# How the ideas of connectivity have evolved

BRAIN CONNECTIVITY WORKSHOP DÜSSELDORF 2022

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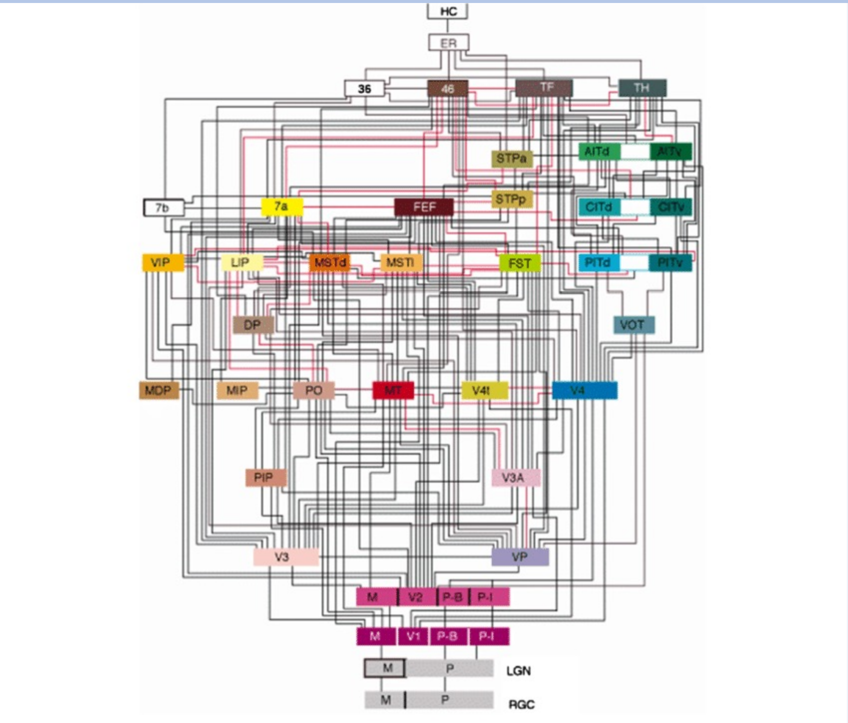
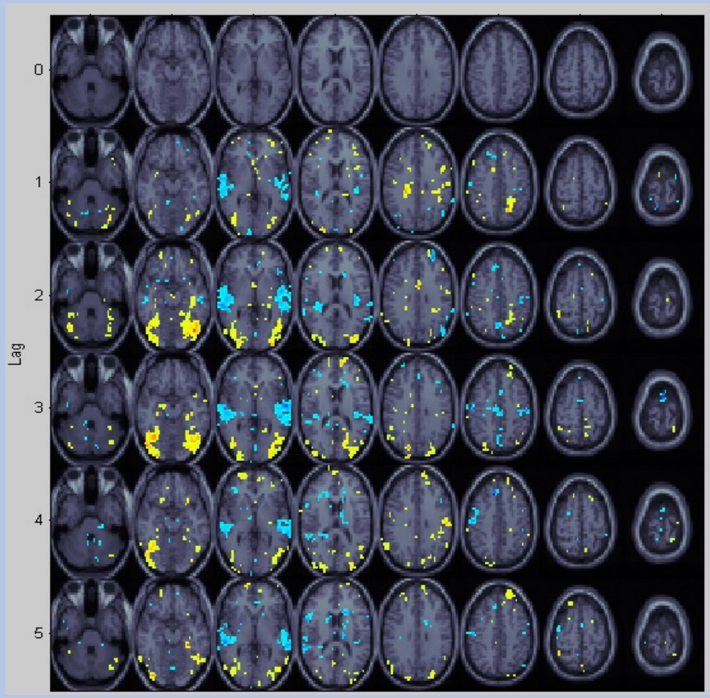
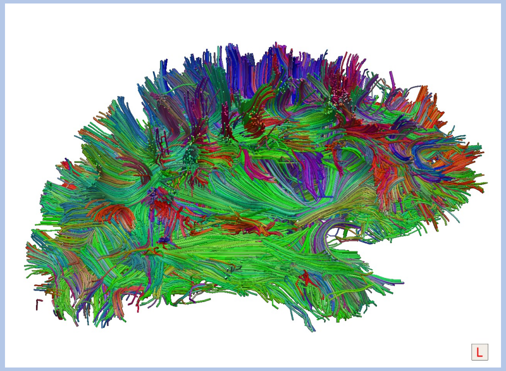
https://github.com/McIntosh-Lab/BCW2022

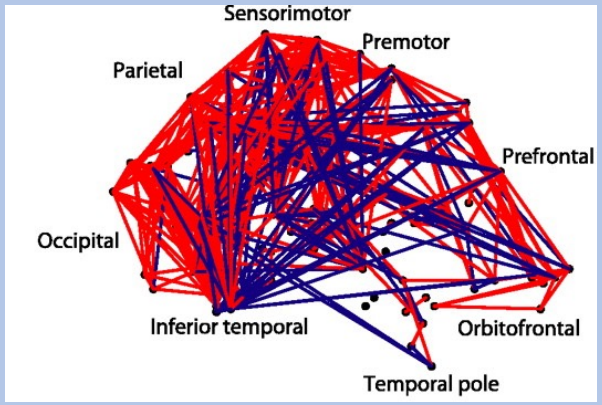
SFU


BRAIN CONNECTIVITY WORKSHOP DÜSSELDORF 2022
BRAIN CONNECTIVITY WORKSHOP 2021
MAY 25-28 online
BRAIN CONNECTIVITY WORKSHOP 2019
MAY 26 - 28, REYKJAVÍK, ICELAND
Brain Connectivity Workshop 2018
Stanford, USA
brain connectivity workshop 2017
Zurich, CH
BRAIN CONNECTIVITY WORKSHOP | MARSEILLE 2016
BRAIN CONNECTIVITY WORKSHOP 2015
UCSD, La Jolla California
BRAIN CONNECTIVITY WORKSHOP
Hamburg, DE
BRAIN CONNECTIVITY WORKSHOP
VANCOUVER | JUNE 12-14, 2013
Brain Connectivity Workshop 2012
June 6-8, Chengdu, China
BRAIN CONNECTIVITY WORKSHOP Montréal 2011
brain connectivity workshop 2010
1st-4th June | Berlin
Brain Connectivity Workshop 2009
Course, 1 May | Workshop, 2-3 May | Maastricht, NL
brain connectivity workshop 2008
June 12-13 | Sydney, Australia
BRAIN CONNECTIVITY WORKSHOP 2007
May 28-30, 2007 / BARCELONA
TOHOKU UNIVERSITY
2006
Brain Connectivity Workshop
Boca Raton, USA
Brain Connectivity Workshop
April 26 - 29, 2004, Havana City, Cuba
Brain Connectivity Workshop
May 1 - 3, 2003, Cambridge, England
Organized by : Ed Bullmore, Lee Harrison, Lucy Lee & Andrea Mechelli
UNIVERSITY OF CAMBRIDGE
UCL
Dusseldorf, DE, 2002





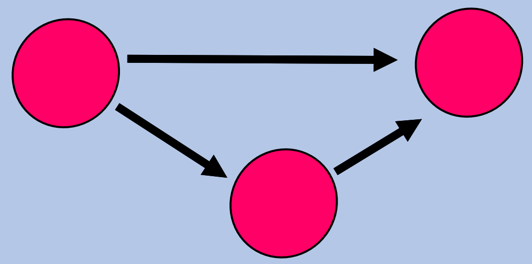

Anatomy

*conduit*

Function/dynamics

*communication*

# What kinds of connectivity do we talk about in neuroscience?



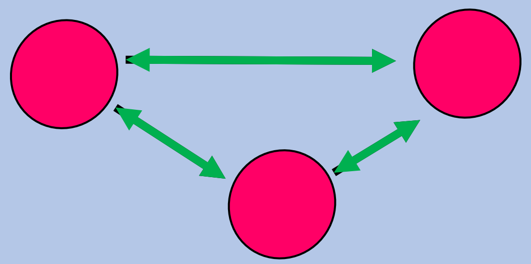
Structural

Indicates an axonal connection between region

Directional

Inferred from tracers or tractography

Varies slowly across time



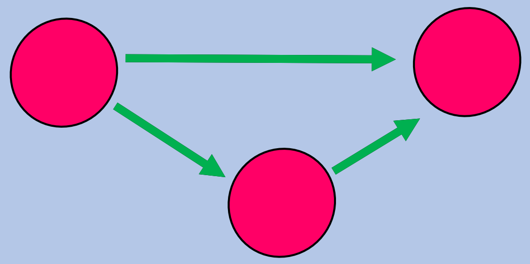
Functional

Statistical dependence of activity (across time)

Nondirectional

Estimated by measures of association

Varies across many time scales



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Indicates a causal dependence between nodes

Directional

Many methods to estimate with differing underlying

Varies across time scale

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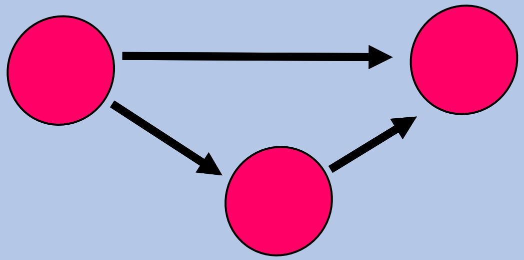

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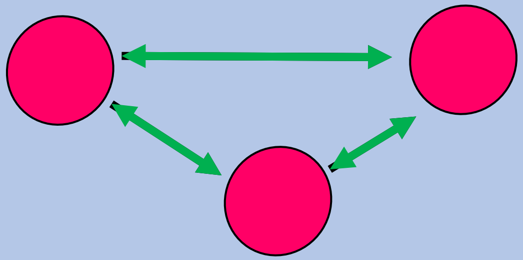
***"Anatomy is destiny." Tononi, BCW2021***



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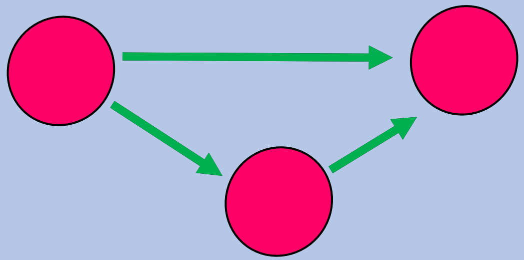

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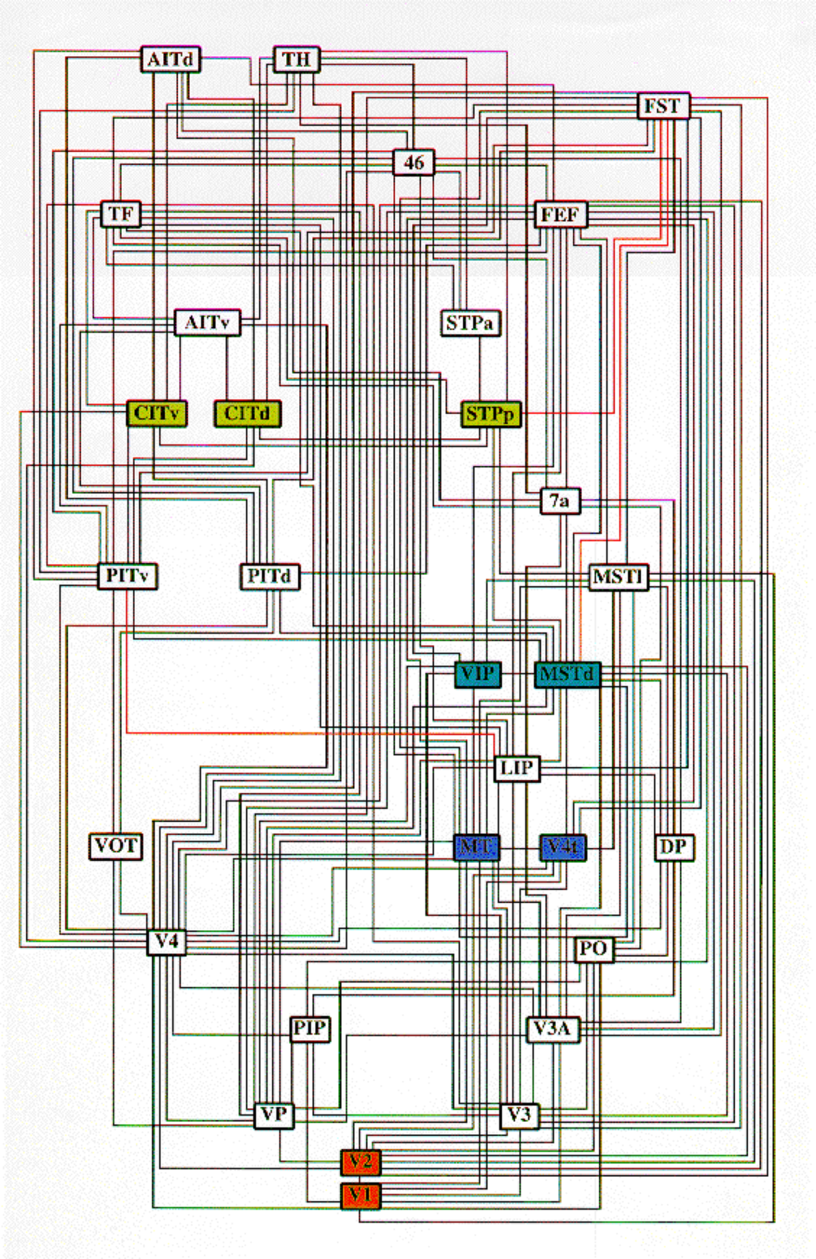
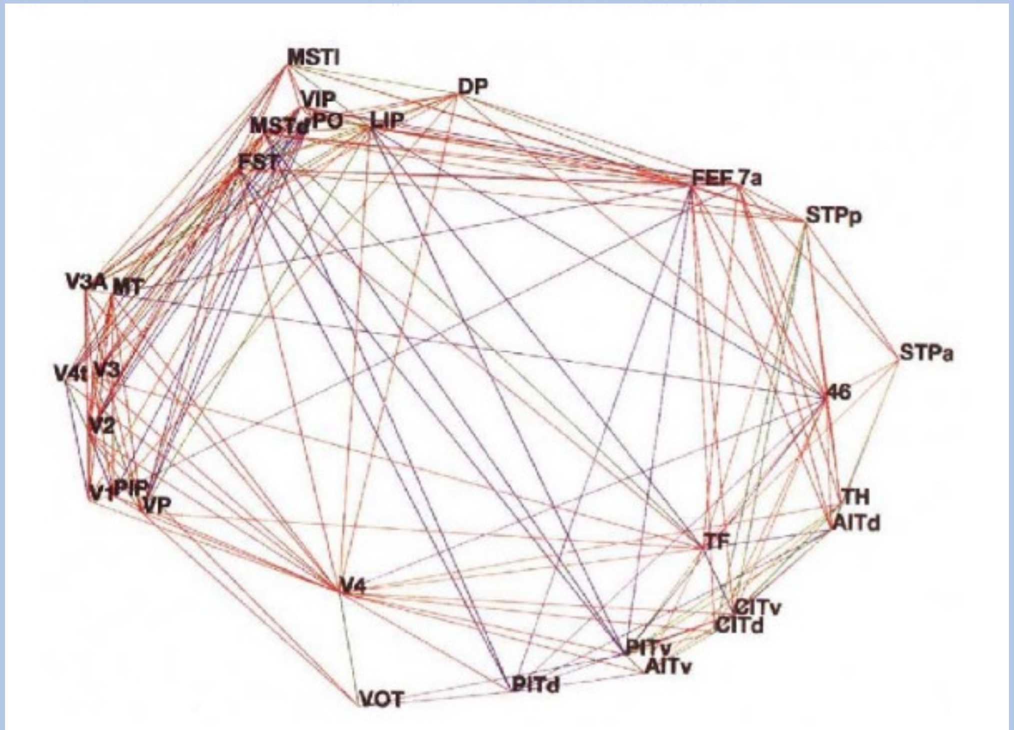



