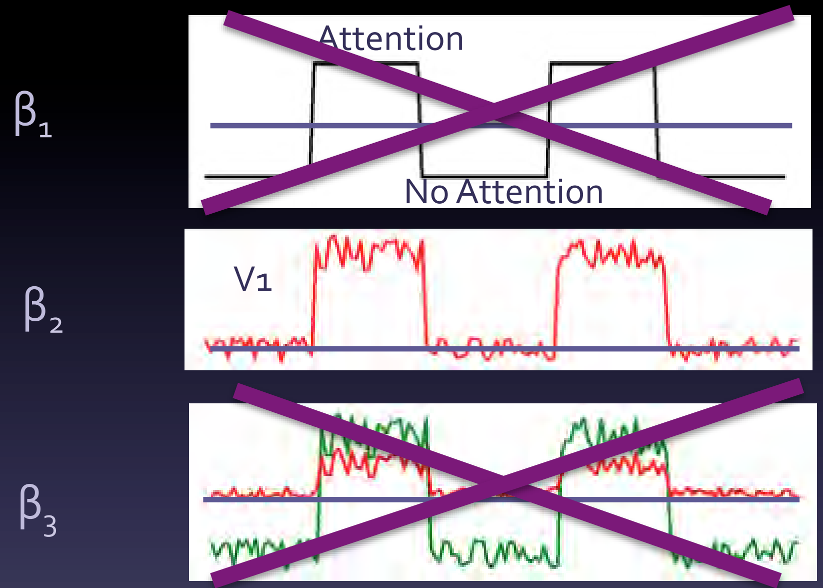


- Collinearity in this model will decrease power of detecting β_3
- Factorial designs are preferable because they ensure variance in ROI independent of main effect
  - 2 crossed independent variables in design (e.g., attention, speed)
  - identify seed using one of the factors (e.g., speed***)
  - replace factor (speed) with activity of seed



- Must include main effect regressors (β_1 and β_2) to test unique variance due to interaction term
  - If don't include main effects => spuriously significant interaction term
  - If do include main effects => may have poor power (collinearity) to detect interaction

- PPI "concept" can be used to test for differences in connectivity comparing **pre-post intervention** and **subject groups**



- 'psychological' variable is now a between subject variable; compare ROI connectivity between sessions or groups

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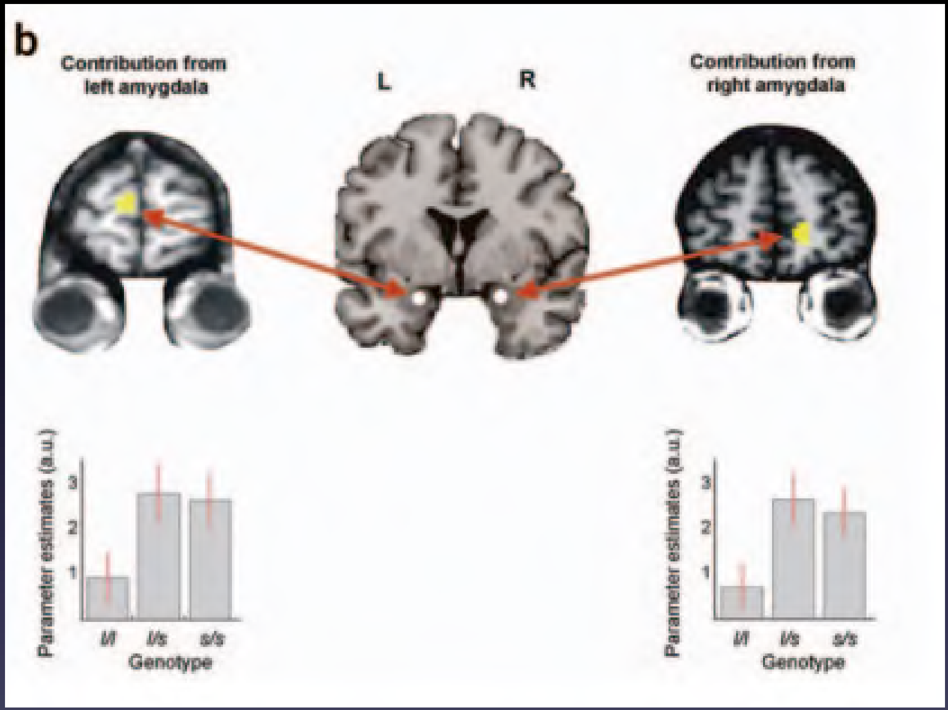
EXAMPLE:
AMY-PFC interactions vary as a function of depression correlated genotype



