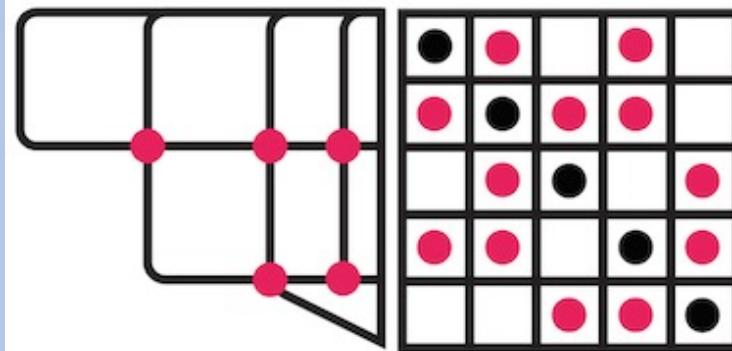


# How the ideas of connectivity have evolved



**BRAIN  
CONNECTIVITY  
WORKSHOP  
DÜSSELDORF  
2022**

**Randy McIntosh**

Institute for Neuroscience & Neurotechnology  
Dept of Biomedical Physiology & Kinesiology

Simon Fraser University

Vancouver, Canada

randy\_mcintosh@sfu.com

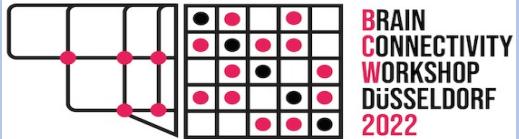
Website: armcintosh.com

Twitter: @ar0mcintosh

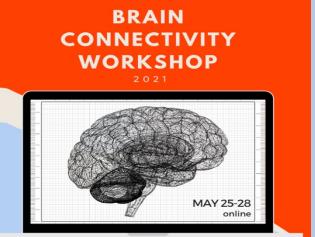
Twitter: @SFUNeuro

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

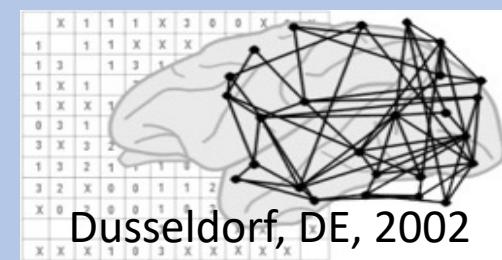
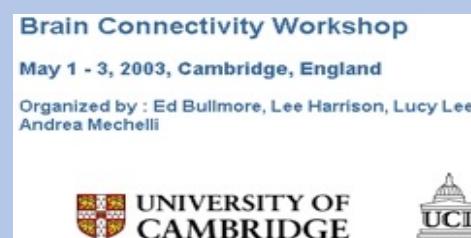
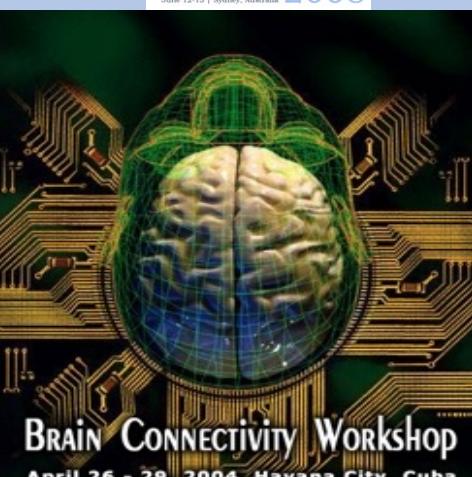
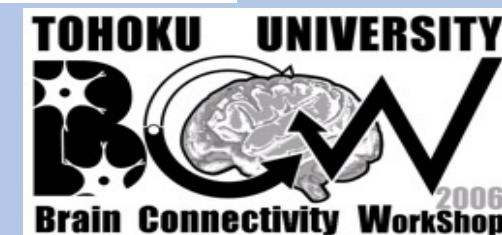
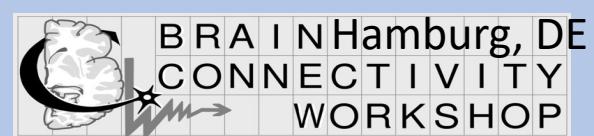
**SFU**

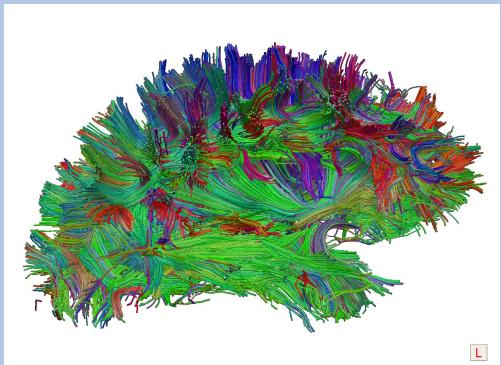
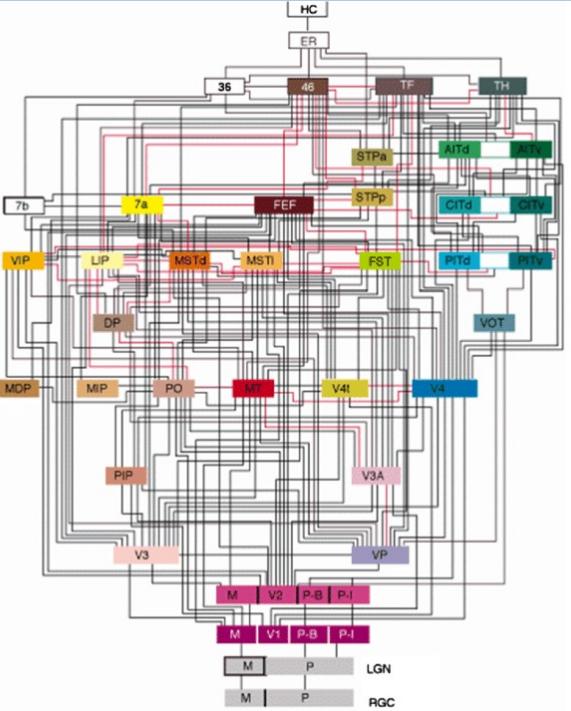


BRAIN  
CONNECTIVITY  
WORKSHOP  
DÜSSELDORF  
2022

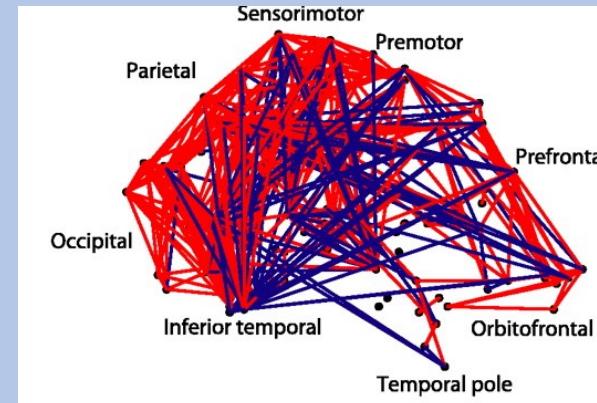
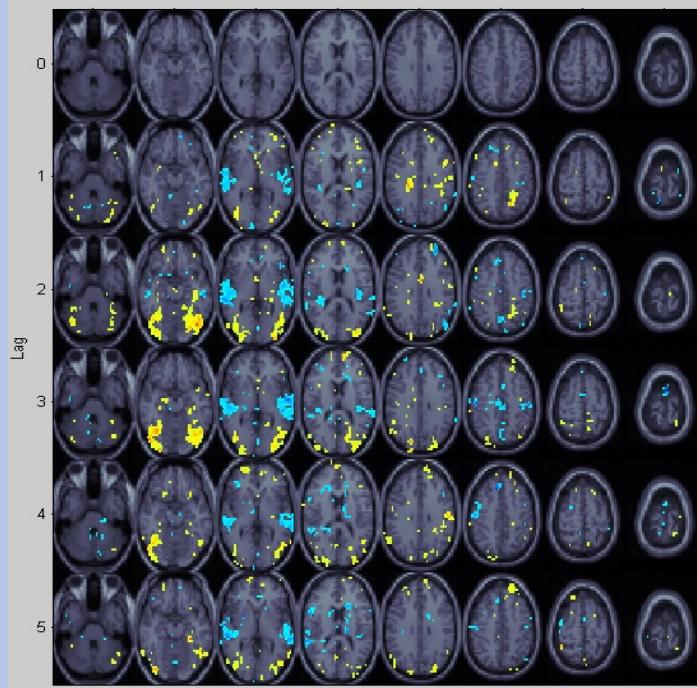


Brain Connectivity  
Workshop 2018



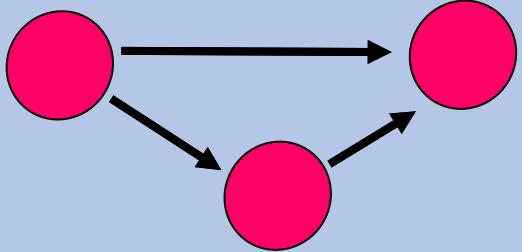


Anatomy  
*conduit*



Function/dynamics  
*communication*

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



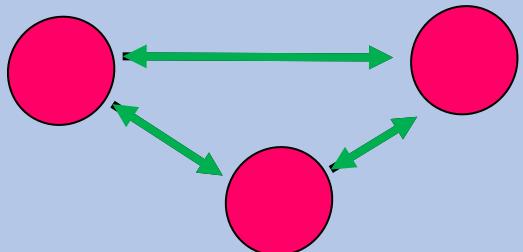
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Indicates an axonal connection between region

## Directional

Inferred from tracers or tractography

Varies slowly across time



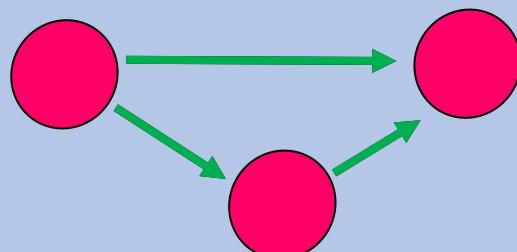
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Statistical dependence of activity (across time)

## Nondirectional

Estimated by measures of association

Varies across many time scales



## Effective

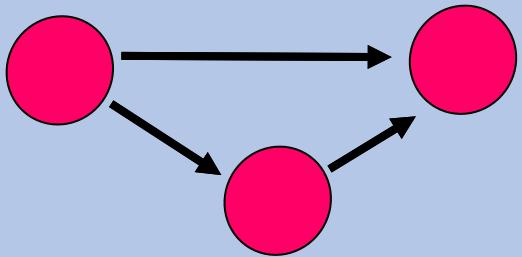
Indicates a causal dependence between nodes