Published: 09 July 1992

# Objective analysis of the topological organization of the primate cortical visual system

Malcolm P. Young

*Nature* **358**, 152–155 (1992) | Cite this article

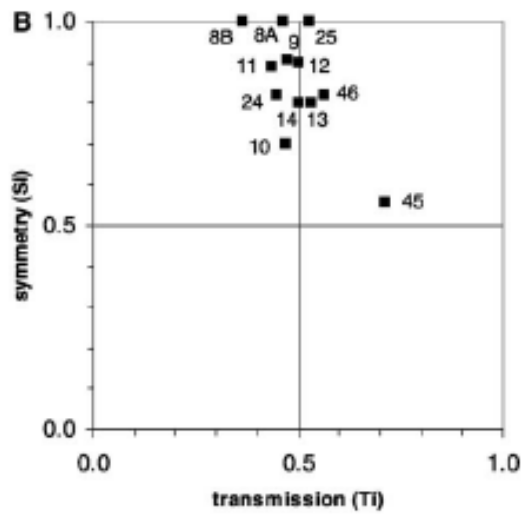



Used adjacency matrix from anatomical connectivity and expressed as “distances” using non-metric multidimensional scaling

# Network participation indices: characterizing component roles for information processing in neural networks

Rolf Kötter[a,*], Klaas E. Stephan[b,c]

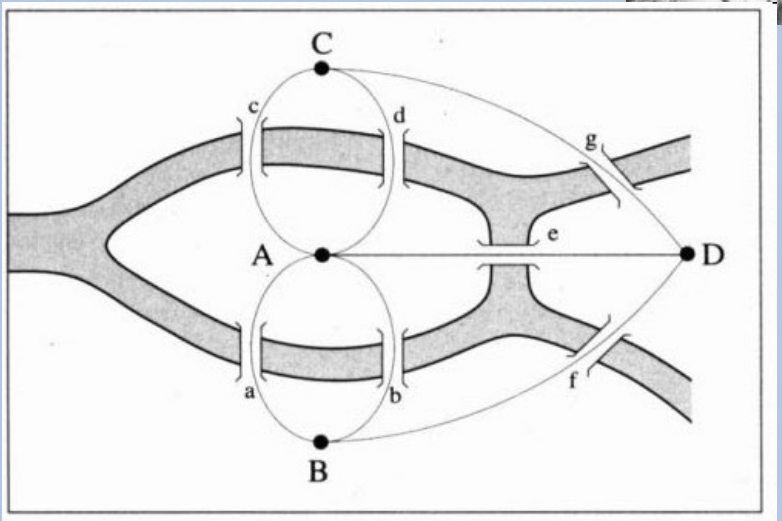
| | 10 | 11 | 12 | 13 | 14 | 24 | 25 | 45 | 46 | 8A | 8B | 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | U | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 1 |
| 11 | 1 | U | 1 | 1 | 1 | 1 | 1 | U | 0 | 0 | 0 | 1 |
| 12 | 1 | 1 | U | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| 13 | 1 | 1 | 1 | U | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| 14 | 1 | 1 | 1 | 1 | U | 1 | 1 | 0 | 0 | 0 | 0 | 1 |
| 24 | 0 | 1 | 1 | 0 | 1 | U | 1 | 1 | 1 | 1 | 1 | 1 |
| 25 | 1 | 1 | 1 | 1 | 1 | 1 | U | 0 | 1 | 0 | 1 | 1 |
| 45 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | U | 1 | 1 | 1 | 1 |
| 46 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | U | 1 | 1 | 1 |
| 8A | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | U | U | 1 |
| 8B | U | U | U | U | U | 1 | U | U | 1 | 1 | U | 1 |
| 9 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | U |




*Neural Networks 2003*

# Historical Origins of Graph Theory

Leonhard Euler's 1736 publication on the bridges of Königsberg (Kaliningrad) is the origin of graph theory.

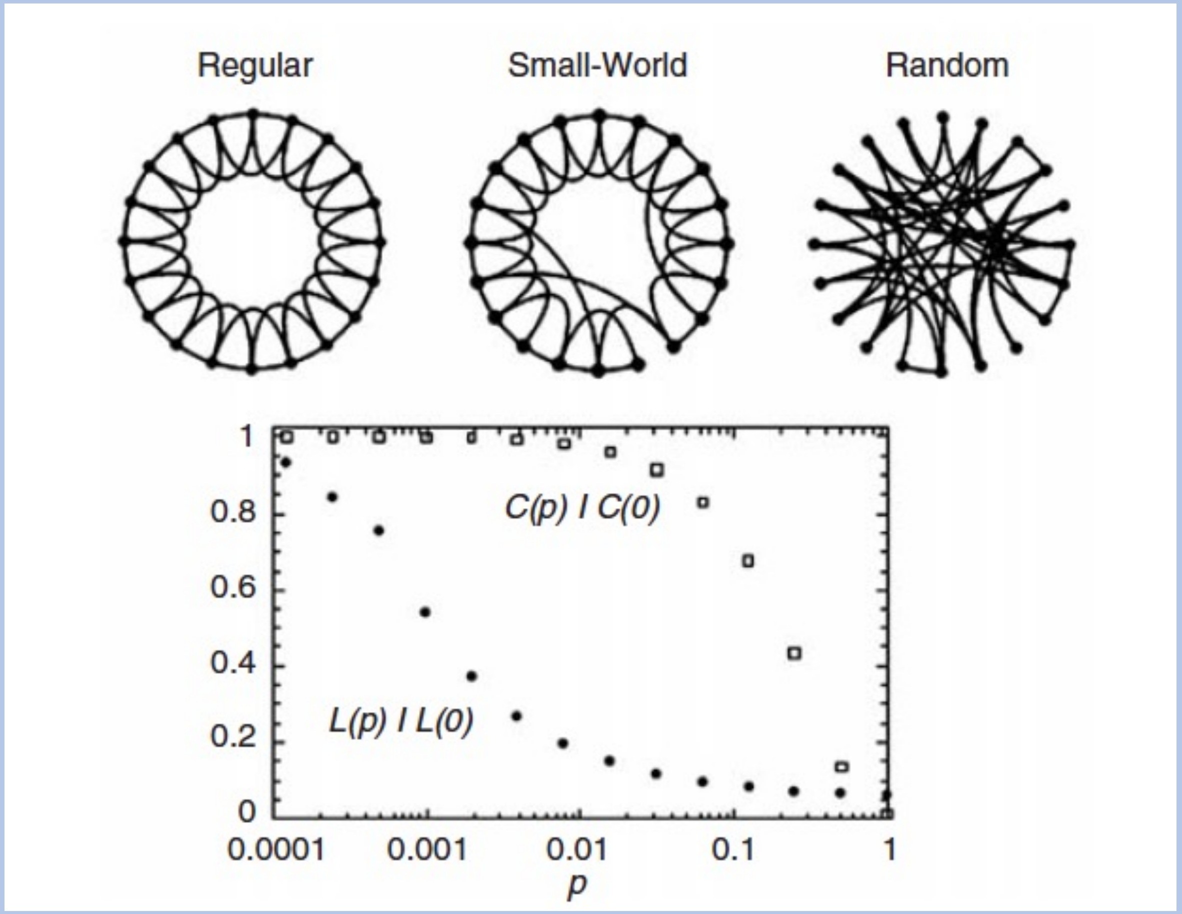



19th century graph theory was developed further by Kirchhoff (electrical networks) and Sylvester (chemical isomers).

Graph theory is now widely applied across all fields of science.

Euler L (1736) *Commentarii Academiae Scientiarum Imperialis Petropolitanae* 8, 128-140.

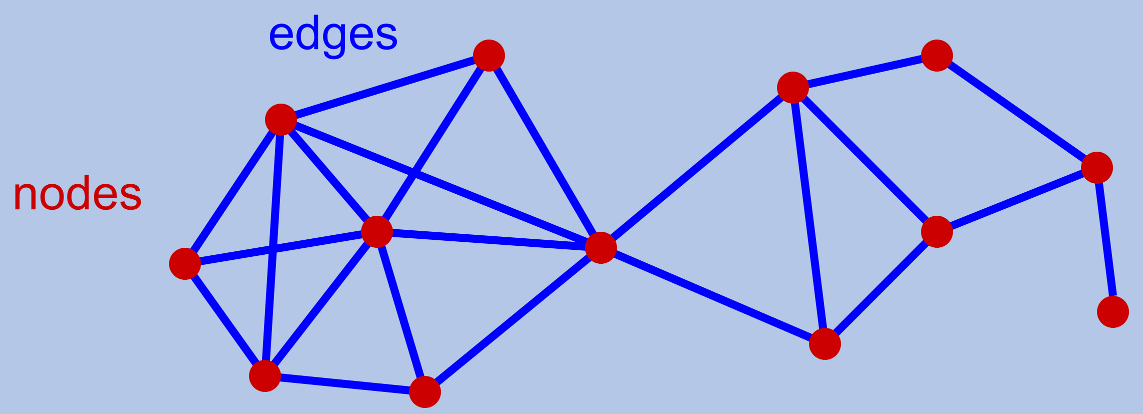
# Graph Theory and Network Architectures




*Optimal* balance of clustering and path length in Small-World Networks

*Watts & Strogatz, 1998, Nature*

# Graphs: Basic Definitions




Graphs (networks) consist of nodes and edges, and can be directed or undirected, weighted or binary.

Graph metrics differ in their mathematical definition and calculation depending on the type of network.

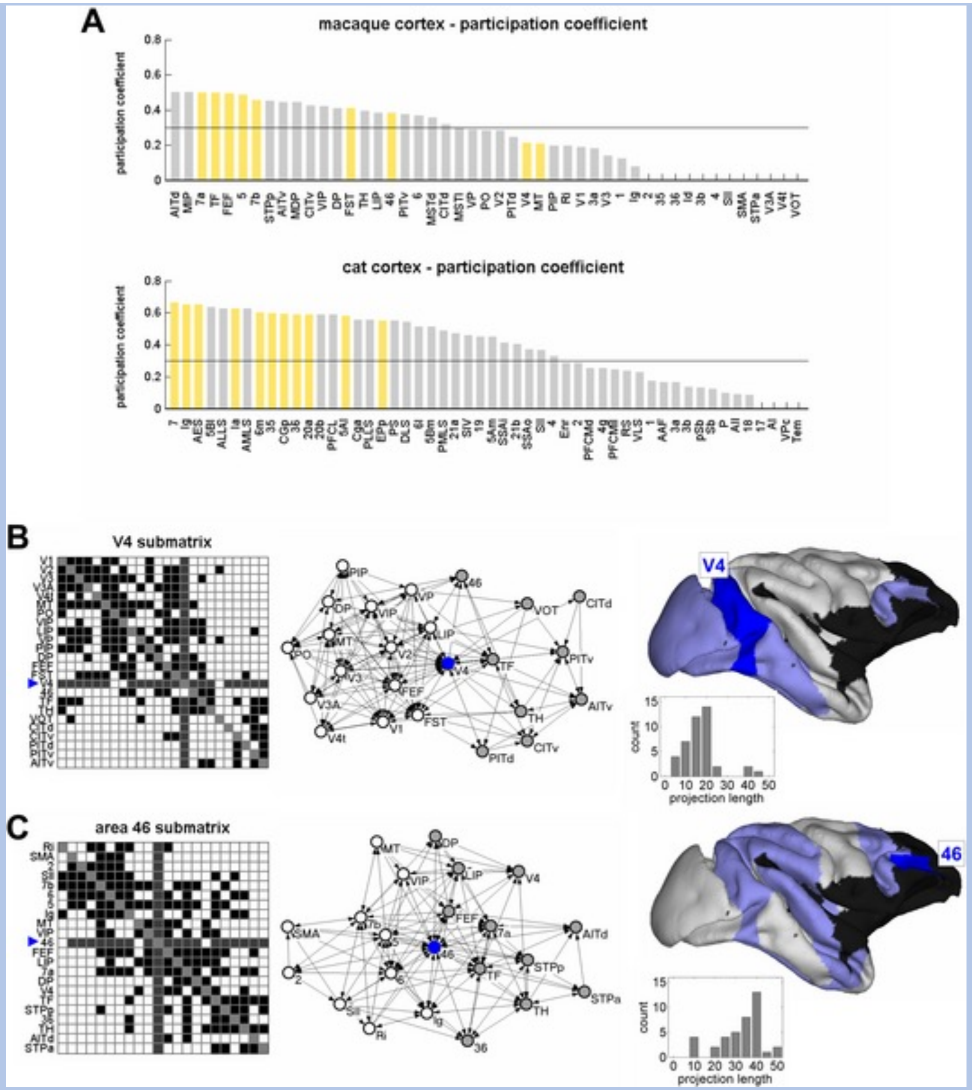
Graphs may be converted from weighted to binary by thresholding – often across a range of thresholds or "costs"

Brain Connectivity Toolbox
www.brain-connectivity-toolbox.net

Rubinov & Sporns (2010)
NeuroImage 52, 1059

# Identification and Classification of Hubs in Brain Networks

Olaf Sporns[1]*, Christopher J. Honey[1], Rolf Kötter[2,3]




PLoS One, 2007

# The Human Connectome: A Structural Description of the Human Brain

Olaf Sporns, Giulio Tononi, Rolf Kötter

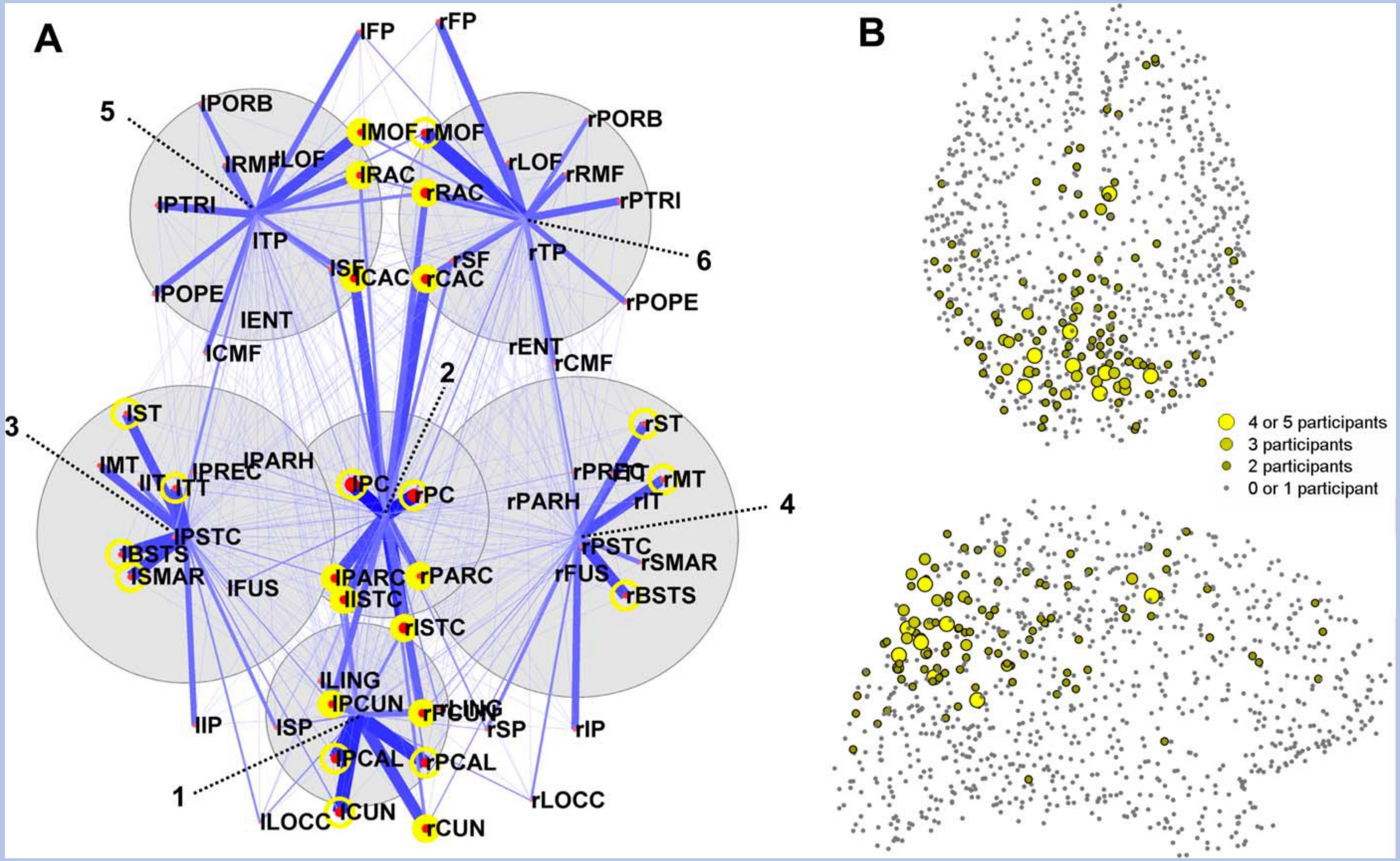
Published: September 30, 2005 • https://doi.org/10.1371/journal.pcbi.0010042