Heinz, A., et al., (2005), Nat Neuro, 8(1): 20—21

- PSY = genotype (group), ROI = AMY, no PPI

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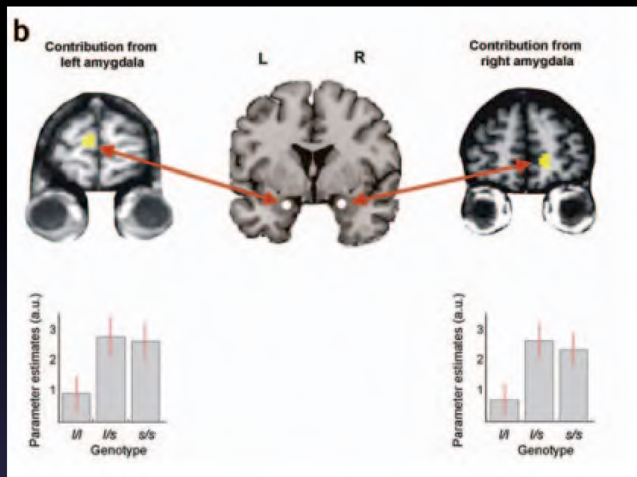
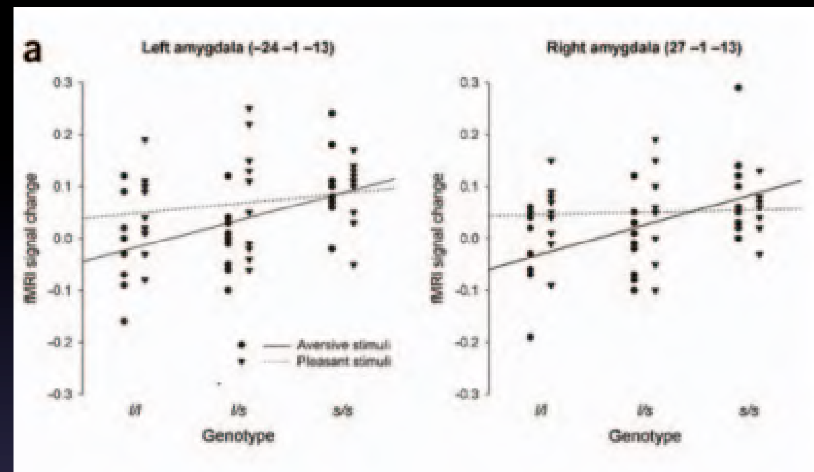
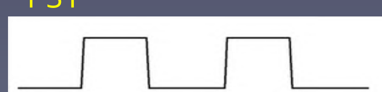
EXAMPLE:
AMY-PFC interactions vary as a function of depression correlated genotype





- Response of AMY to task (aversive/pleasant) also greater in ls/ss gentypes
- If compare y=AMY+e across groups, will observe differences primarily due to task response of AMY to aversive stimuli
- If compare y=AMY+task+e across groups, will obtain estimate of task-independent difference in AMY connectivity between groups