## Directional

Many methods to estimate with differing underlying

Varies across time scale

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



## Structural

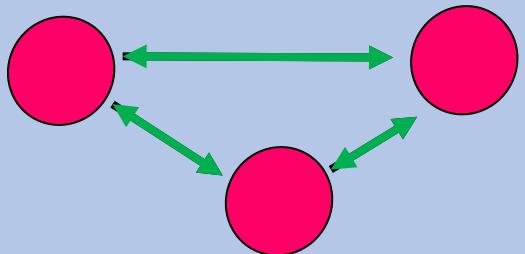
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*"Anatomy is destiny." Tononi, BCW2021*



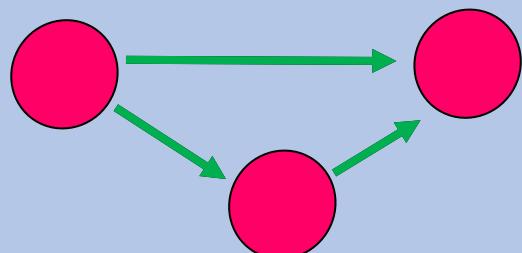
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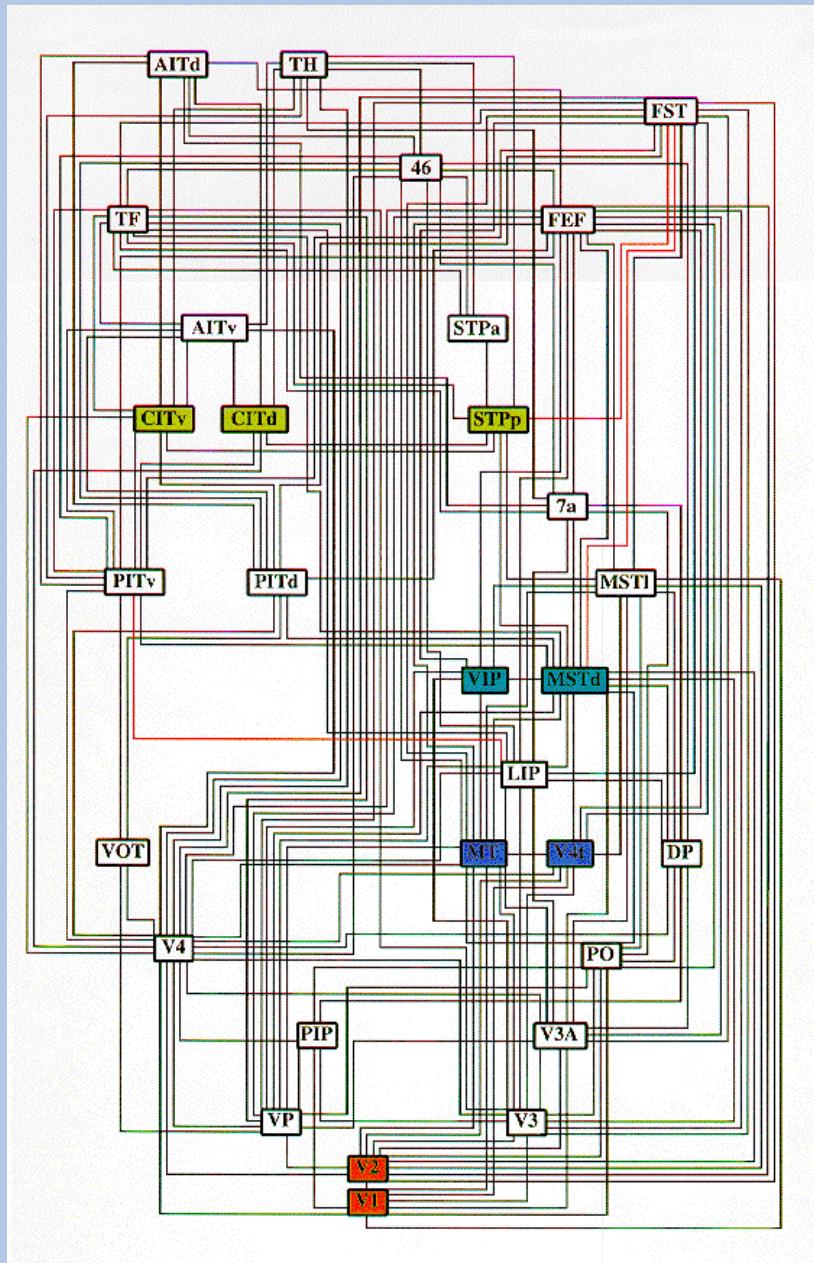
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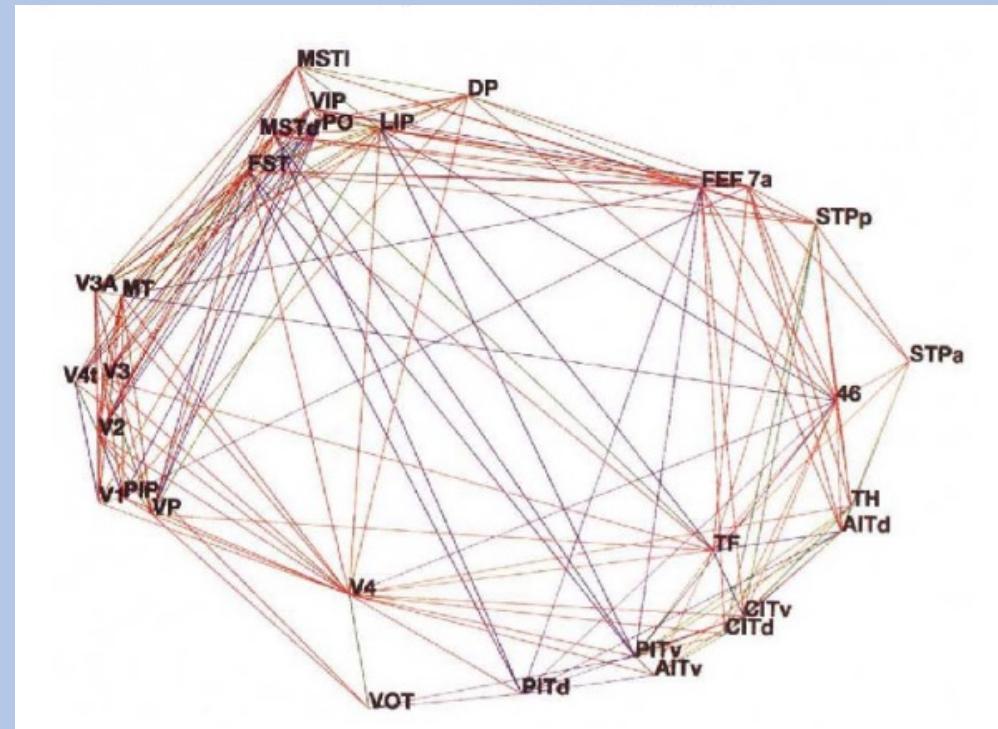


Published: 09 July 1992

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

Malcolm P. Young

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



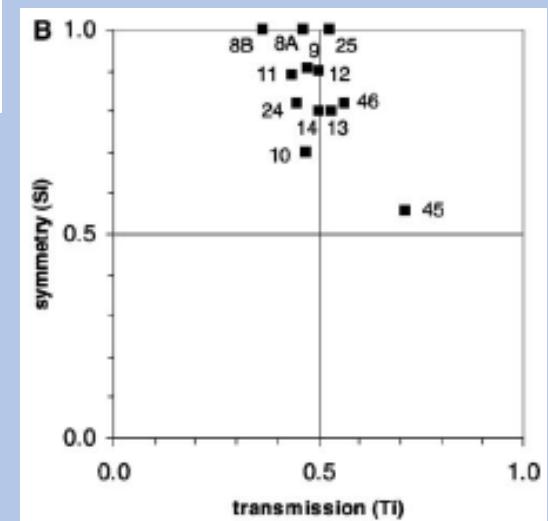
Used adjacency matrix from anatomical connectivity and expressed as “distances” using non-metric multidimensional scaling

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

Rolf Kötter<sup>a,\*</sup>, Klaas E. Stephan<sup>b,c</sup>



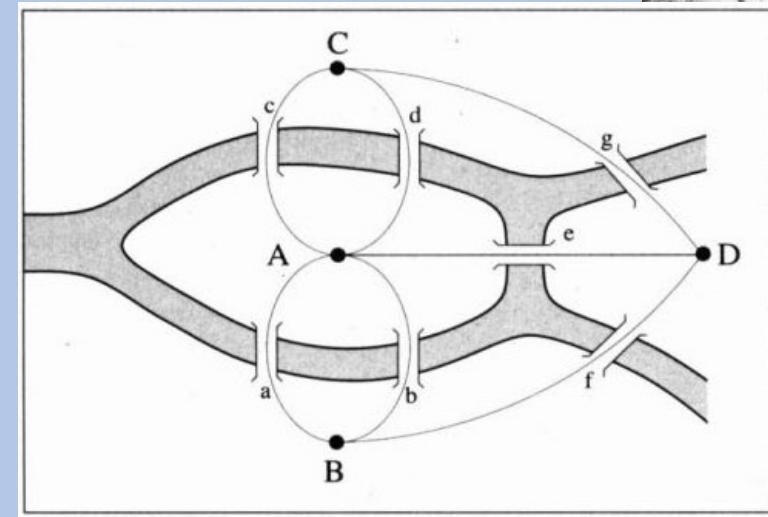
	10	11	12	13	14	24	25	45	46	8A	8B	9
10	U	1	1	1	1	1	1	0	0	1	0	1
11	1	U	1	1	1	1	1	U	0	0	0	1
12	1	1	U	1	1	1	1	0	1	1	1	1
13	1	1	1	U	1	1	1	0	0	0	1	1
14	1	1	1	1	U	1	1	0	0	0	0	1
24	0	1	1	0	1	U	1	1	1	1	1	1
25	1	1	1	1	1	1	U	0	1	0	1	1
45	1	1	1	1	1	1	1	0	U	1	1	1
46	1	1	1	0	0	1	1	1	U	1	1	1
8A	1	0	1	0	0	1	0	1	1	U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