The connection matrix of the human brain (the human “connectome”) represents an indispensable foundation for basic and applied neurobiological research. However, the network of anatomical connections linking the neuronal elements of the human brain is still largely unknown. While some databases or collations of large-scale anatomical connection patterns exist for other mammalian species, there is currently no connection matrix of the human brain, nor is there a coordinated research effort to collect, archive, and disseminate this important information. We propose a research strategy to achieve this goal, and discuss its potential impact.

# Mapping the Structural Core of Human Cerebral Cortex

Patric Hagmann, Leila Cammoun, Xavier Gigandet, Reto Meuli, Christopher J Honey, Van J Wedeen, Olaf Sporns

Published: July 1, 2008 • https://doi.org/10.1371/journal.pbio.0060159



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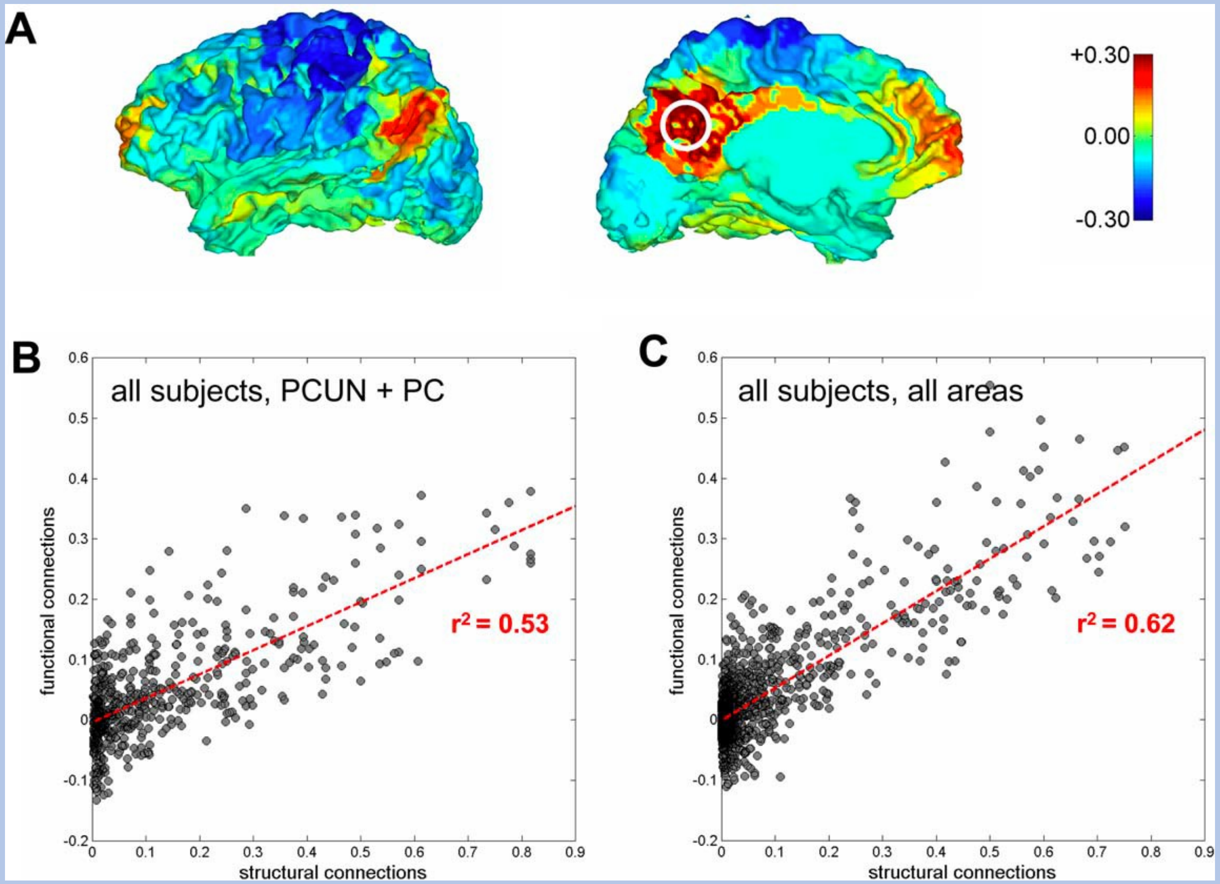
Published: July 1, 2008 • https://doi.org/10.1371/journal.pbio.0060159

Structure and function are correlated, but not perfectly…



# Cautions on DTI & structural connectivitiy

## Exploring the limits of network topology estimation using diffusion-based tractography and tracer studies in the macaque cortex

Kelly Shen [a], Alexandros Goulas [b], David S. Grayson [c], John Eusebio [a], Joseph S. Gati [d], Ravi S. Menon [d, e], Anthony R. McIntosh [a, f], Stefan Everling [d, e]

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## The challenge of mapping the human connectome based on diffusion tractography

Klaus H. Maier-Hein, Peter F. Neher, ... Maxime Descoteaux  + Show authors

*Nature Communications* **8**, Article number: 1349 (2017) | Cite this article

RESEARCH ARTICLE | BIOLOGICAL SCIENCES

## Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited

Cibu Thomas, Frank Q. Ye, M. Okan Irfanoglu, +3, and Carlo Pierpaoli  Authors Info & Affiliations

**November 3, 2014** | 111 (46) 16574-16579 | https://doi.org/10.1073/pnas.1405672111

Limitations of estimation of structural connectivity from tractography

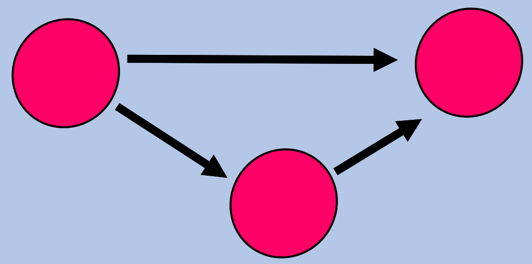
-false positive/negative depends on estimation type

-resolution cannot resolve endpoints (cf. tracers)

-bidirectional

-imaging artifacts can vary across groups (e.g., aging) confounding group comparisons

# What kinds of connectivity do we talk about in neuroscience?



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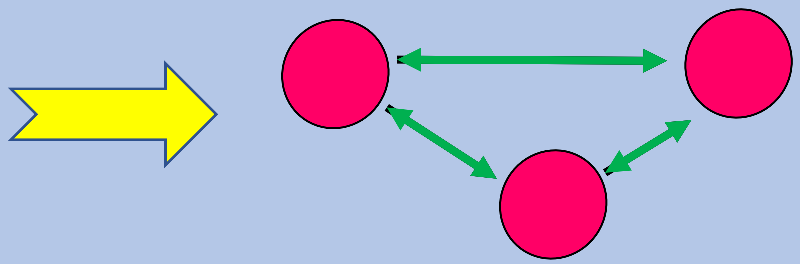

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Statistical dependence of activity (across time)
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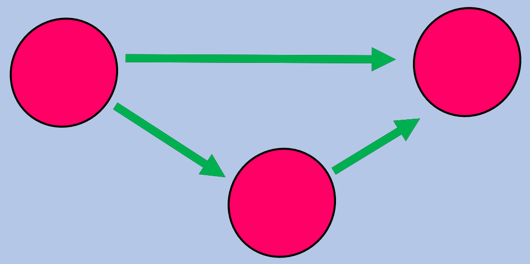


Effective
Indicates a causal dependence between nodes
Directional
Many methods to estimate with differing underlying
Varies across time scale

# Why would we want to estimate functional or effective connectivity?

- Only way to explicitly measure "networks"
  - *activation does not mean covariation*
- Anatomy of nervous systems guarantees that if activity changes, then neural interactions will have changed
  - *may be the case that neural interaction changes precede activity changes (e.g., Ahissar, et al, Science, 1992)*

# Functional Connectivity
# When did it start?

THE BRAIN'S RECORD OF AUDITORY AND VISUAL EXPERIENCE[1]

A FINAL SUMMARY AND DISCUSSION

BY

WILDER PENFIELD AND PHANOR PEROT

We have argued before, that since excision of these areas does not abolish memory, they do not contain the actual record of the past. They are, however, functionally connected with that neuronal record (Penfield, 1958*b*). Since stimulation produces at times detailed recall of past experience in these areas and nowhere else, and since, at other times, it produces a sudden alteration in the patient's present interpretation of things heard or seen, it seems likely that these areas play in adult life some role in the subconscious recall of past experience making it available for present interpretation. This recall makes possible that sudden flash of awareness that things have been seen or heard or experienced before, or that they are dangerous, coming near, or changing pace.

Brain, 1963

# Voxel-wise methods

- Simple correlation
  - Horwitz, 1984
- Linear regression approaches
  - “Psychophysiological interactions” (PPI, Friston et al, 1997)
- Sometimes functional connectivity is enough

**Intercorrelations of Glucose Metabolic Rates between Brain Regions: Application to Healthy Males in a State of Reduced Sensory Input**

Barry Horwitz, Ranjan Duara, Stanley I. Rapoport

First Published December 1, 1984 | Research Article | Find in PubMed
https://doi.org/10.1038/jcbfm.1984.73

Article information

Altmetric 17

Abstract

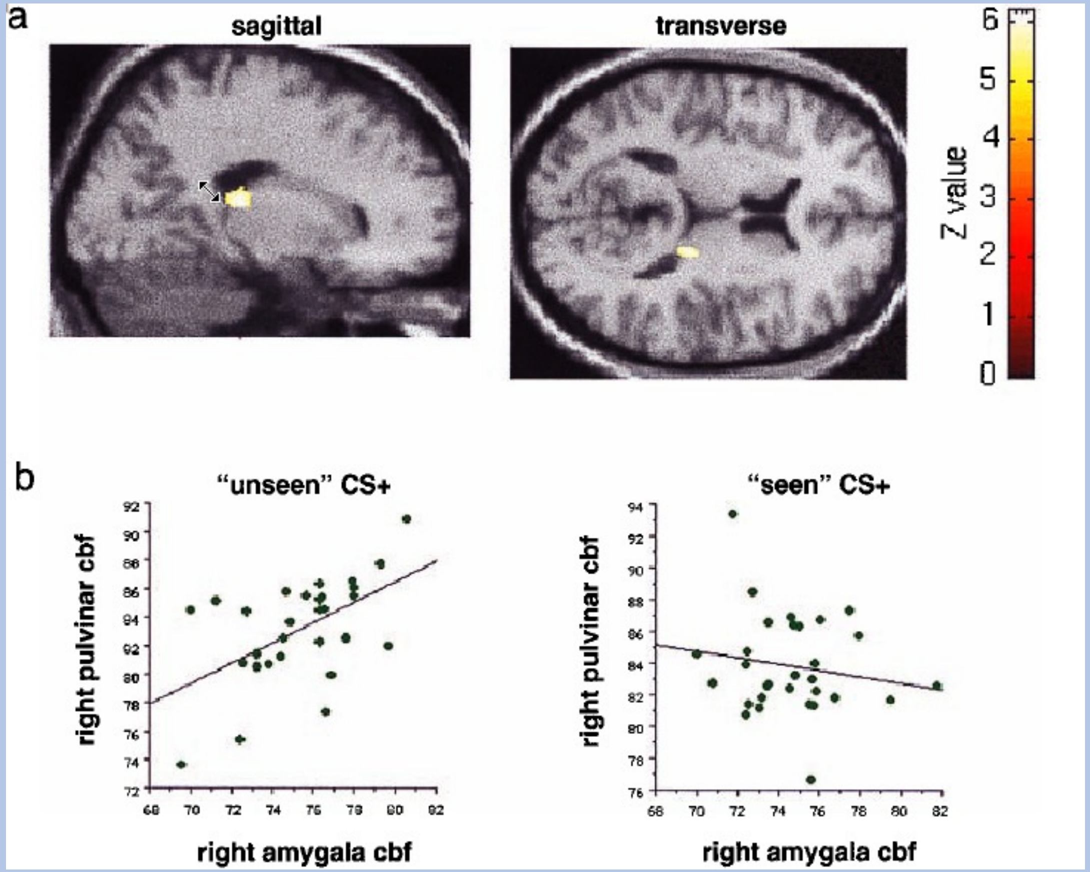
We use a correlational analysis of regional metabolic rates to characterize relations among different brain regions. Starting with rates of local glucose metabolism (rCMRglc) obtained by positron emission tomography using [$^{18}$F]fluorodeoxyglucose, we propose that pairs of brain regions whose rCMRglc values are significantly correlated are functionally associated, and that the strength of the association is proportional to the magnitude of the correlation coefficient. Partial correlation coefficients, controlling for whole brain glucose metabolism, are used in the analysis. We also introduce a graphical technique to display simultaneously all the correlations, allowing us to examine patterns of relations among them. The method was applied to 40 very healthy males under conditions of reduced auditory and visual inputs (the “resting state”). Dividing the brain into 59 regions, and keeping only those partial correlation coefficients significant to $p < 0.01$, we found the following: (a) All regions were significantly correlated with their contralateral homologues. For the most part, the largest partial correlation coefficients were between homologous brain regions. (b) Generally, the pattern of significant correlations between any two lobes in the left hemisphere did not differ statistically from the corresponding pattern in the right hemisphere. (c) Strong correlations were observed between primary somatosensory areas and premotor association areas. Correlations between these association areas and primary visual and auditory regions were not statistically significant. (d) Significant correlations between inferior occipital and temporal areas were found. Metabolic rates in the superior part of the occipital lobe were not correlated significantly with metabolic rates in regions of the temporal lobe, nor with metabolism in the parietal lobe. (e) As a whole, there were numerous correlations among frontal and parietal lobe regions, on the one hand, and among temporal and occipital lobe regions, on the other, but few statistically significant correlations between these two domains. We relate our results to various aspects of known brain anatomy, physiology, and cognitive functioning.