PSY

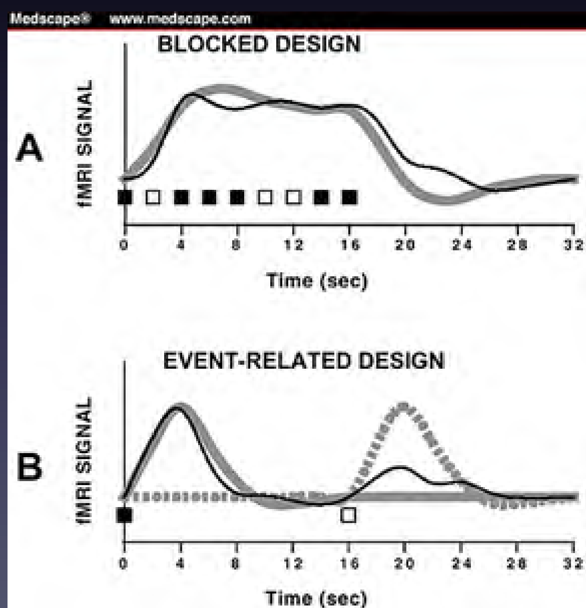


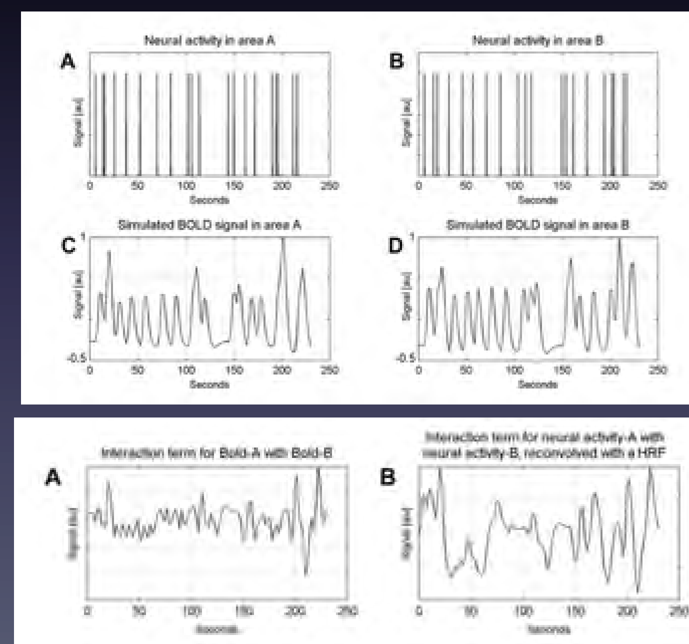
l/l

s/s

PPI in Event-Related Designs

- Low power
  - Lower power in event-related response that can be made variable due to sub-par model fit
  - Layering on top of this variability is the structured variability that we test with PPI
  - Additional concern due to effects of convolution with HRF on interactions
  - Recommended with caution in fast designs in which deconvolution adds further variance; better approach beta series correlation (recall Rissman talk)





Gitelman et al., (2003), NeuroImage, 19: 200-207
hrf(A)*hrf(B) ≠ hrf(A*B)

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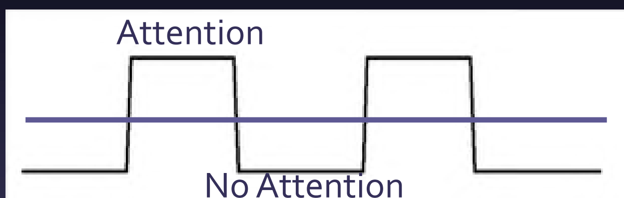
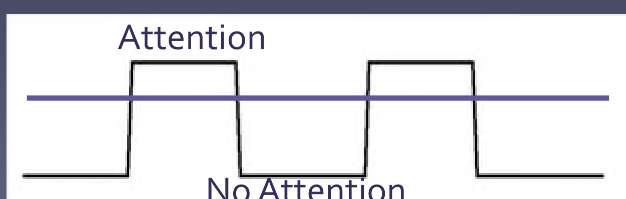
Generalized PPI Model

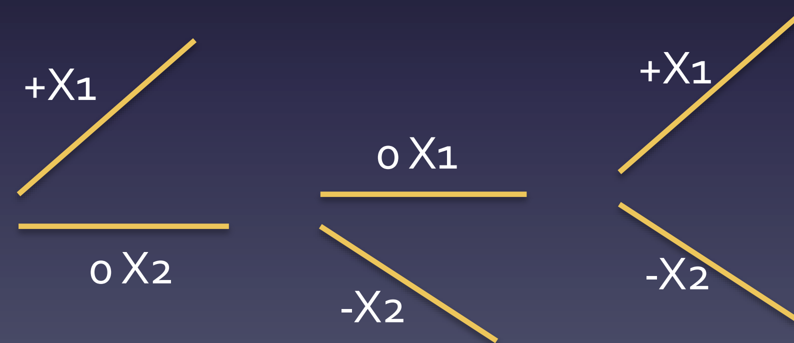
- 1997 subtraction model is limited
  - Limited to 2 conditions
  - Dependent on accurate centering of PSY and PPI regressors
  - Doesn't make interpretation easy

$$Y = c + \beta_1 (X1\text{-}X2) + \beta_2 \, ROI + \beta_3 (X1\text{-}X2) * ROI$$



If you were to mean center and there were more time points in Attention condition than in No Attention condition, the zero point would be biased upwards. Zero-center (min-max) more appropriate.