# Network Architectures and Metrics

## Historical Origins of Graph Theory

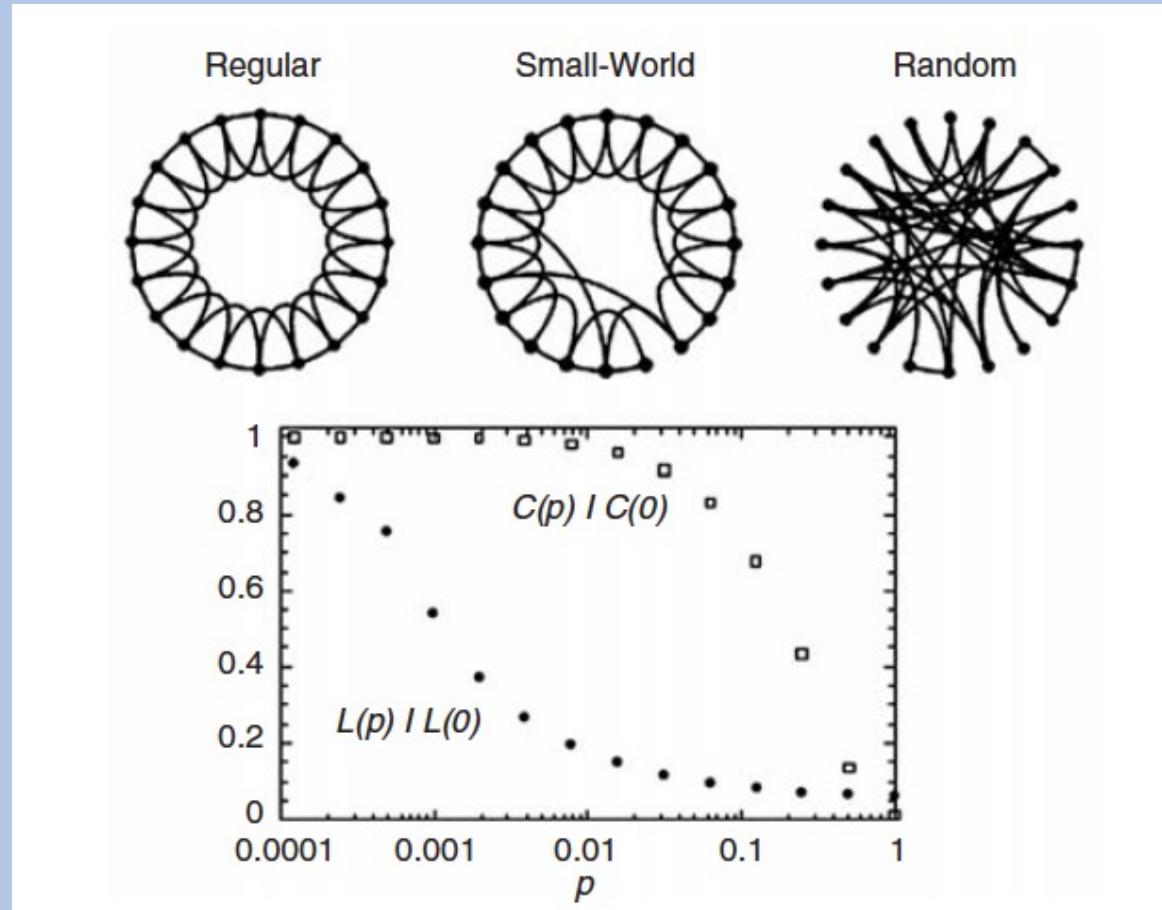
Leonhard Euler's 1736 publication on the bridges of Königsberg (Kalininograd) is the origin of graph theory.



19<sup>th</sup> 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.

# Graph Theory and Network Architectures

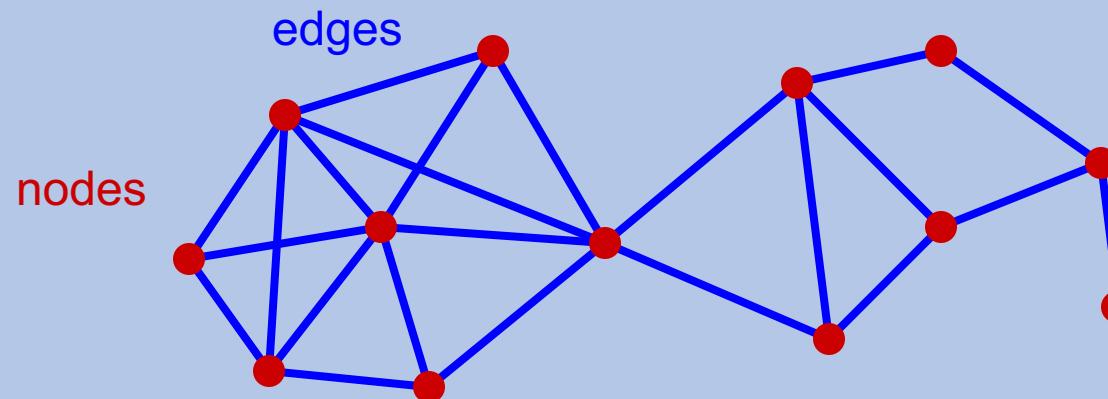


*Optimal* balance of clustering and path length in Small-World Networks

Watts & Strogatz, 1998, Nature

# Network Architectures and Metrics

## 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.

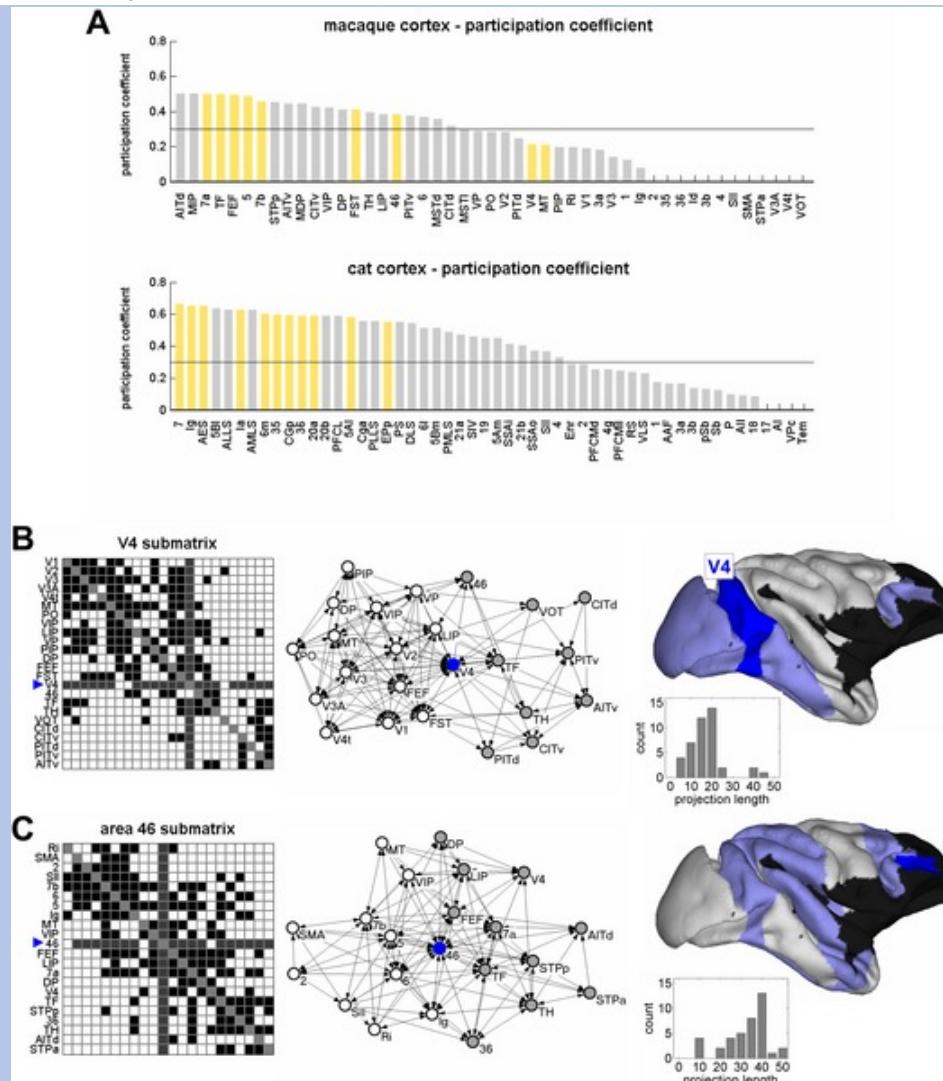
Graphs may be converted from weighted to binary by **thresholding** – often across a range of thresholds or “costs”

Brain Connectivity Toolbox  
[www.brain-connectivity-toolbox.net](http://www.brain-connectivity-toolbox.net)

Rubinov & Sporns (2010)  
NeuroImage 52, 1059

# Identification and Classification of Hubs in Brain Networks

Olaf Sporns<sup>1\*</sup>, Christopher J. Honey<sup>1</sup>, Rolf Kötter<sup>2,3</sup>