Keywords

Correlation matrix, [$^{18}$F]Fluorodeoxyglucose, Hemispheric symmetry, Positron emission tomography, Regional cerebral metabolic rate for glucose, Resting state

Journal of Cerebral Blood Flow and Metabolism 1984

# Amygdala-Thalamus Interactions in Fear Conditioning – Psychophysiological Interactions

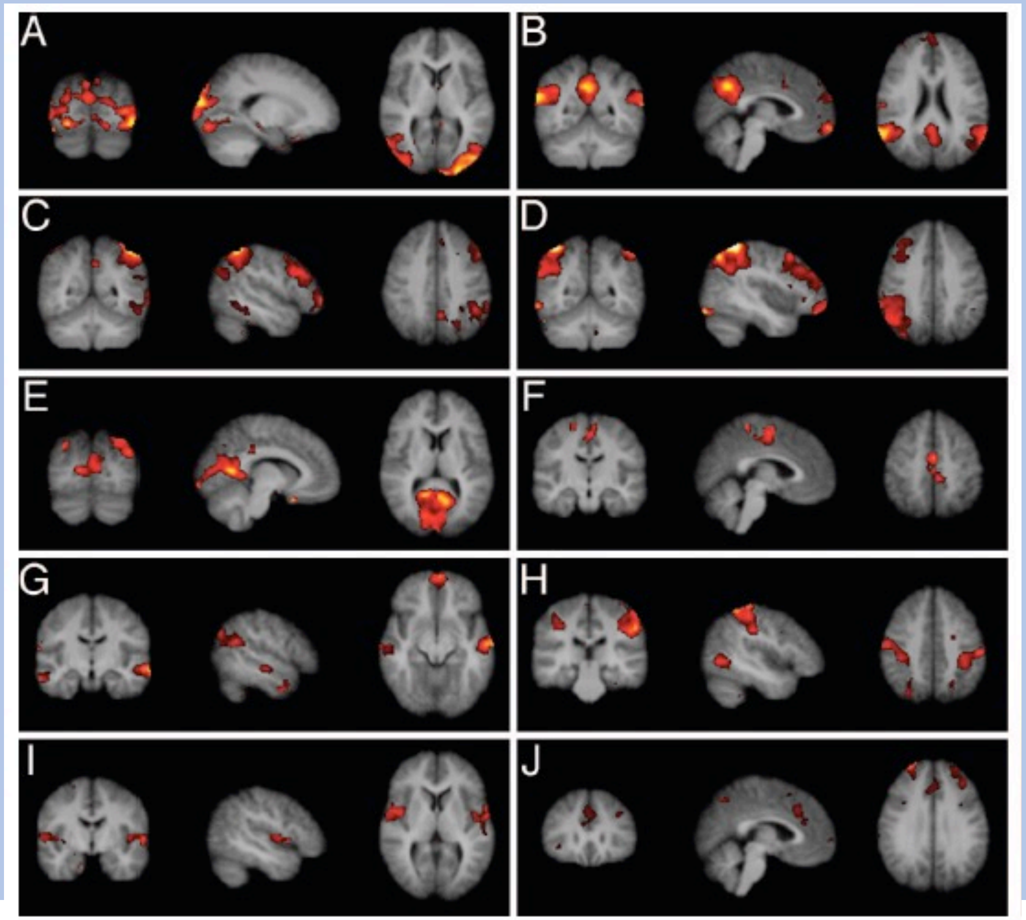



*Morris, et al, 1999, PNAS*

# Independent Components Analysis

- Many variations
  - EEGLAB/FMRILAB (Makeig)
  - MELODIC (Beckman, FSL)
  - GIFT (Calhoun)
- Like PCA, decomposes the entire data matrix into spatial or temporal modes that capture some dynamics of the data
  - Not always obvious what the dynamics are…
- Excellent for eliminating artifact that are not captured by motion correction
  - Be careful of nonlinear/super-Gaussian artifacts

# Resting State Networks & ICA

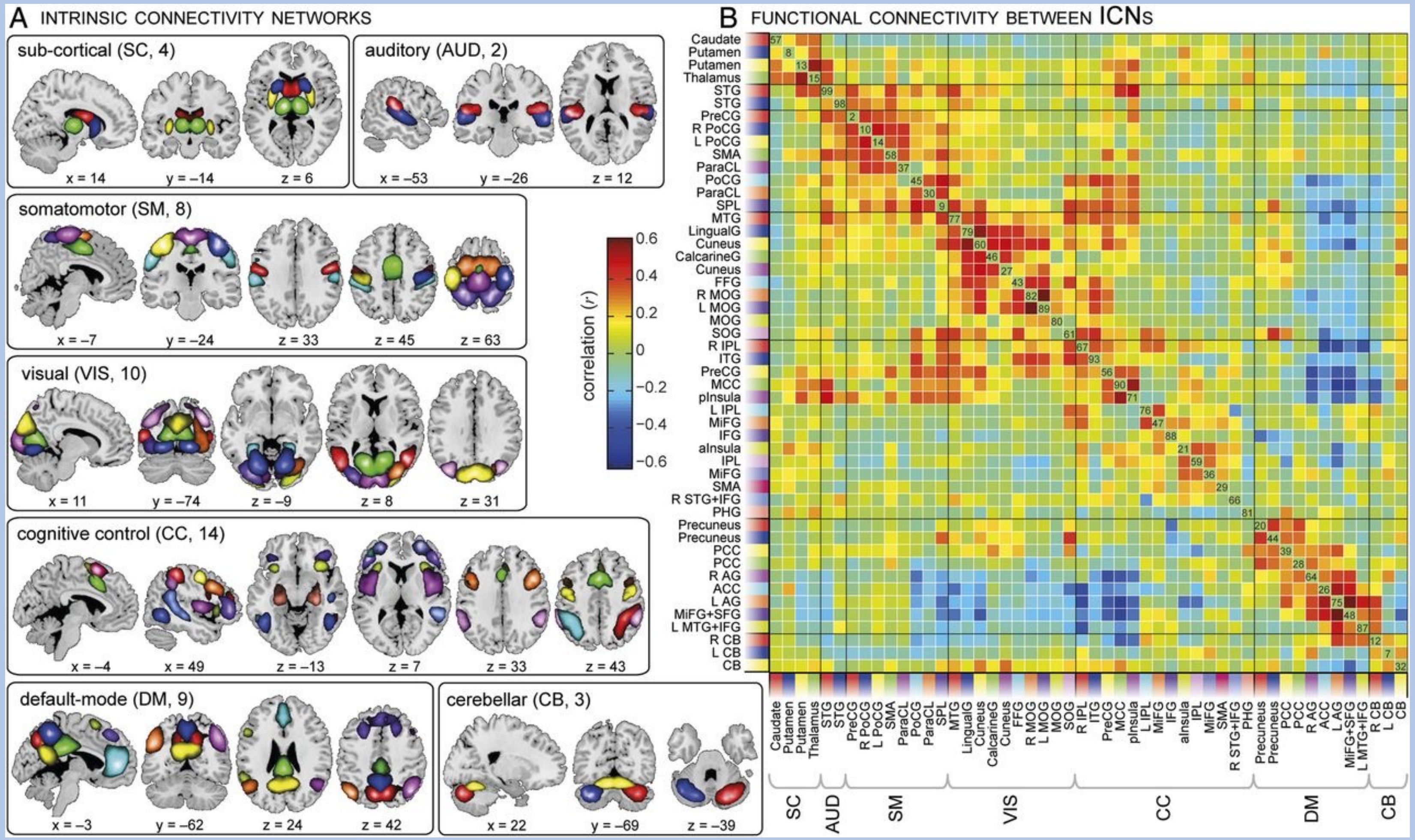



**Consistent resting-state networks across healthy subjects**

J. S. Damoiseaux[†‡], S. A. R. B. Rombouts[§¶], F. Barkhof[‖], P. Scheltens[†], C. J. Stam[††], S. M. Smith[‡‡], and C. F. Beckmann[‡‡]

*Proc Nat Acad Sci, USA, 2006*

# Independent Component Networks and the stationary Functional Connectivity between them



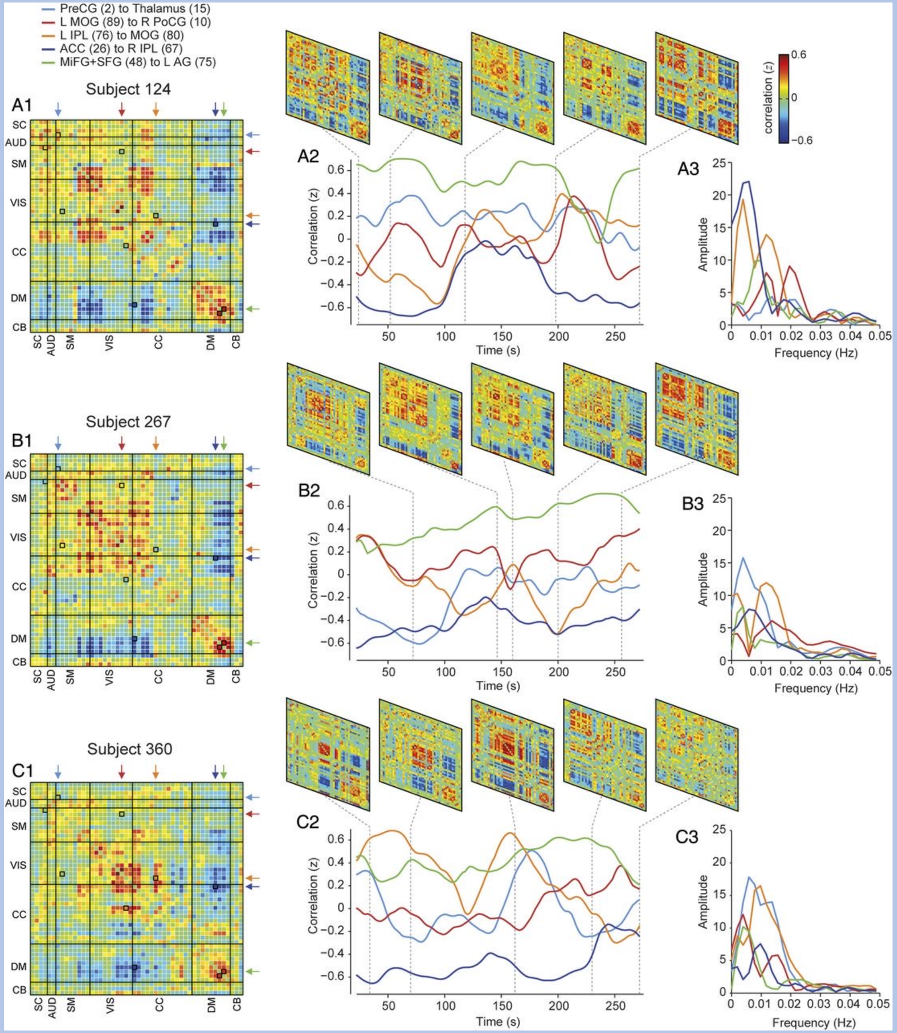

Allen E A et al. Cereb. Cortex 2012;cercor.bhs352

Allen et al, Cereb Cortex, 2013

Cerebral CORTEX

# Examples of Functional Connectivity dynamics.

- Patterns of functional connectivity can change across time
- Network affiliations can also change
- The nature of these transitions may provide more insight into cognitive dynamics




Allen E A et al. Cereb. Cortex 2012;cercor.bhs352

Allen et al, Cereb Cortex, 2013

Cerebral CORTEX

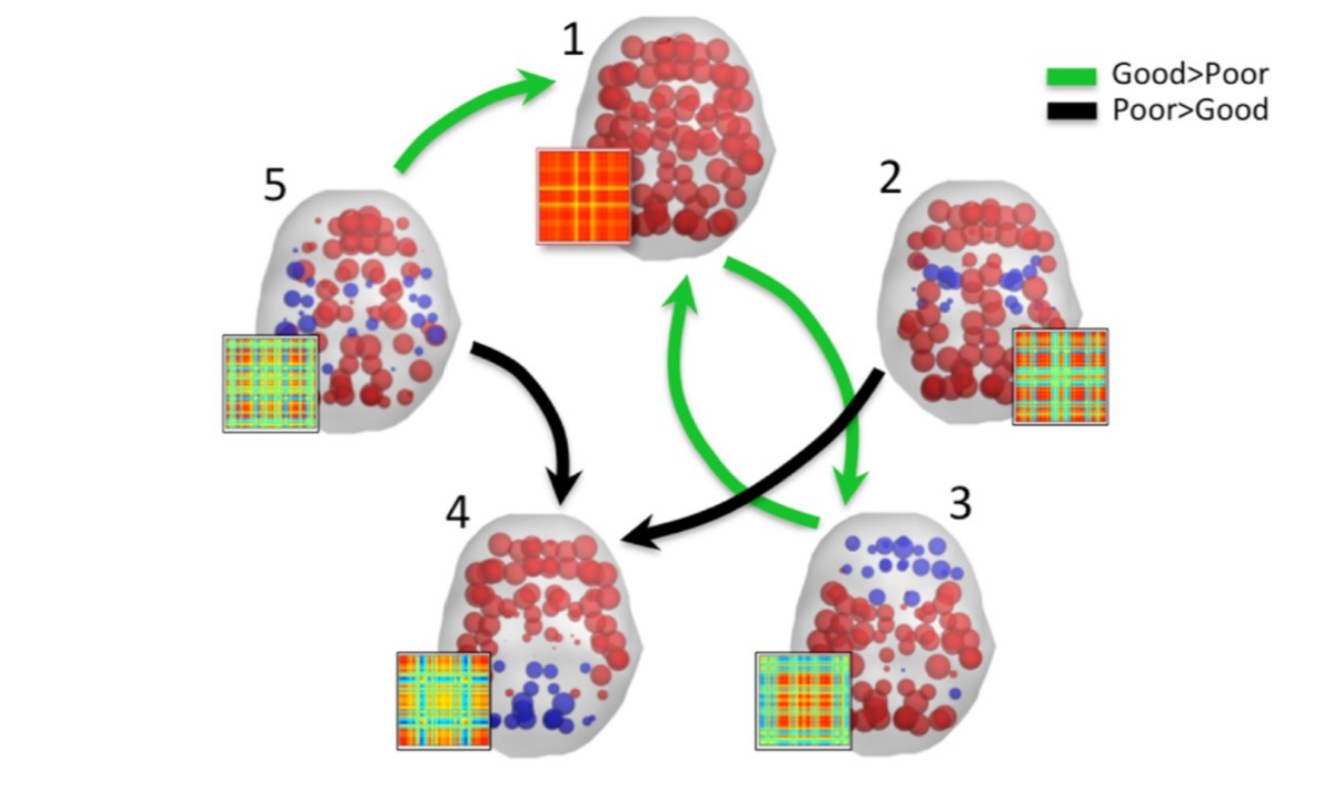
SCIENTIFIC REPORTS

OPEN

# Cognitive performance in healthy older adults relates to spontaneous switching between states of functional connectivity during rest

Received: 19 December 2016
Accepted: 30 May 2017
Published online: 11 July 2017

Joana Cabral[1,2], Diego Vidaurre[3], Paulo Marques[4,5,6], Ricardo Magalhães[4,5,6], Pedro Silva Moreira[4,5,6], José Miguel Soares[4,5,6], Gustavo Deco[7,8,9,10], Nuno Sousa[4,5,6] & Morten L. Kringelbach[1,2,11]