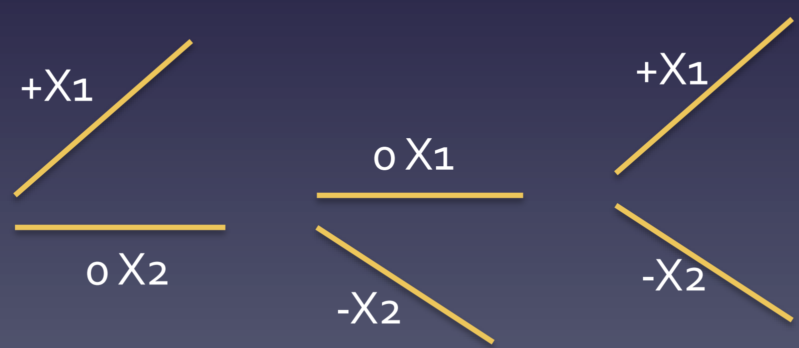
Generalized PPI Model

- Generalized form of the model
  - Initially developed by Jeanette Mumford ~2010 (not published)
  - Independently formalized by McLaren et al. (2012) NeuroImage 61: 1277-1286

$$Y = c + \beta_{1a}\,X1 + \beta_{1b}X2 + \beta_2\ ROI + \beta_{3a}\,(X1)*ROI + \beta_{3b}\,(X1)*ROI$$

To test for slope difference: $\beta_{3a} - \beta_{3b}$

To test for within condition ROI correlations: $\beta_{3a},\ \beta_{3b}$



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More on PPI?

doi:10.1093/scan/nss055 SCAN (2012) 7, 604–609

Tools of the trade: psychophysiological interactions and functional connectivity

Jill X. O'Reilly,[1] Mark W. Woolrich,[1,2] Timothy E.J. Behrens,[1,3] Stephen M. Smith,[1] and Heidi Johansen-Berg[1]
[1]FMRIB Centre, Department of Clinical Neurosciences, Oxford University, John Radcliffe Hospital, Oxford, OX3 9DU, [2]Oxford Centre for Human Brain Activity (OHBA), Department of Psychiatry, Oxford University, Warneford Hospital, Oxford, OX3 7JX and [3]Wellcome Trust Centre for Neuroimaging, University College London, Wellcome Trust Centre for Neuroimaging, 12 Queen Square, London, WC1N 3BG, UK

Psychophysiological interactions (PPIs) analysis is a method for investigating task-specific changes in the relationship between activity in different brain areas, using functional magnetic resonance imaging (fMRI) data. Specifically, PPI analyses identify voxels in which activity is more related to activity in a seed region of interest (seed ROI) in a given psychological context, such as during attention or in the presence of emotive stimuli. In this tutorial, we aim to give a simple conceptual explanation of how PPI analysis works, in order to assist readers in planning and interpreting their own PPI experiments.

Keywords: psychophysiological interactions; PPI; functional connectivity; resting state

NeuroImage 61 (2012) 1277–1286

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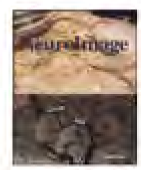

Technical Note

A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches

Donald G. McLaren [a,b,c,d,e,f,g], Michele L. Ries [a,c], Guofan Xu [a,c], Sterling C. Johnson [a,c,*]

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Phys-Phys Interactions

- Interactions are not unique to Psych-ROI – this is a general approach and one that can by used to evaluate interactions between timeseries
- “Does connectivity of region X, vary with level of activity in region Y?”