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

Olaf Sporns , Giulio Tononi, Rolf Kötter

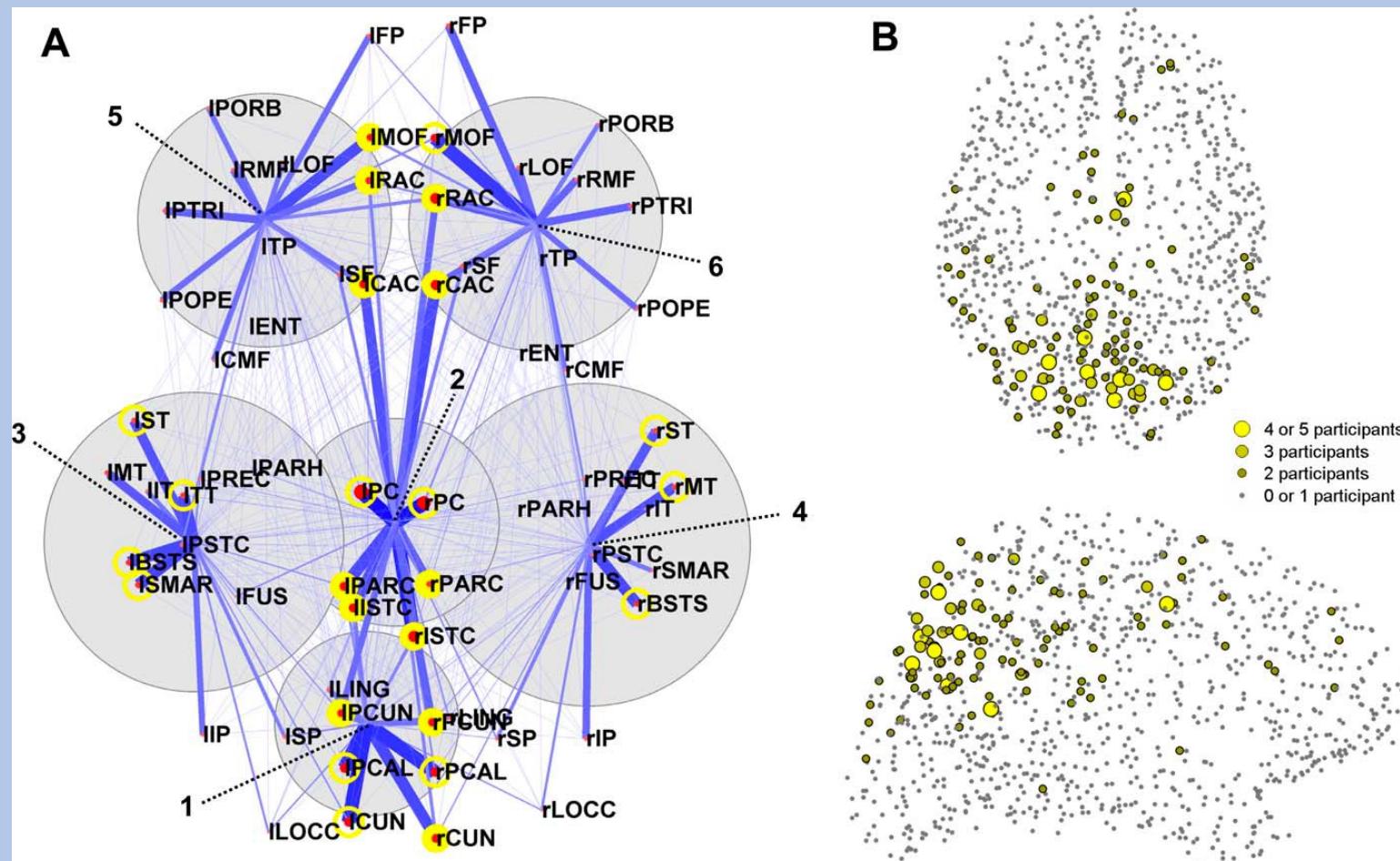
Published: September 30, 2005 • <https://doi.org/10.1371/journal.pcbi.0010042>

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 

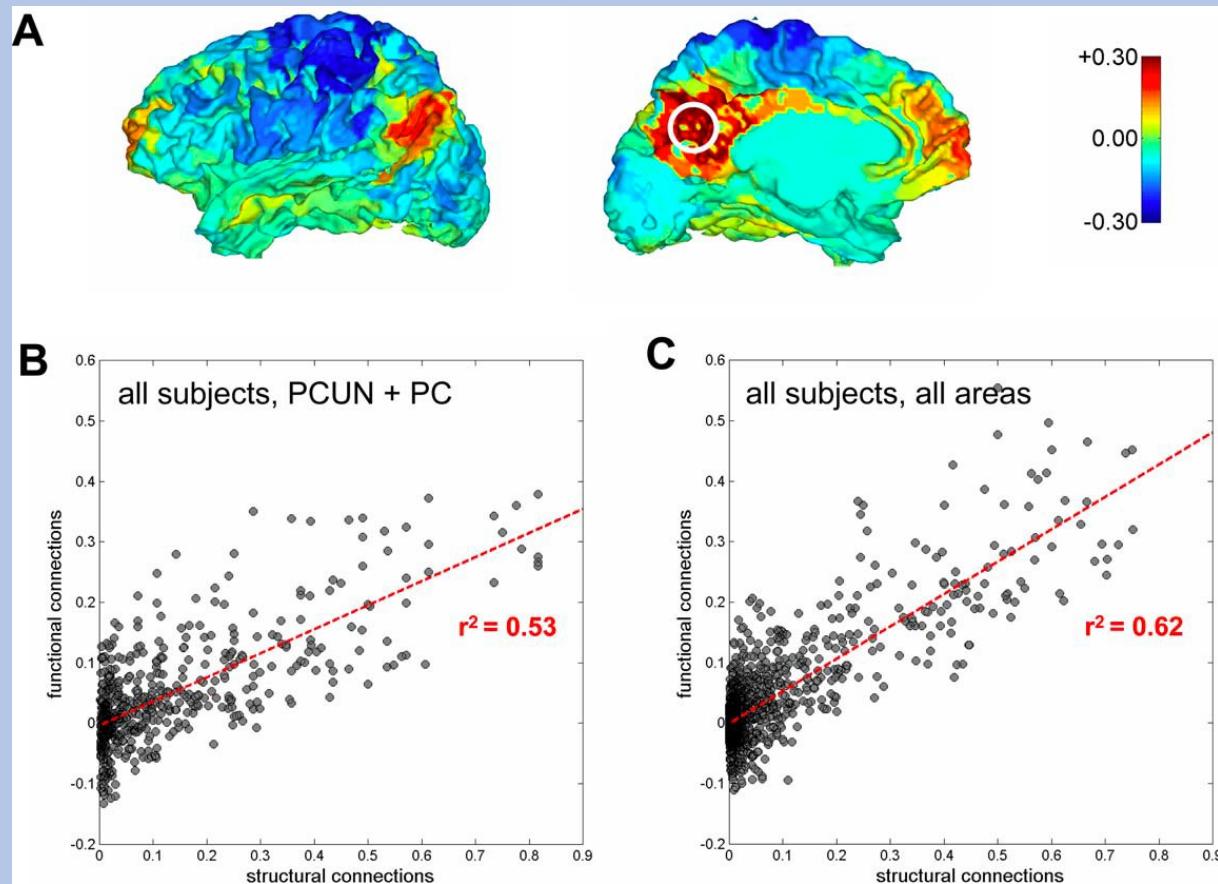
Published: July 1, 2008 • <https://doi.org/10.1371/journal.pbio.0060159>



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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 connectivity

## 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, , and Carlo Pierpaoli [Authors Info & Affiliations](#)

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

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

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

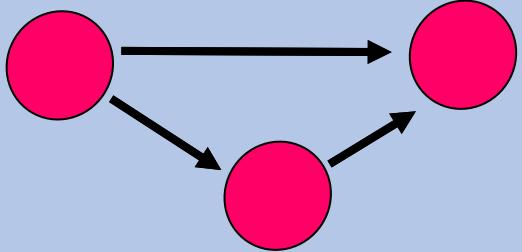
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Limitations of estimation of structural connectivity from tractography

- 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?



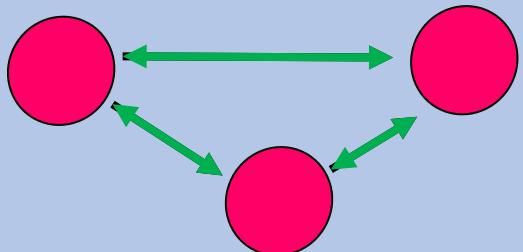
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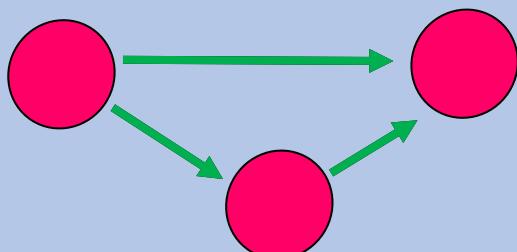
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## Nondirectional

Estimated by measures of association

Varies across many time scales



## 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<sup>1</sup>

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 ▾



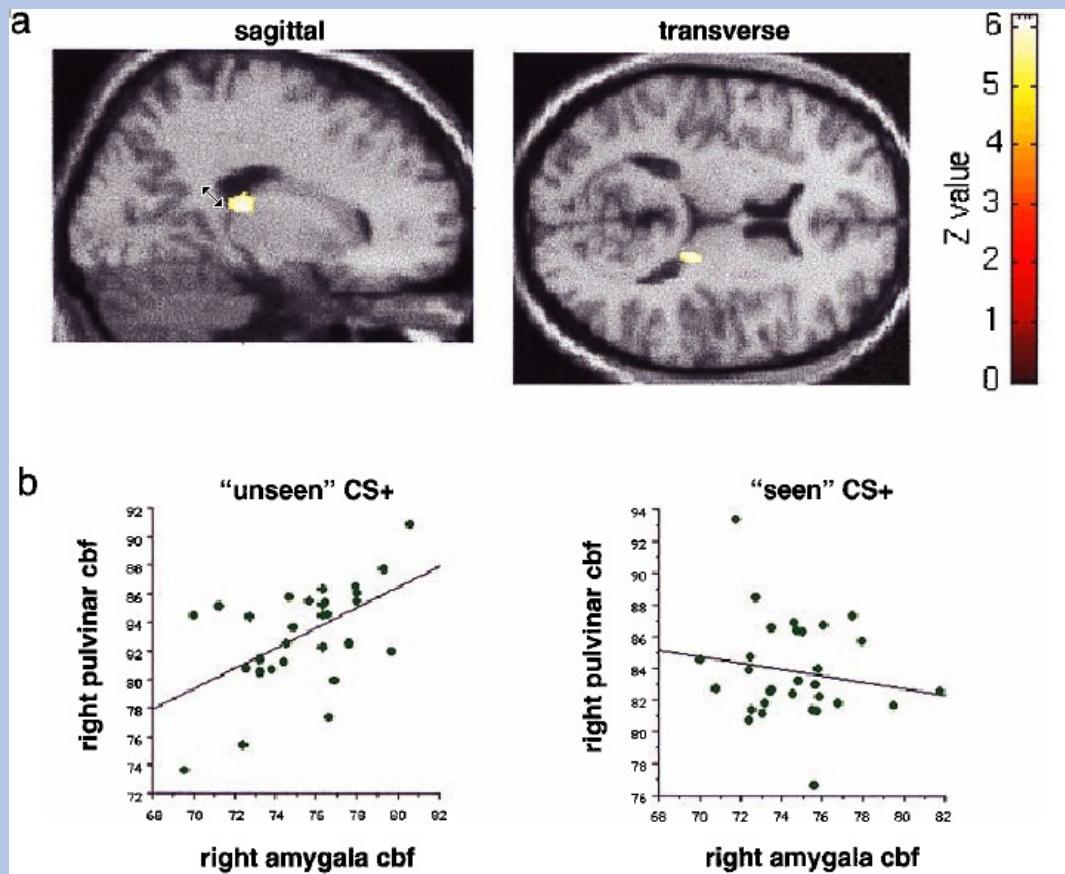
### Abstract

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 [<sup>18</sup>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, [<sup>18</sup>F]Fluorodeoxyglucose, Hemispheric symmetry, Positron emission tomography, Regional cerebral metabolic rate for glucose, Resting state