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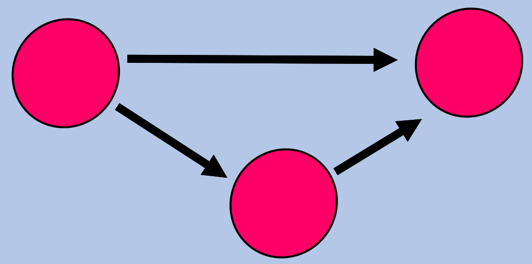

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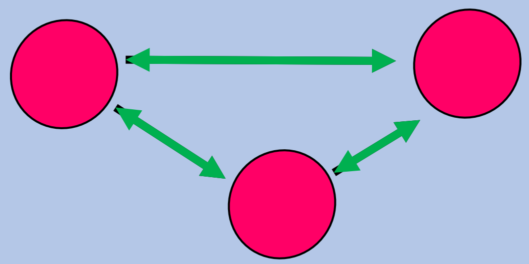

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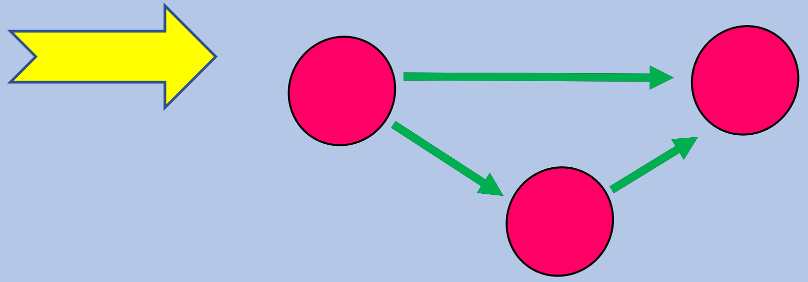

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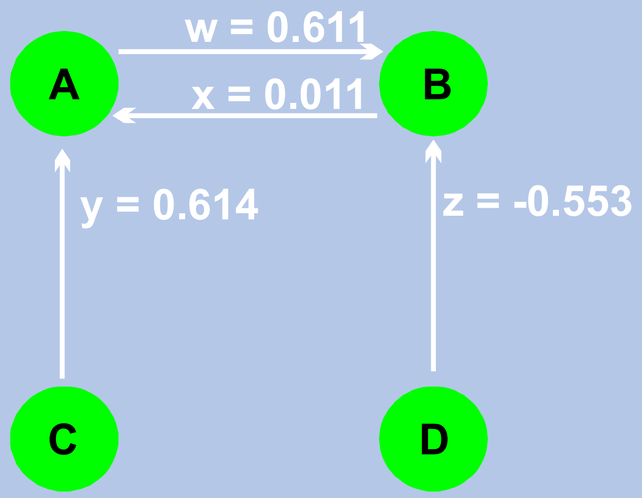
# Structural Equation Modeling

(McIntosh & Gonzalez-Lima, 1991, McIntosh et al, 1994, Buchel & Friston, 1997)




| | A | B | C | D |
|---|---|---|---|---|
| A | 1.00 | | | |
| B | 0.48 | 1.00 | | |
| C | 0.62 | 0.16 | 1.00 | |
| D | 0.24 | -.41 | 0.06 | 1.00 |

$$\begin{pmatrix} A \\ B \\ C \\ D \end{pmatrix} = \begin{pmatrix} 0 & x & y & 0 \\ w & 0 & 0 & z \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} * \begin{pmatrix} A \\ B \\ C \\ D \end{pmatrix} + \begin{pmatrix} \psi_A & 0 & 0 & 0 \\ 0 & \psi_B & 0 & 0 \\ 0 & 0 & \psi_C & 0 \\ 0 & 0 & 0 & \psi_D \end{pmatrix}$$

$$\Sigma = inv(I-\beta)^T * (\psi^T * \psi) * inv(I-\beta)$$

**Structural Equations**

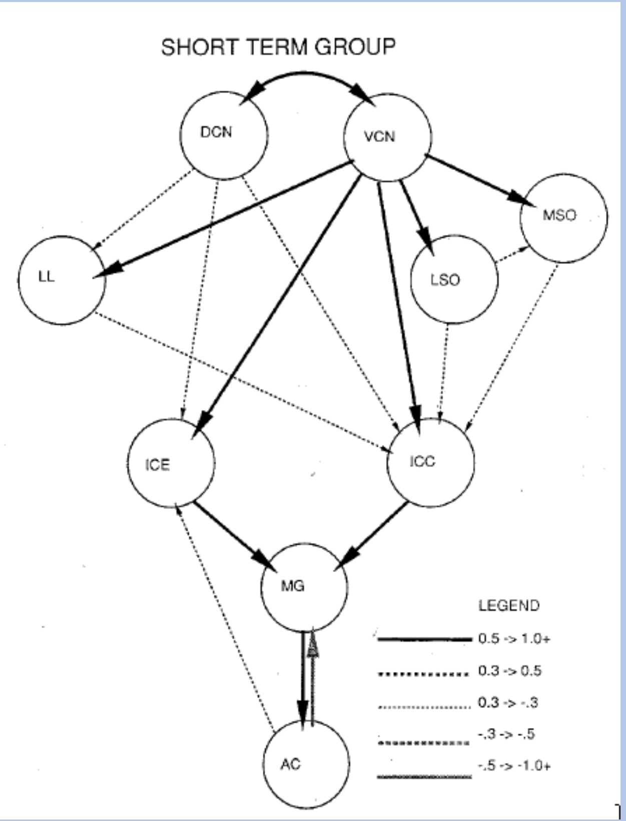
$A = xB + yC + \psi_A$

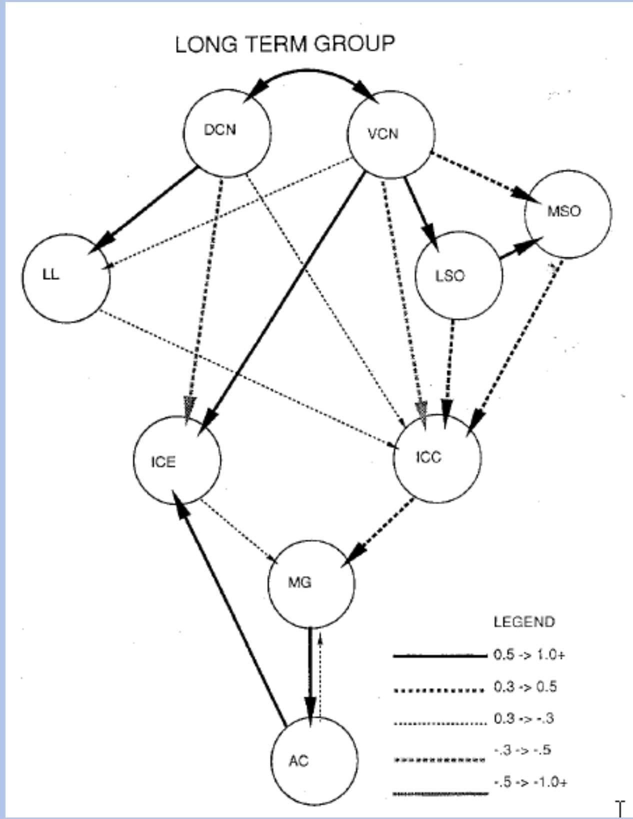
$B = wA + zD + \psi_B$

# 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

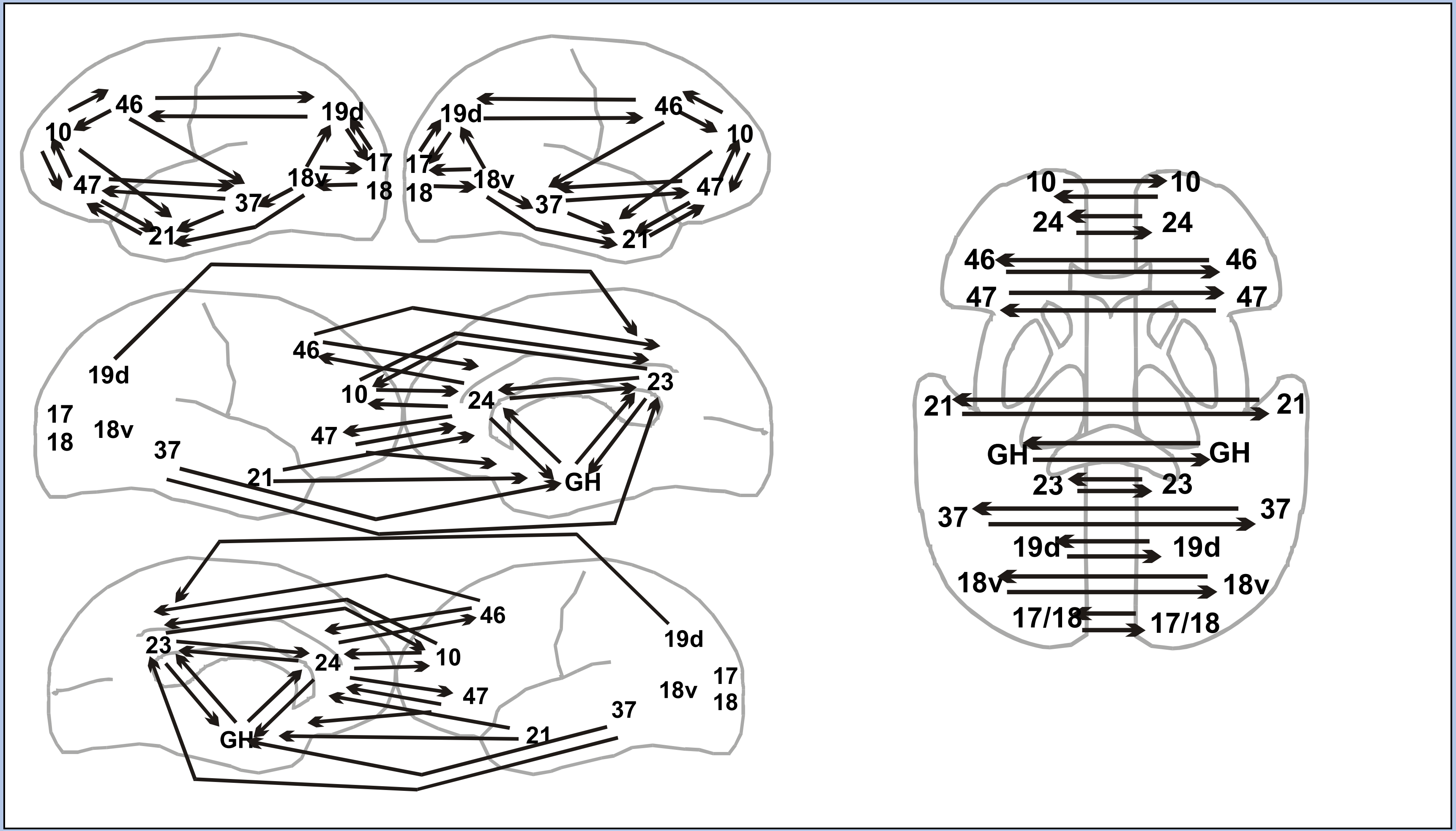
*Department of Anatomy, College of Medicine, Texas A&M University, College Station, TX 77843 (U.S.A.)*