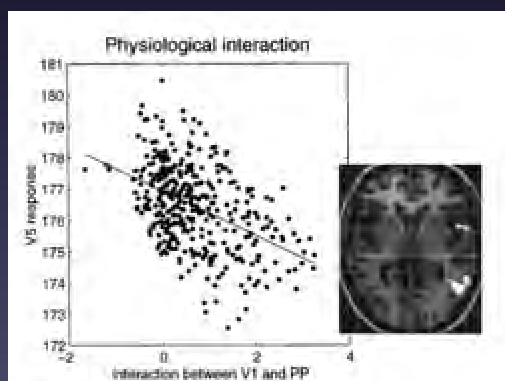
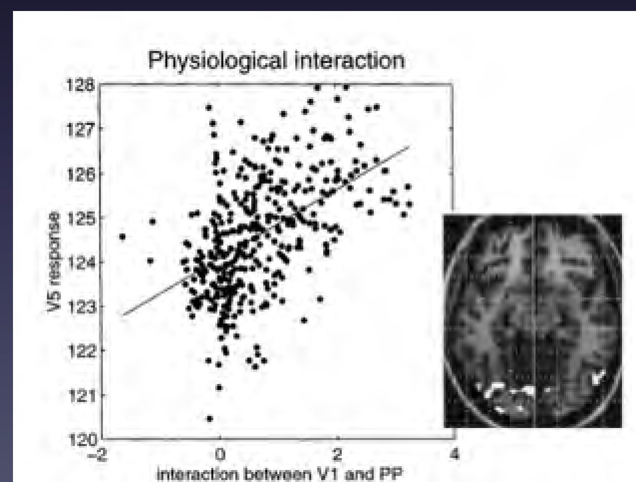


FIG. 2. As for Fig. 1 but for a voxel more anteriorly and superiorly laced in relation to V5 (57, −57 6 mm). In this instance the egression slope is negative, suggesting a negative modulation of /1 → V5 influences by PP activity [$Z = 5.32$, $P = 0.007$ (corrected)].



Friston, K.J., et al., (1997), NeuroImage, 6: 218-229

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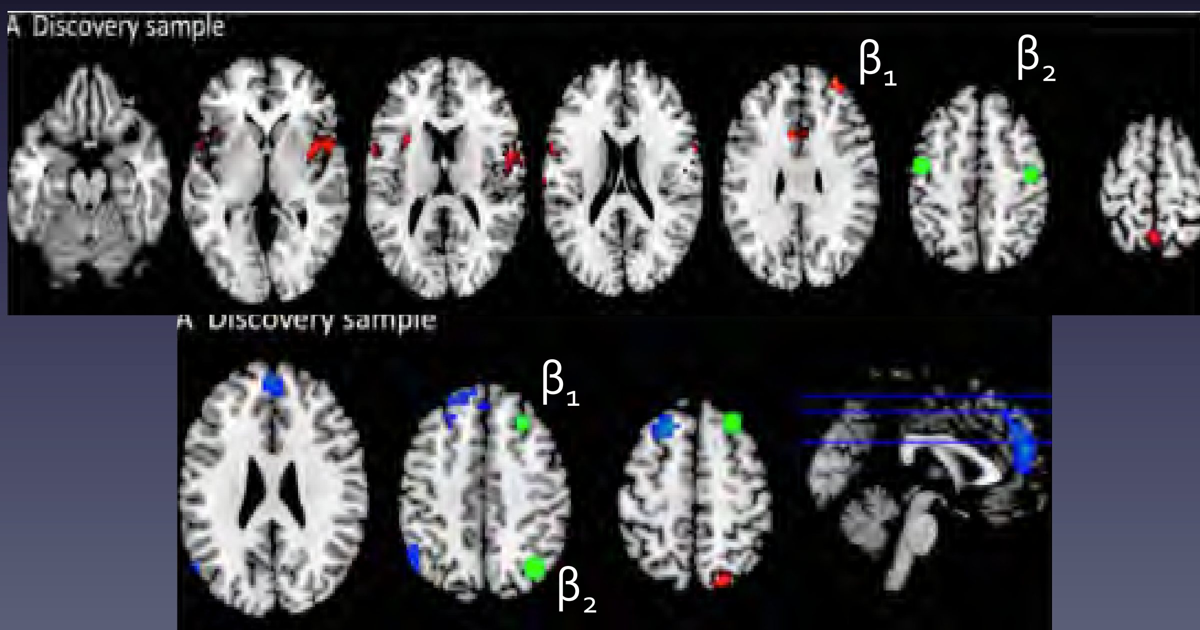
Phys-Phys Interactions

- Emerging use of PPI construct is to evaluate **physio**-**physio**logical interactions (Friston et al., 1997), but during **resting state**
- β_1 = L Motor, β_2 = R Motor, β_3 = L Motor * R Motor
- Does connectivity within one region vary with activation level of another region