# Amygdala-Thalamus Interactions in Fear Conditioning – Psychophysiological Interactions

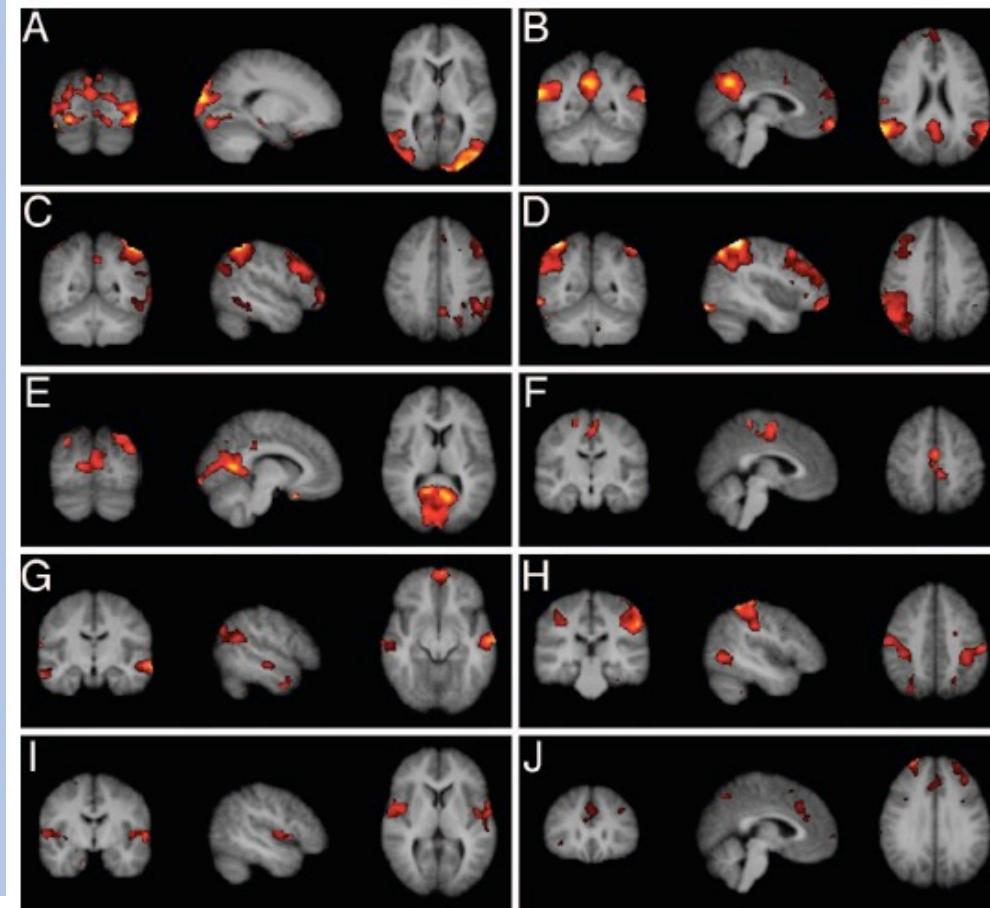


Morris, et al, 1999, PNAS

# 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

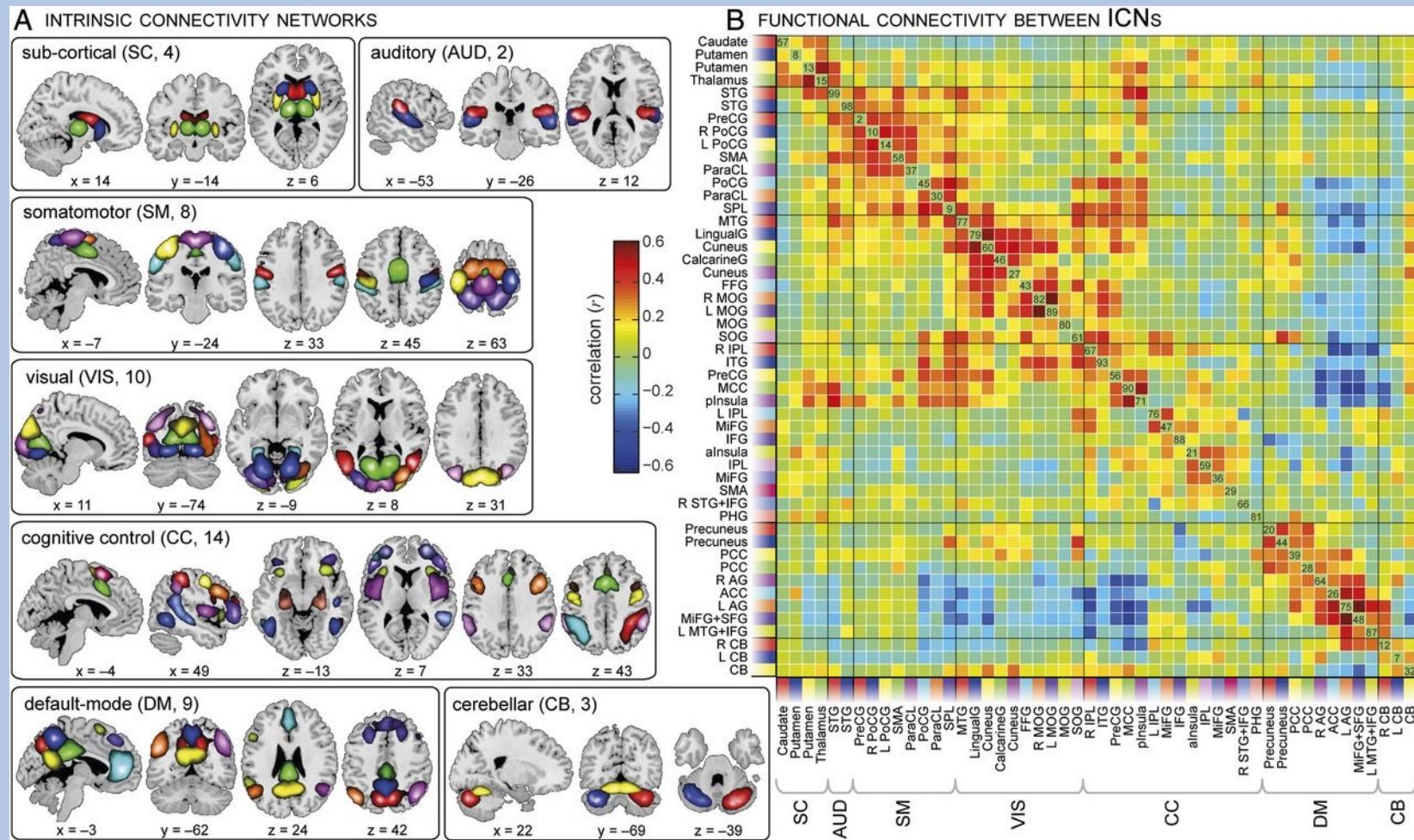


**Consistent resting-state networks  
across healthy subjects**

J. S. Damoiseaux<sup>†‡</sup>, S. A. R. B. Rombouts<sup>§¶</sup>, F. Barkhof<sup>||</sup>, P. Scheltens<sup>†</sup>, C. J. Stam<sup>††</sup>, S. M. Smith<sup>‡‡</sup>, and C. F. Beckmann<sup>‡‡</sup>

*Proc Nat Acad Sci, USA, 2006*

# Independent Component Networks and the stationary Functional Connectivity between them



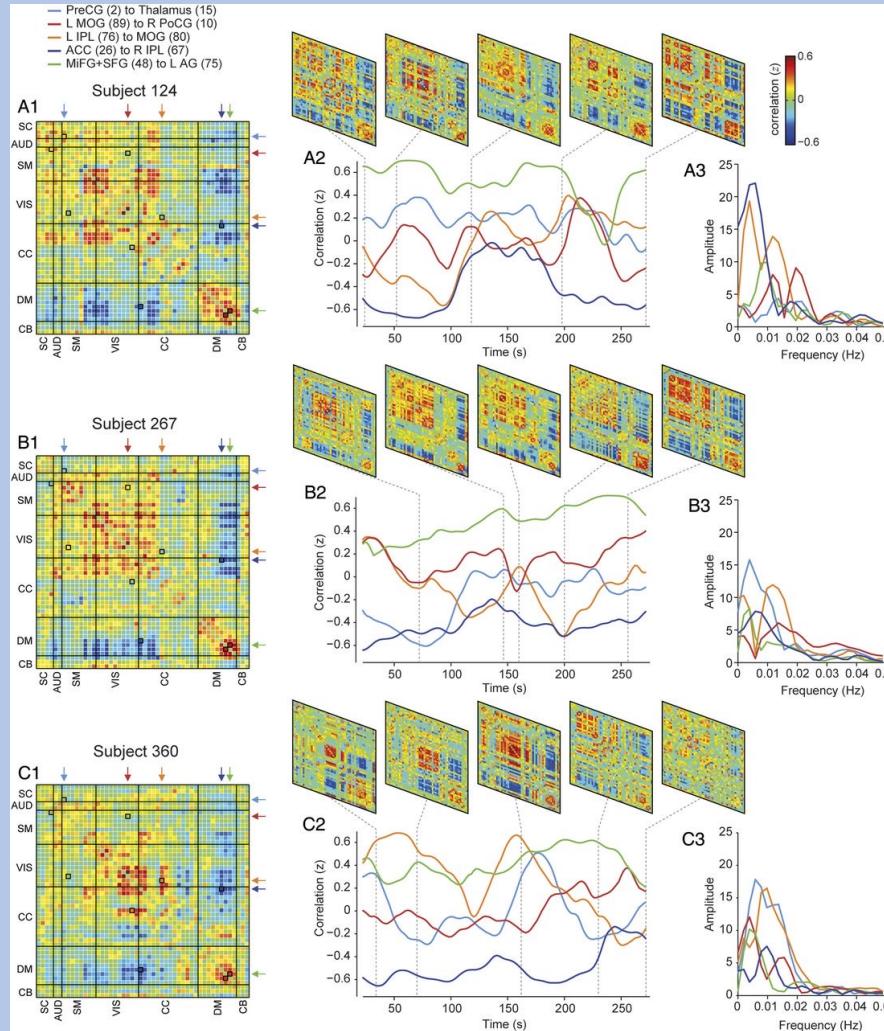
Allen E A et al. Cereb. Cortex 2012;cercor.bhs352

Allen et al, Cereb Cortex, 2013



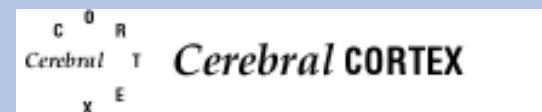
## Examples of Functional Connectivity dynamics.