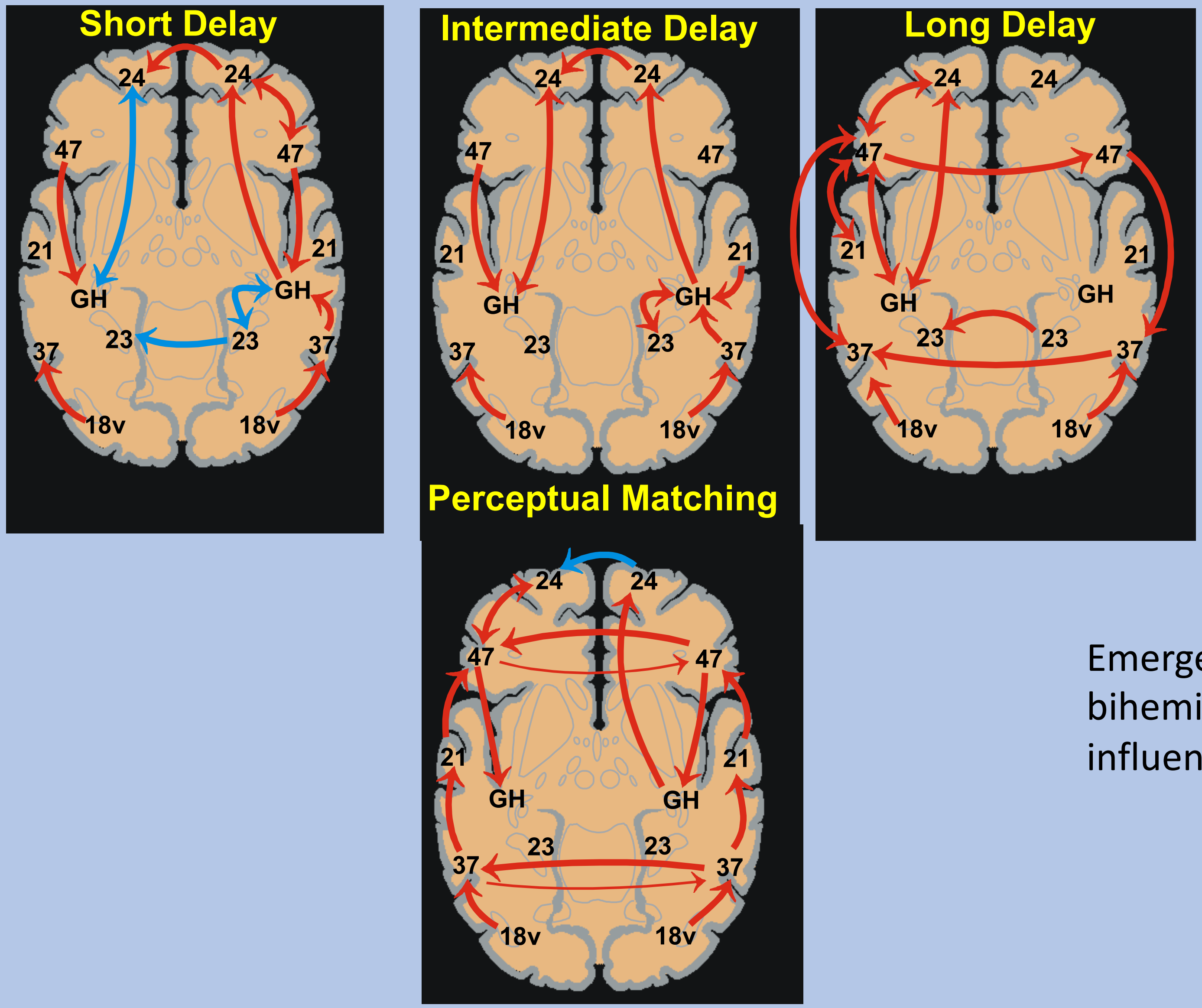

*Brain Res, 1991*

# Anatomical Network
# Working Memory




*McIntosh et al, Cerebral Cortex, 1996*

# Functional Networks in Working Memory for Faces



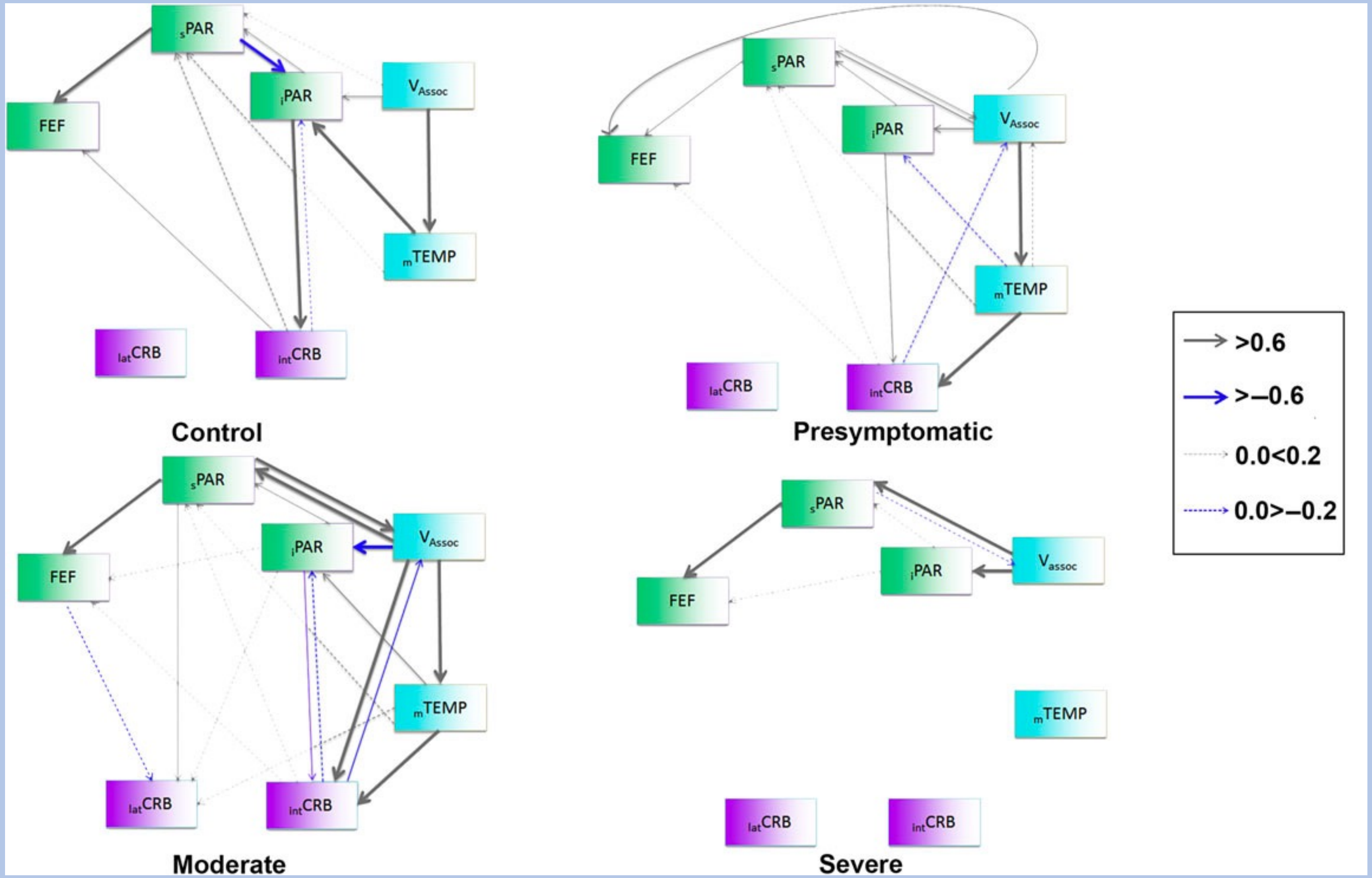

Emergence of stronger bihemispheric influences with delay

# Early Cerebellar Network Shifting in Spinocerebellar Ataxia Type 6

M.I. Falcon[1], C.M. Gomez[3], E.E. Chen[1], A. Shereen[1], and A. Solodkin[1,2]

[1]Department of Anatomy and Neurobiology, [2]Department of Neurology, UC Irvine School of Medicine, Irvine, CA 92697, USA and [3]Department of Neurology, University of Chicago, Chicago, IL 60637, USA

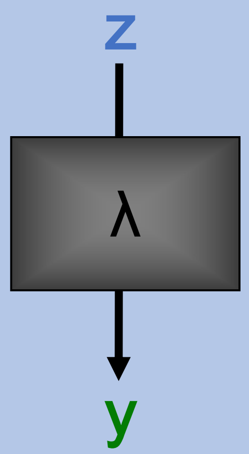
Rise and fall of effective connections in patients with increasing severity




Cerebral Cortex, 2016

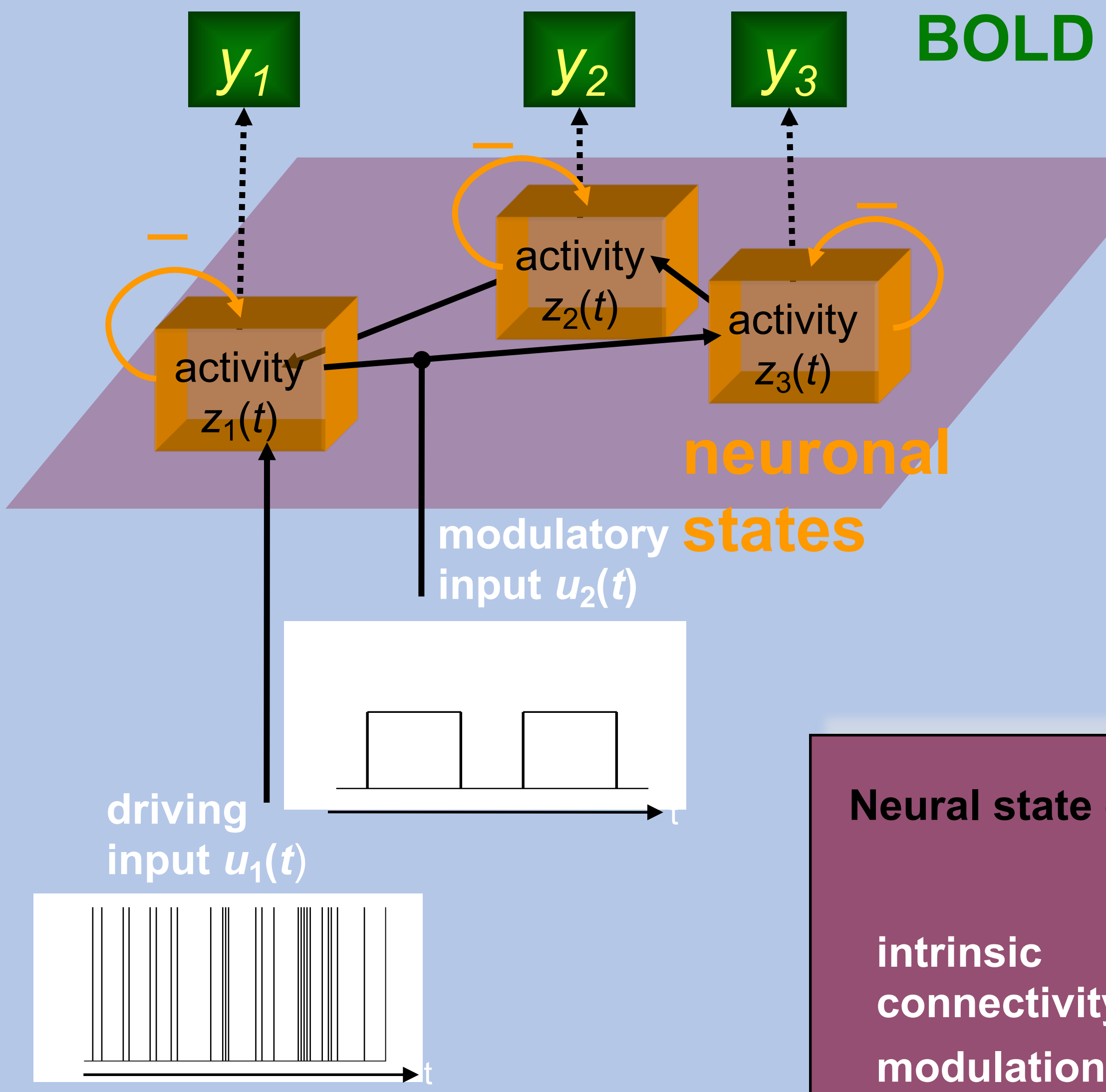
# Dynamic Causal Modeling for fMRI

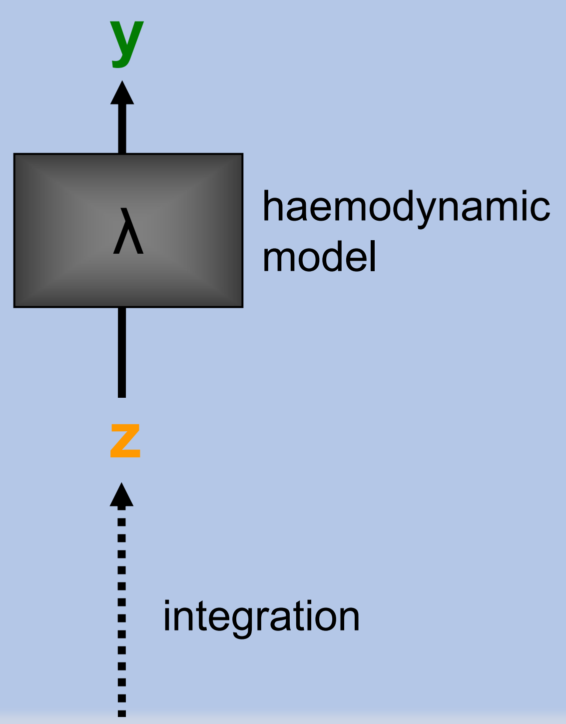
- Using a bilinear state equation, a putative cognitive system is modelled at its underlying <u>neuronal level</u> (which is not directly accessible for fMRI).
- The modelled neuronal dynamics (*z*) is transformed into area-specific BOLD signals (*y*) by a hemodynamic forward model (*λ*).




> The aim of DCM is to estimate <u>parameters at the neuronal level</u> such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals.

*Friston et al., Neuroimage, 2003*




**Neural state equation** $\dot{z} = (A + \sum u_j B^{(j)})z + Cu$

**intrinsic connectivity** $\rightarrow$ $A = \frac{\partial \dot{z}}{\partial z}$

**modulation of connectivity** $\rightarrow$ $B^{(j)} = \frac{\partial}{\partial u_j}\frac{\partial \dot{z}}{\partial z}$

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

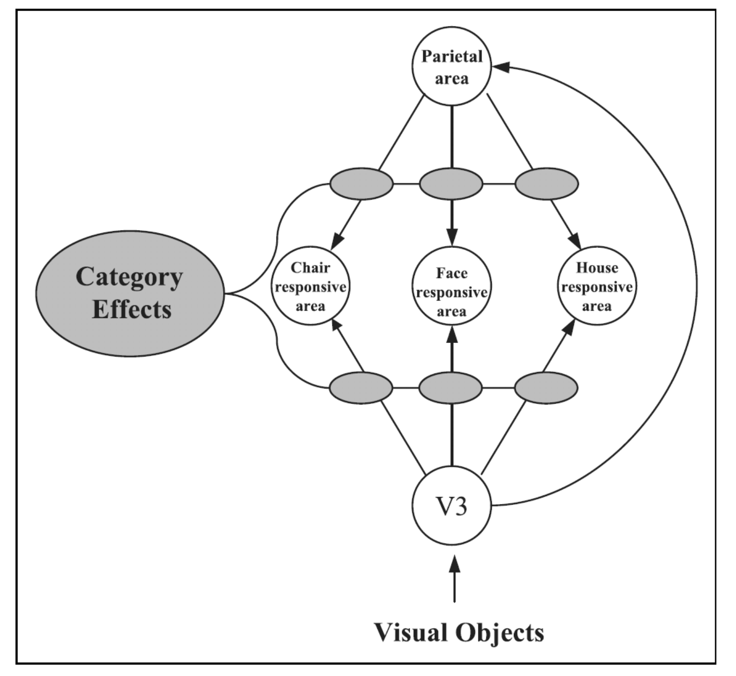
Stephan & Friston 2007,
*Handbook of Brain Connectivity*
*(Eds. Jirsa & McIntosh)*