Di & Biswal, (2013), PLOS ONE, 8(8): e71163

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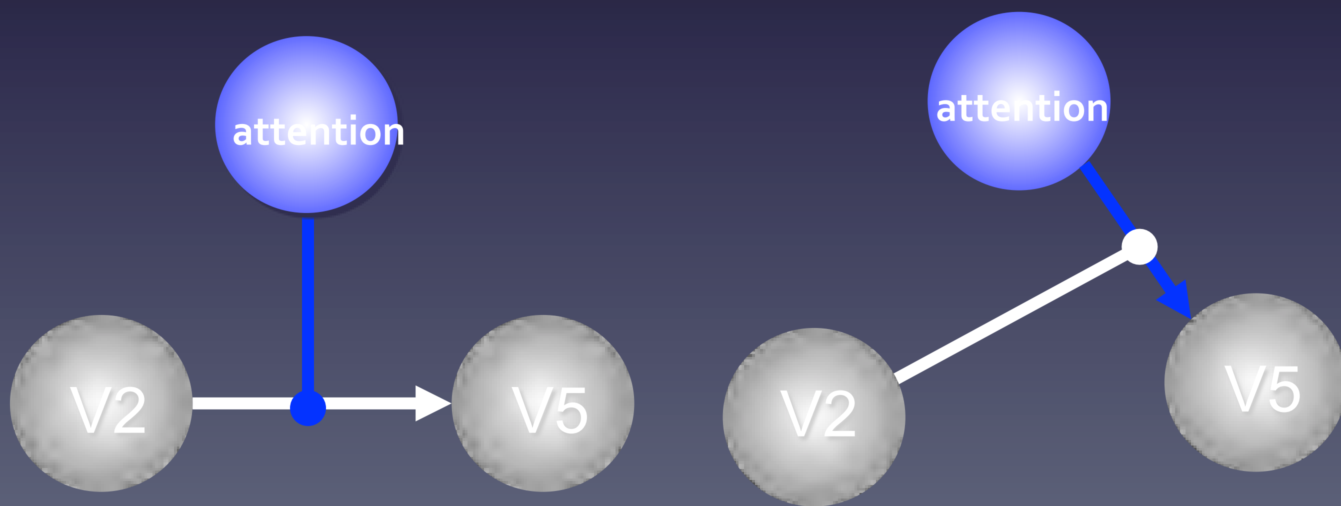
PPI Summary

- PPI is accessible and powerful as a tool to study connectivity across context (condition, intervention, group, activity of another region)
  - Requires attention to model, inclusion of ‘task’ regressors, regressor collinearity and centering (for difference-based regressors); it’s a statistic interaction model
  - Typically limited to single region (except for physio-physio interactions) and so not as powerful as other multivariate techniques such as MVPA or PLS
  - However it provides a starting point for causality analysis



Images courtesy of UCL group

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Which method?

MVPA, PPI, PLS grouped as task-related connectivity methods

MVPA (Machine Learning)

$X(label) = b_1Y_1 + b_2Y_2 + b_3Y_3 \ldots.$

Objective is to predict class label (not really a network analysis) – more like log regression. It is multivariate (voxels independent variables) but goal is not to understand the correlations (connectivity patterns) and weights are only indirectly related to connectivity.

Partial Least Squares

$a_1Y_1 + a_2Y_2 + a_3Y_3 \ldots = b_1X_1$

Truly multivariate (voxels dependent variables), aiming to discover combination of activity patterns that covary across context (e.g., condition X_1 levels). Not model based.

PPI

$Y= b_1X_1 + b_2X_2 + b_3ROI + b_4X_1{*}ROI \ldots$

Mass univariate (GLM), but bound by ROI correlation across conditions. We are testing connectivity hypotheses. Model based. Conceptually a precursor to causality.

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Which method?

MVPA, PPI, PLS grouped as task-related connectivity methods

MVPA (Machine Learning)

X(label) = b1Y1 + b2Y2 + b3Y3 ….

Can be used in conjunction with a network "identifier" either with the former used in feature selection or adapting cross-validation.

Partial Least Squares

a1Y1 + a2Y2 + a3Y3 … = b1X1

Can be used to identify your network units and polarity of relationships.

PPI

Y= b1X1 + b2X2 + b3ROI + b4X1*ROI …

Begin to probe modulation effects within a network. Helps to come up with plausible models for causal analysis.

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Questions?

…onto the lab…