- 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





OPEN

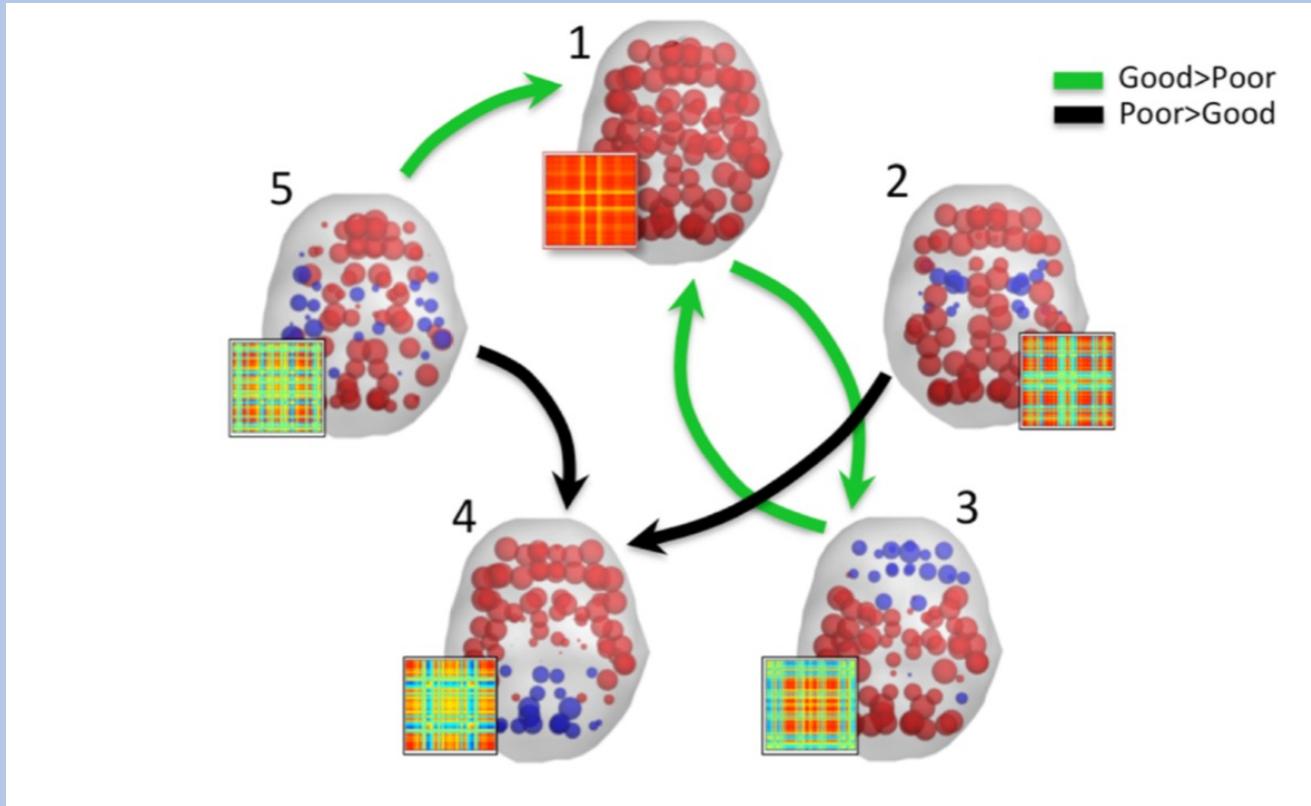
## Cognitive performance in healthy older adults relates to spontaneous switching between states of functional connectivity during rest

Received: 19 December 2016

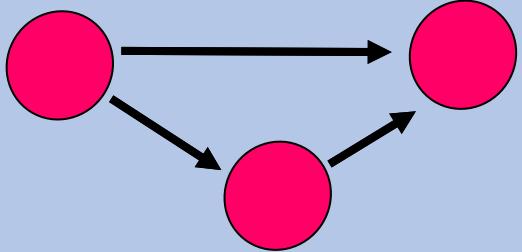
Accepted: 30 May 2017

Published online: 11 July 2017

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



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



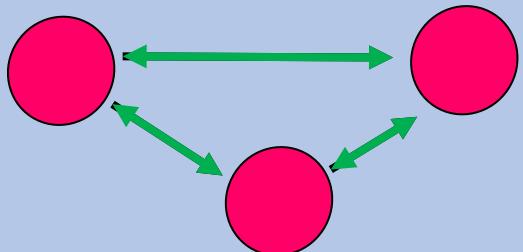
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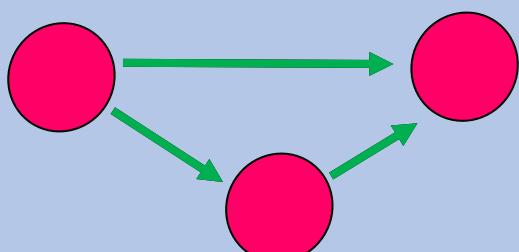
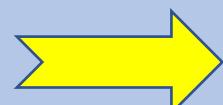
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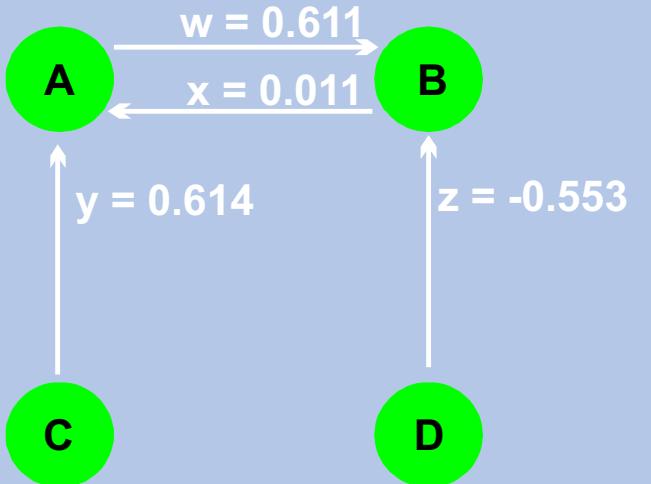
## Directional

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Varies across time scale

# 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	-0.41	0.06	1.00

## Structural Equations

$$A = xB + yC + \psi_A$$

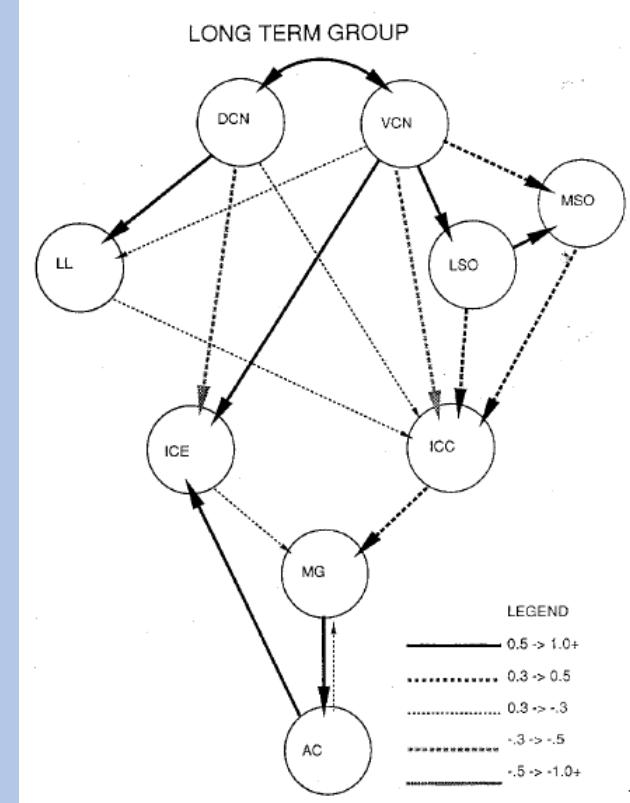
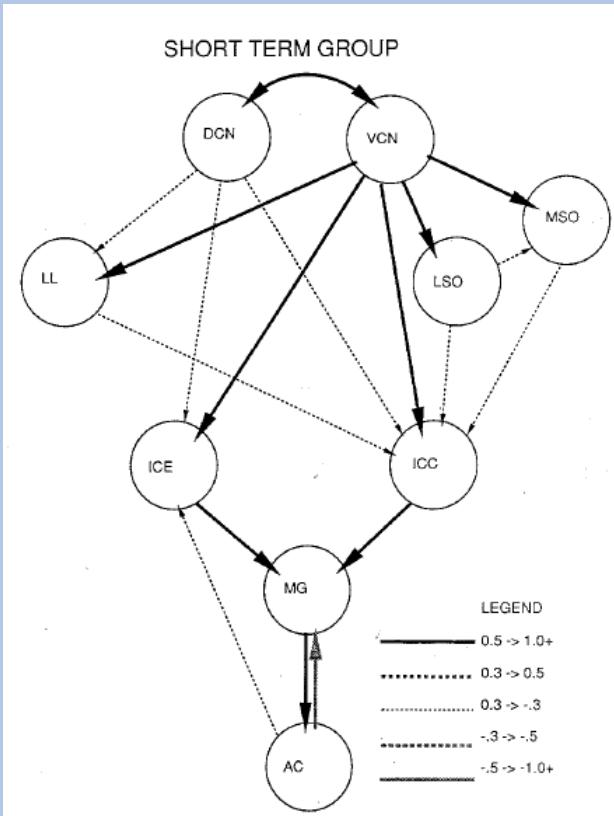
$$B = wA + zD + \psi_B$$

$$\begin{pmatrix} A \\ B \\ C \\ D \end{pmatrix} = \begin{pmatrix} 0 & x & y & 0 \\ w & 0 & 0 & z \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} * \begin{pmatrix} A \\ B \\ C \\ D \end{pmatrix} + \begin{pmatrix} \psi_A & 0 & 0 & 0 \\ 0 & \psi_B & 0 & 0 \\ 0 & 0 & \psi_C & 0 \\ 0 & 0 & 0 & \psi_D \end{pmatrix}$$
$$\Sigma = \text{inv}(I - \beta)^T * (\psi^T * \psi) * \text{inv}(I - \beta)$$