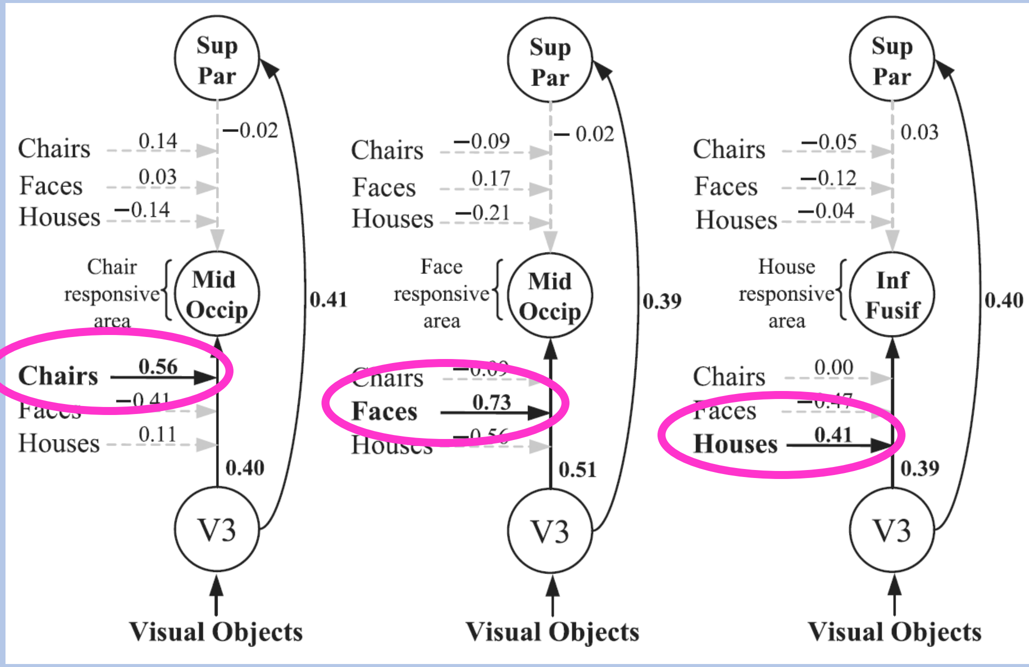
# Hypothesis Testing with DCM

**A Dynamic Causal Modeling Study on Category Effects: Bottom–Up or Top–Down Mediation?**

**Andrea Mechelli, Cathy J. Price, Uta Noppeney, and Karl J. Friston**

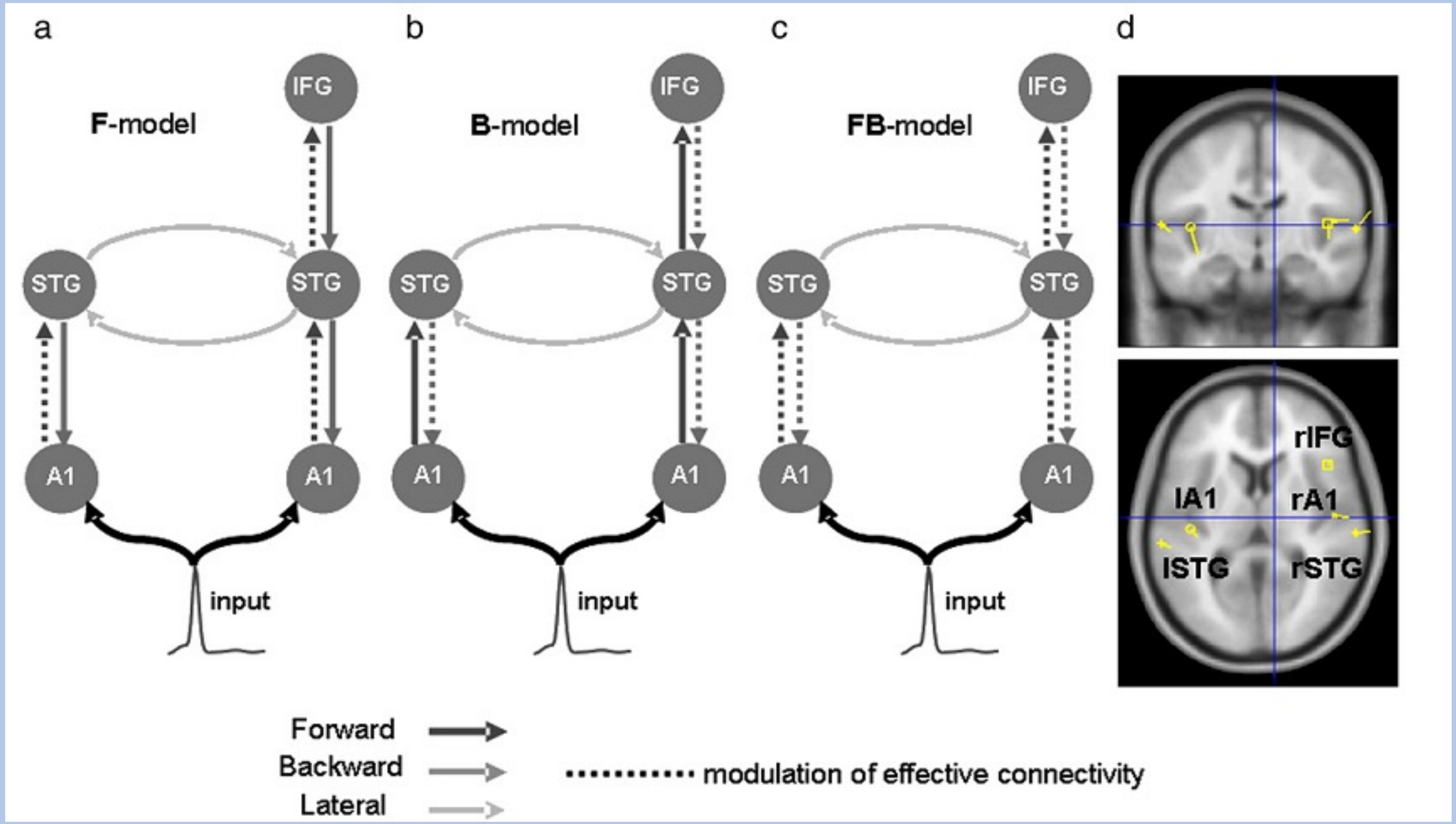
Category effects may be bottom-up!




*J Cognitive Neurosci, 2003*

# DCM for EEG/MEG
# Hierarchical Neural Mass Model



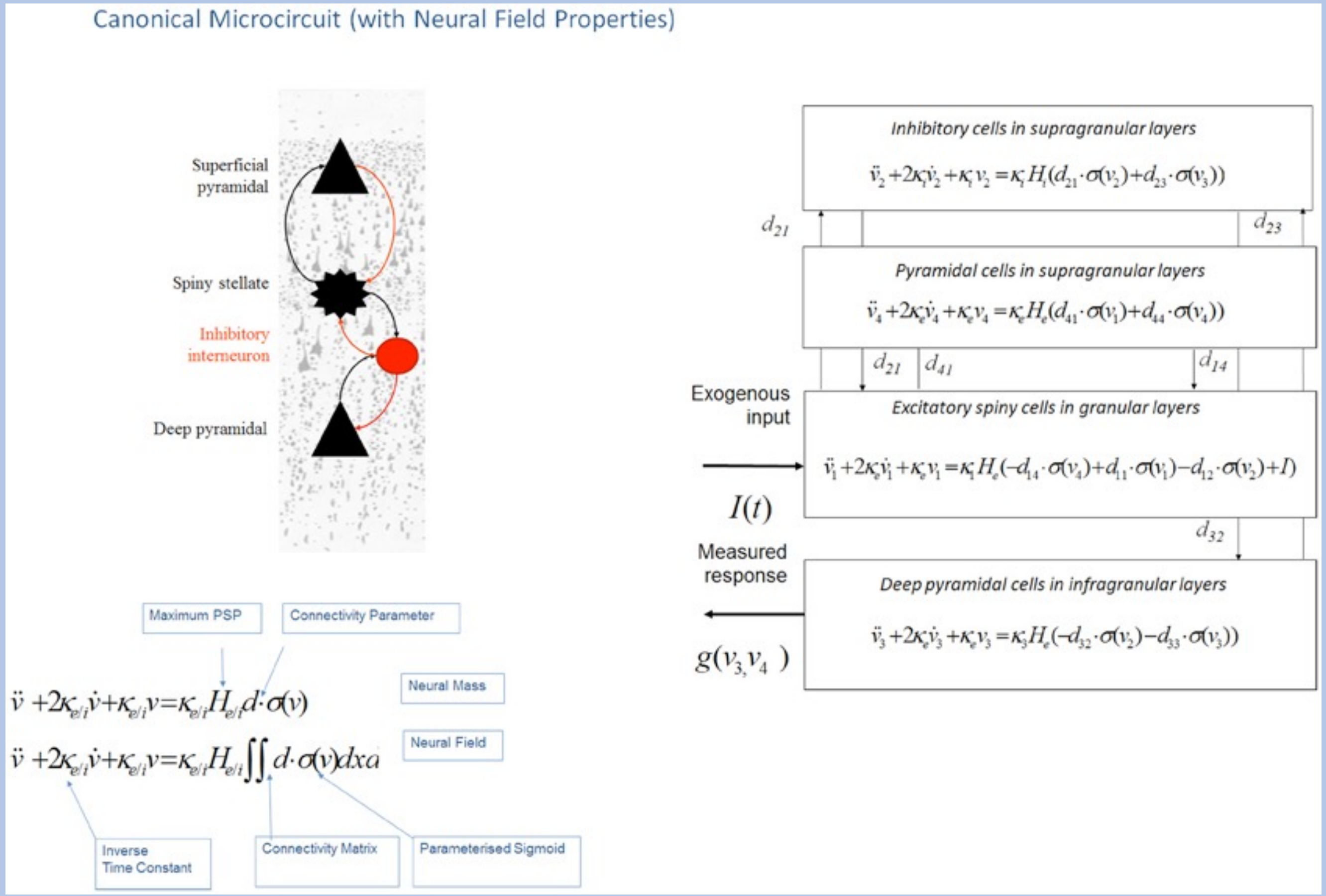

*Garrido, et al, Neuroimage, 2008*

**REVIEW ARTICLE**

Front. Comput. Neurosci., 27 May 2013 | doi: 10.3389/fncom.2013.00057

# Neural masses and fields in dynamic causal modeling

Rosalyn Moran[1,2,3*†], Dimitris A. Pinotsis[1†] and Karl Friston[1]



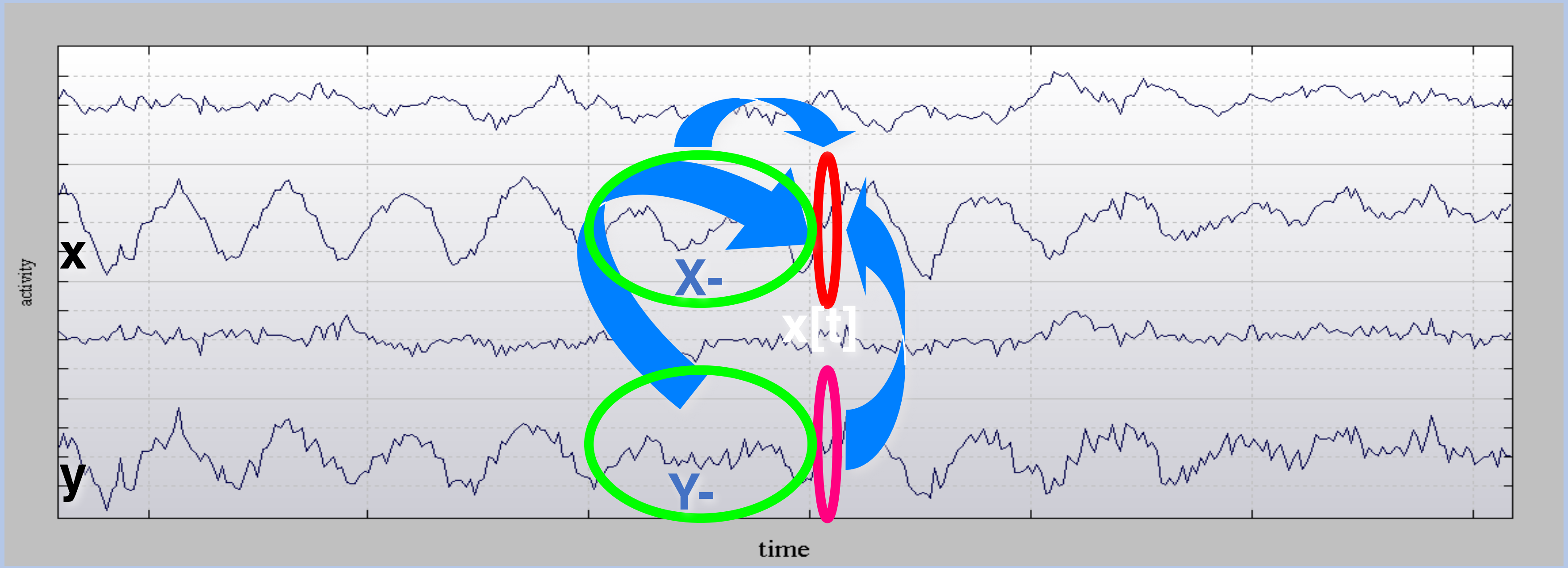

Emphasizes the generative model feature of DCM where inferences are focused at the biophysical level about those causes that generate the observed data

*Front Comp Neurosci, 2013*

# Effective Connectivity Estimation Using Granger Causality

- Explicit use of time series information
- How well does variation in time series "Y" predict variation in time series "X"?
- Previously applied to neuro-physiological data to detect neuronal interactions:
  - Bernasconi & König (1999), LFP-data.
  - Freiwald et al., (1999), LFP-data.
  - Kaminski et al., (2001), Directed Transfer Function.
- fMRI
  - Goebel et al., (2003), *Magnetic Resonance Imaging*, **21**, 1251-1261.
  - Goebel et al., (2004), *Attention & Performance* XX, 439-462.
  - Roebroeck, Formisano & Goebel (2005), *NeuroImage,* **25***, 230-242*.

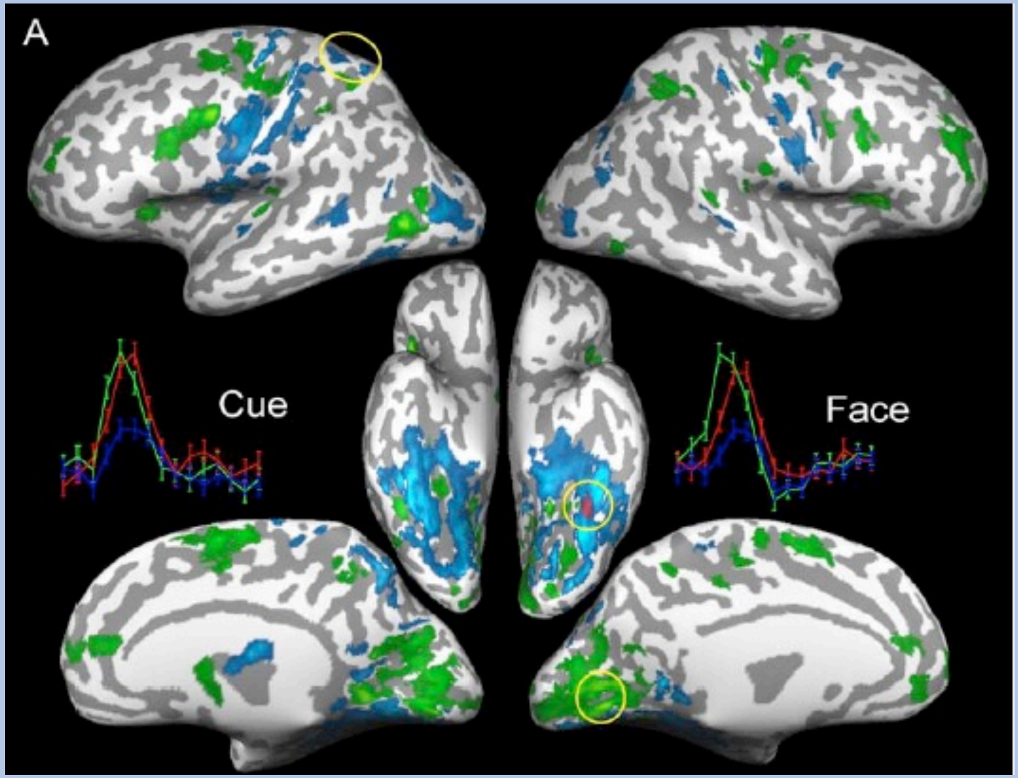
# Granger Causality - *Predictability*




- **Effective connectivity:** If we can predict **x[t]** better using {**X-**, **Y-**} than using {**X-**} alone, then we say that ***y Granger causes x***.

- **Functional connectivity:** If we can predict **x[t]** better using {**X-**, **Y-**, **y[t]**} than using {**X-**, **Y-**}, then we say that there is ***instantaneous causality*** between **y** and **x**.