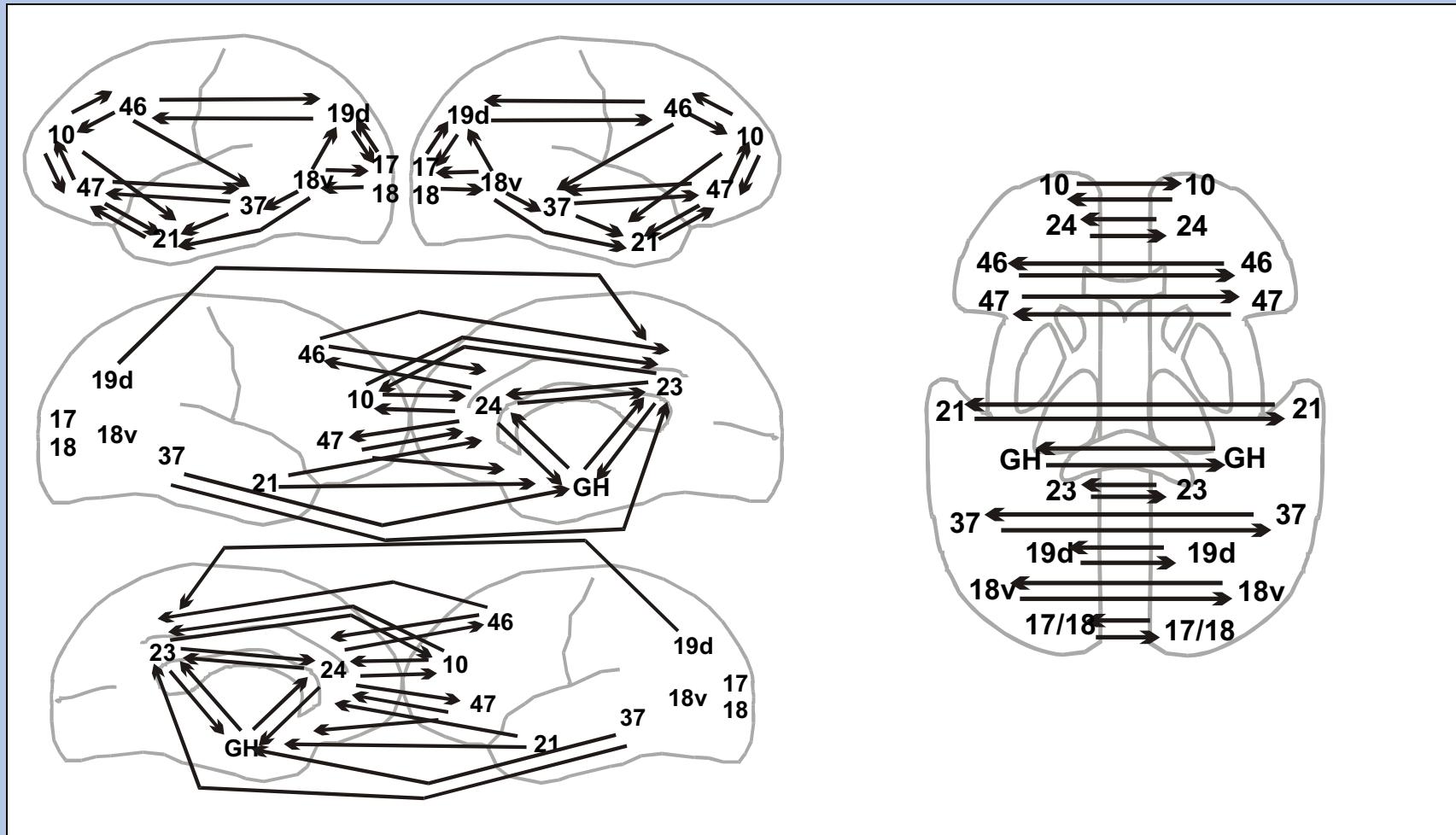
# Structural modeling of functional neural pathways mapped with 2-deoxyglucose: effects of acoustic startle habituation on the auditory system