# Granger Causal Maps




**Mapping directed influence over the brain using Granger causality and fMRI**

Alard Roebroeck,* Elia Formisano, and Rainer Goebel

*Neuroimage, 2005*

# Generative vs Discriminative Models

GENERATIVE

- Simulation,
  - TheVirtualBrain
  - Dynamic Causal Modeling
  - Nengo (Spaun)
- Tests hypotheses of how data were generated.
- Need to identify the key elements

DISCRIMINATIVE/PREDICTIVE

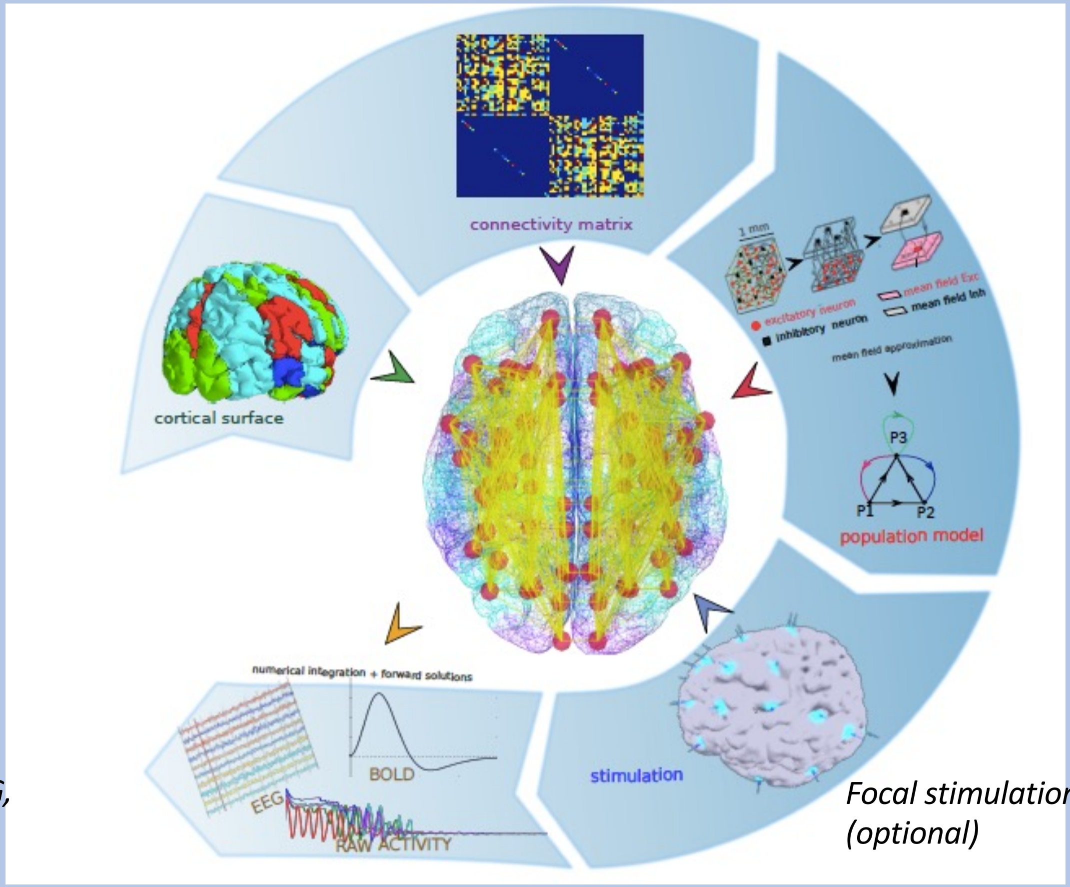
- Machine Learning & Classic Statistics
- Identify data features to maximally differentiate classes
- Cannot inform on mechanisms

# Integration of data using TheVirtualBrain

*Individual tractography to estimate structural connectivity*

*Individual Cortical Geometry*

*Neural mass model to generate node dynamics*



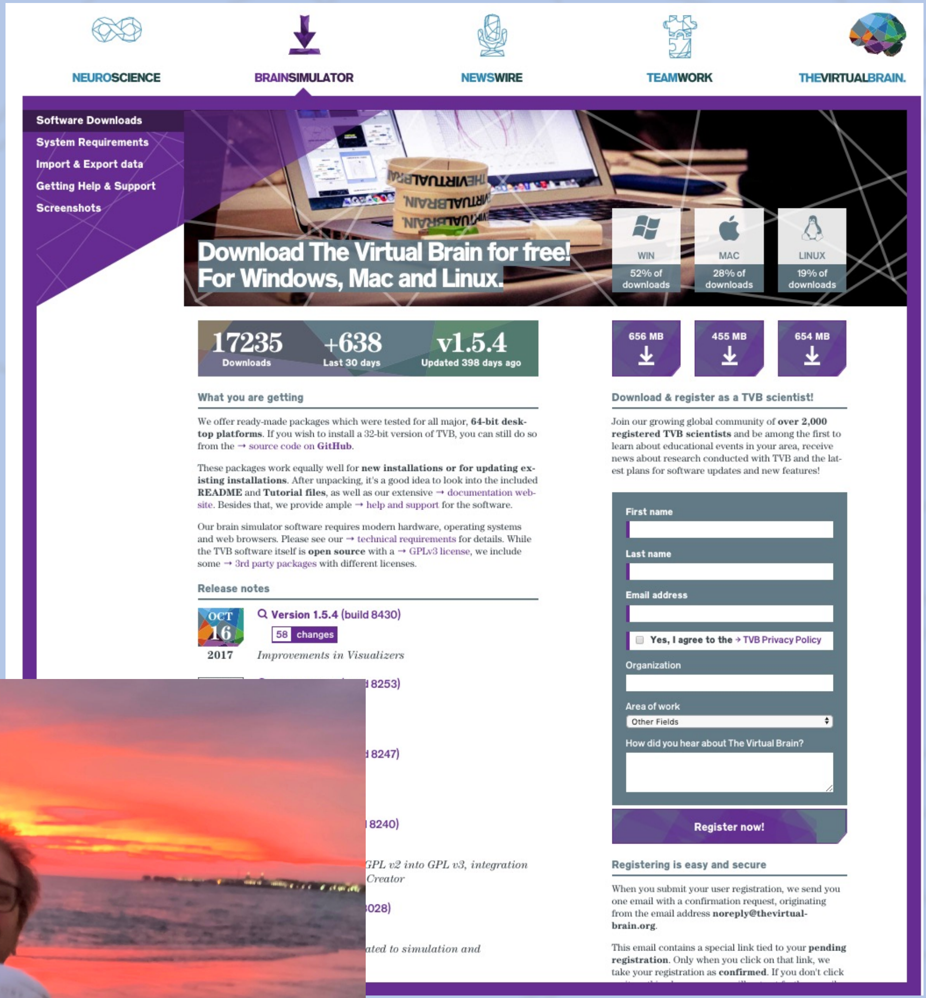

*Output Local Field Potentials or (via forward model) EEG, MEG, sEEG. fMRI*

*Focal stimulation (optional)*

***Sanz Leon et al Front NeuroInformatics 2013***
***Ritter et al, Brain Connectivity, 2013***

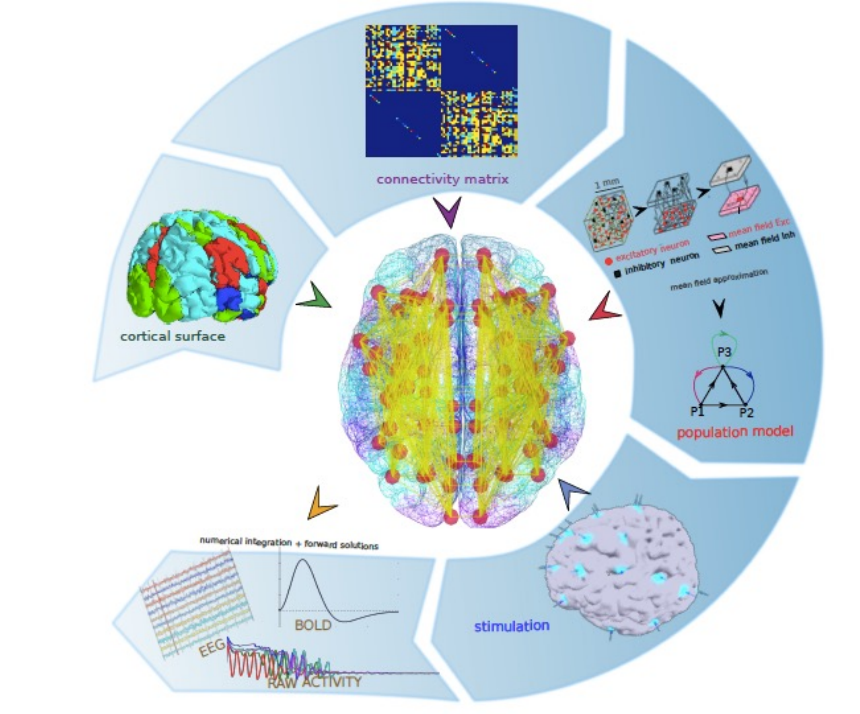
www.thevirtualbrain.org

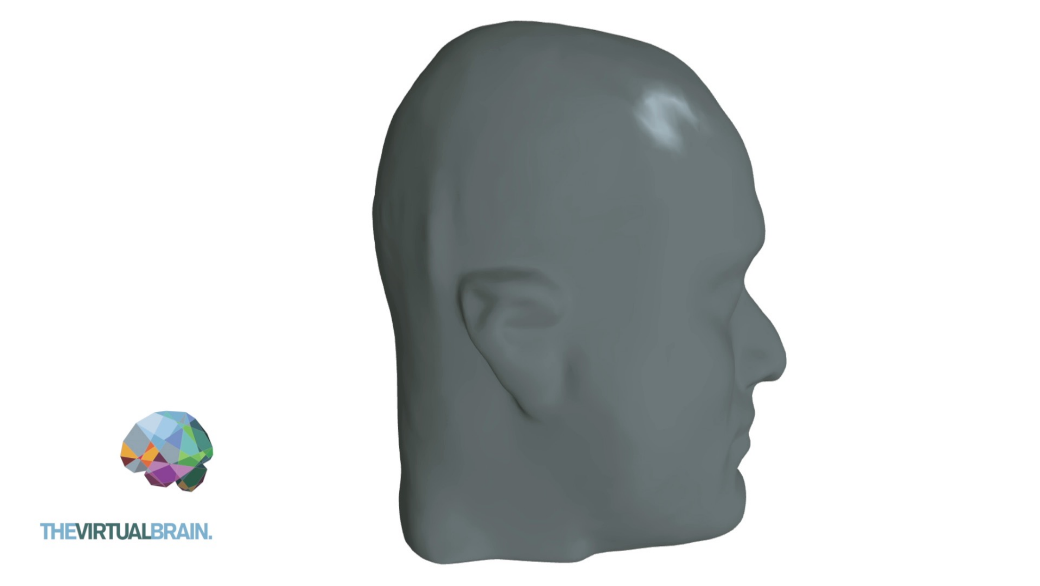

Download: Windows, Mac, Linux




# RESTING STATE

TAKE HOME //
Structural/function convergence shape resting-state (dynamic repertoire)

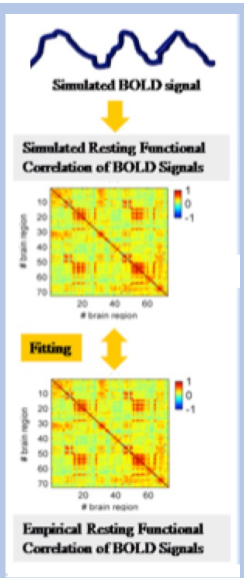



Data Fitting

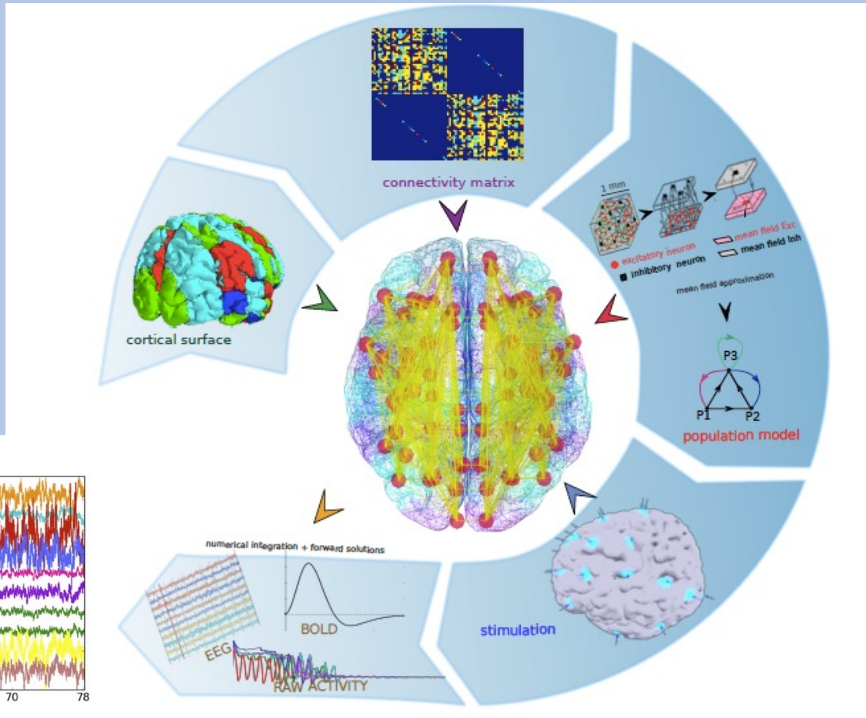
Empirical :: Simulated

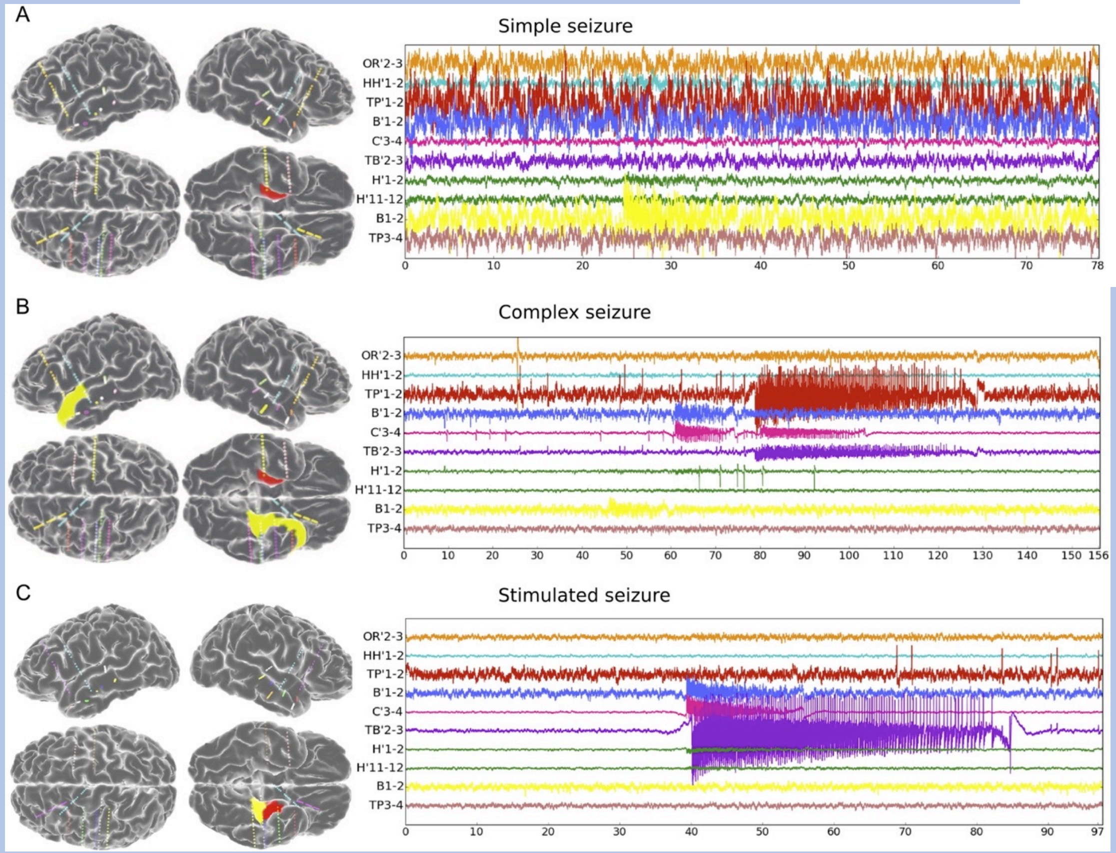
Ritter et al, 2013, Brain Connect.
Deco, Jirsa, & McIntosh, Nature Neuro, 2011



# EPILEPSY

TAKE HOME //
efficacy of TVB's Epileptor model in pre-surgical planning for pharmacoresistent epileptic Px




The Virtual Epileptic Patient
(EPINOV – National Clinical Trial)

Jirsa et al. 2017 NeuroImage

## The elusive concept of brain connectivity

Barry Horwitz*

*Brain Imaging and Modeling Section, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA*

Received 23 October 2002; accepted 11 February 2003

Until it is understood what each definition means in terms of an underlying neural substrate, comparisons of functional and/or effective connectivity across studies may appear inconsistent and should be performed with great caution.

https://github.com/McIntosh-Lab/BCW2022