A.R. McIntosh and F. Gonzalez-Lima

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

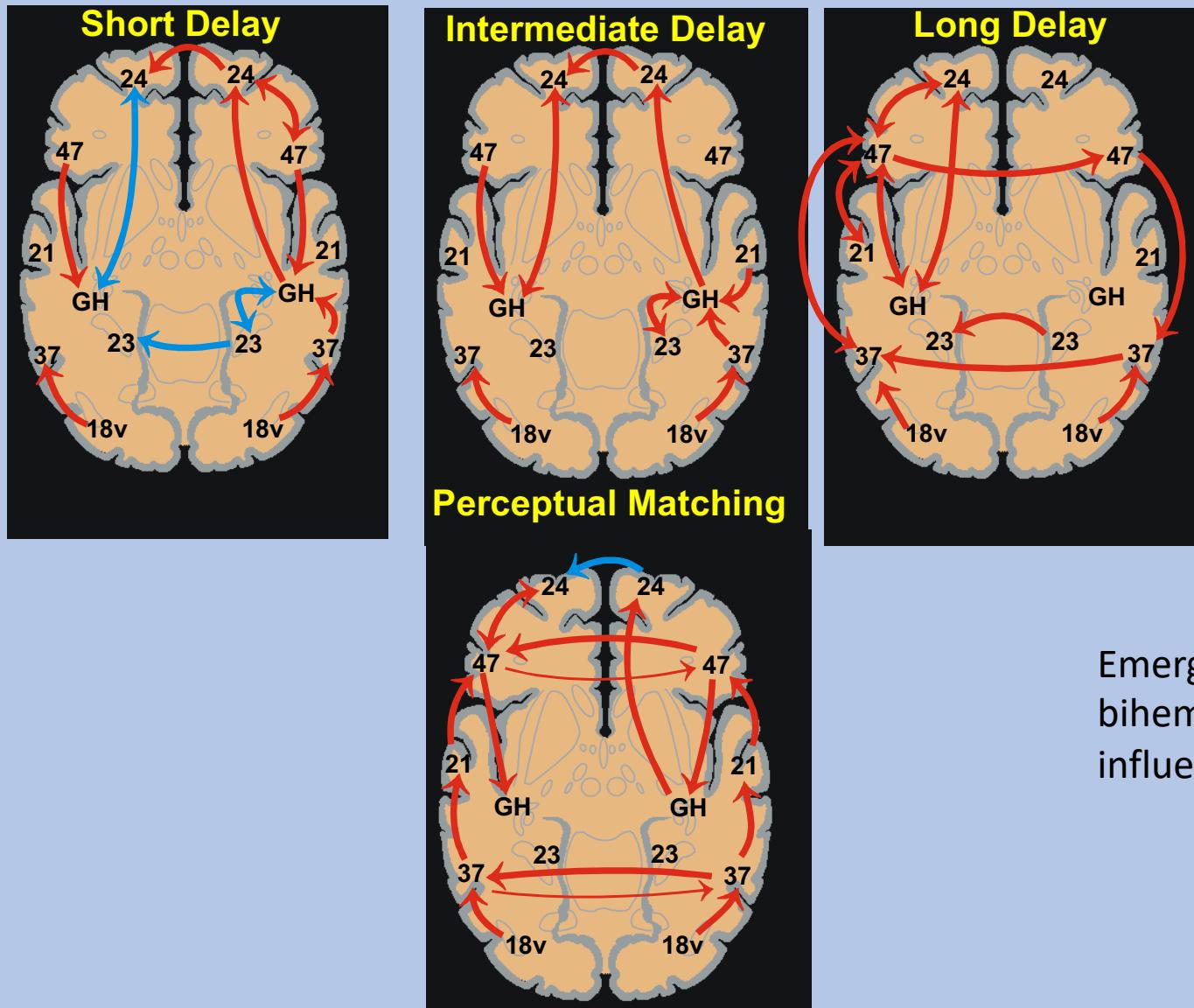


# Anatomical Network Working Memory



McIntosh et al, *Cerebral Cortex*, 1996

# Functional Networks in Working Memory for Faces

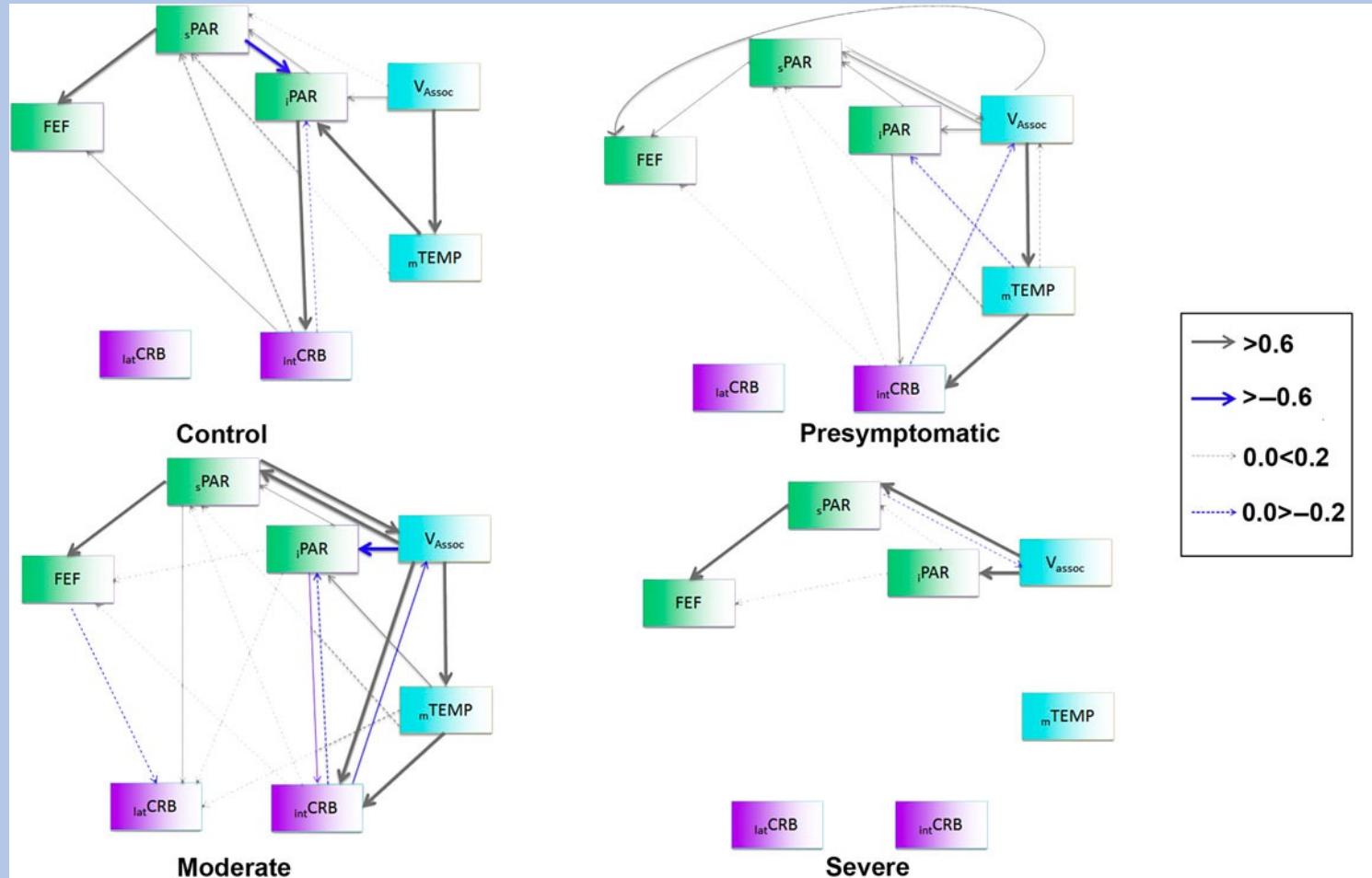


# Early Cerebellar Network Shifting in Spinocerebellar Ataxia Type 6

M.I. Falcon<sup>1</sup>, C.M. Gomez<sup>3</sup>, E.E. Chen<sup>1</sup>, A. Shereen<sup>1</sup>, and A. Solodkin<sup>1,2</sup>

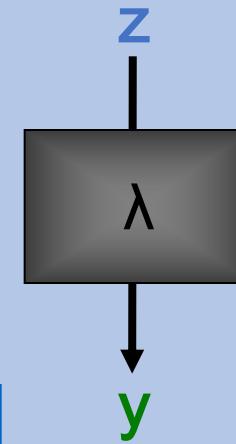
<sup>1</sup>Department of Anatomy and Neurobiology, <sup>2</sup>Department of Neurology, UC Irvine School of Medicine, Irvine, CA 92697, USA and <sup>3</sup>Department of Neurology, University of Chicago, Chicago, IL 60637, USA

Rise and fall of effective connections in patients with increasing severity

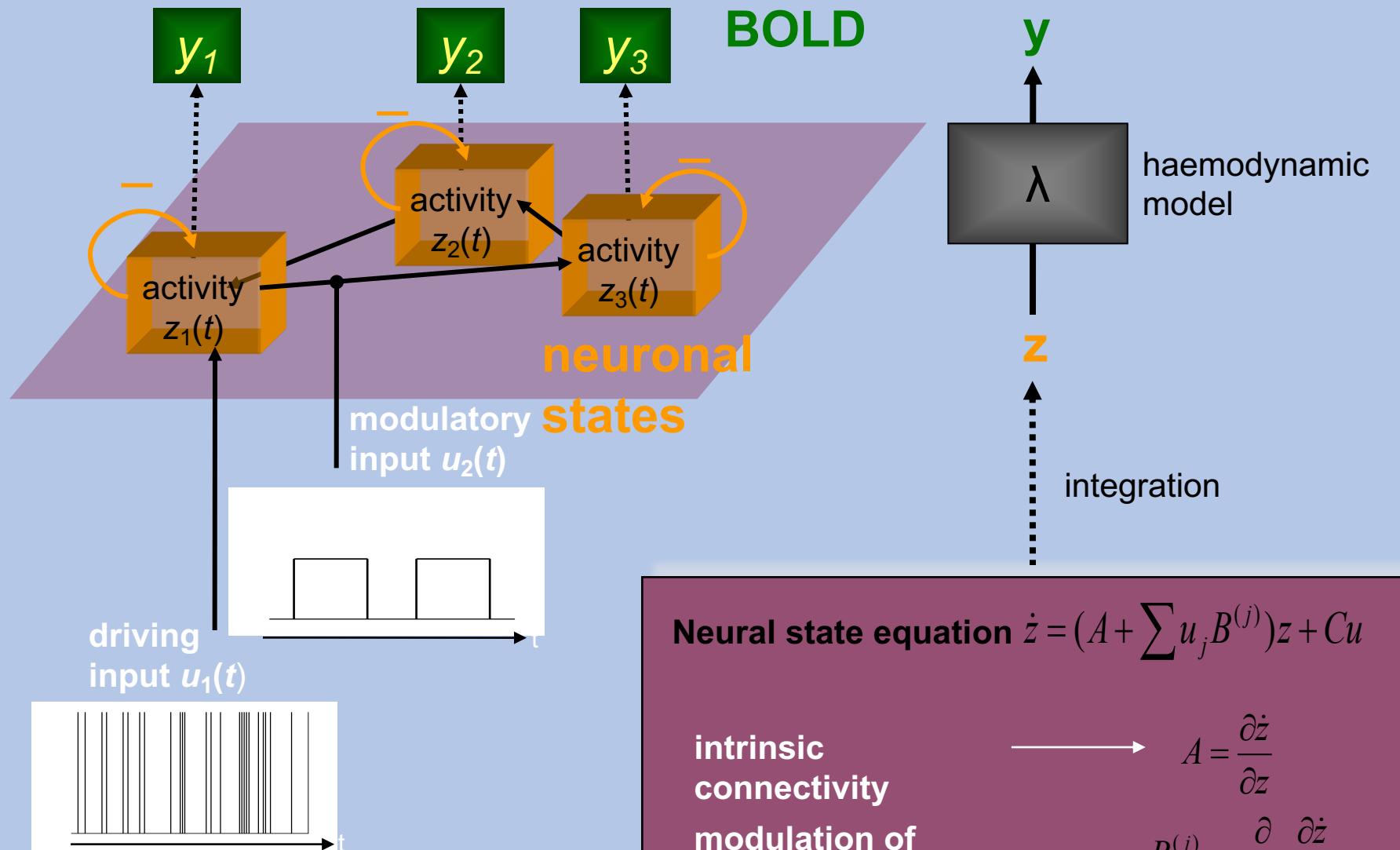


# Dynamic Causal Modeling for fMRI

- Using a bilinear state equation, a putative cognitive system is modelled at its underlying neuronal level (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 ( $\lambda$ ).



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



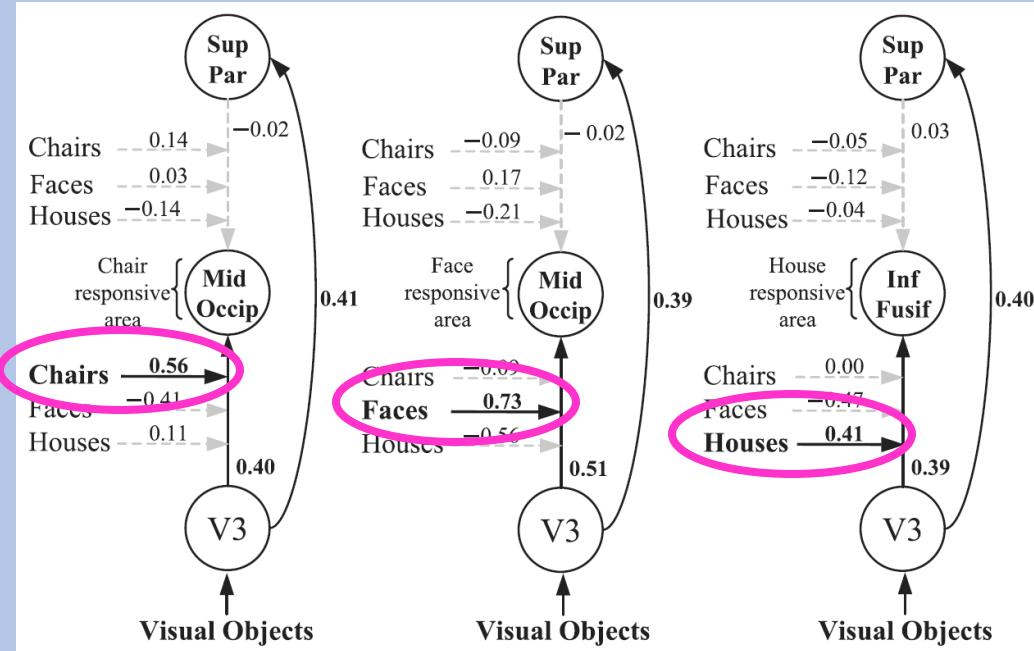
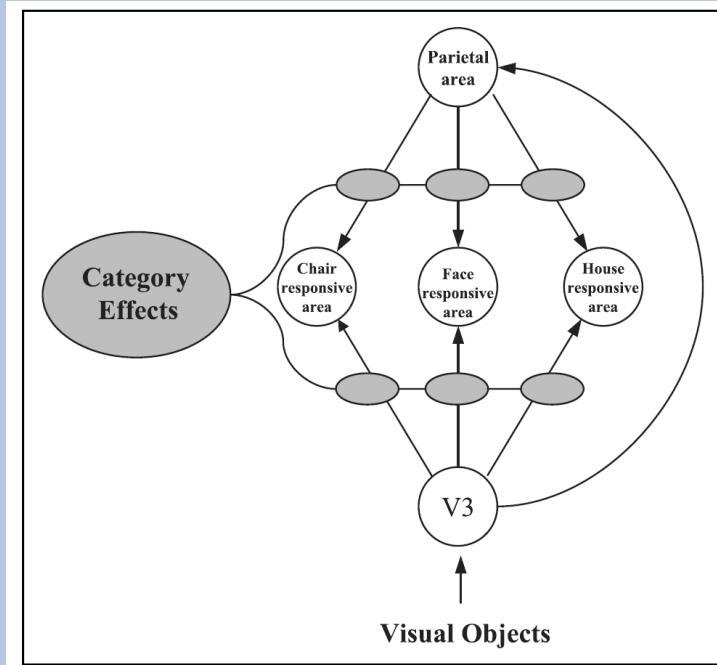
Stephan & Friston 2007,  
*Handbook of Brain Connectivity*  
(Eds. Jirsa & McIntosh)

# Hypothesis Testing with DCM

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

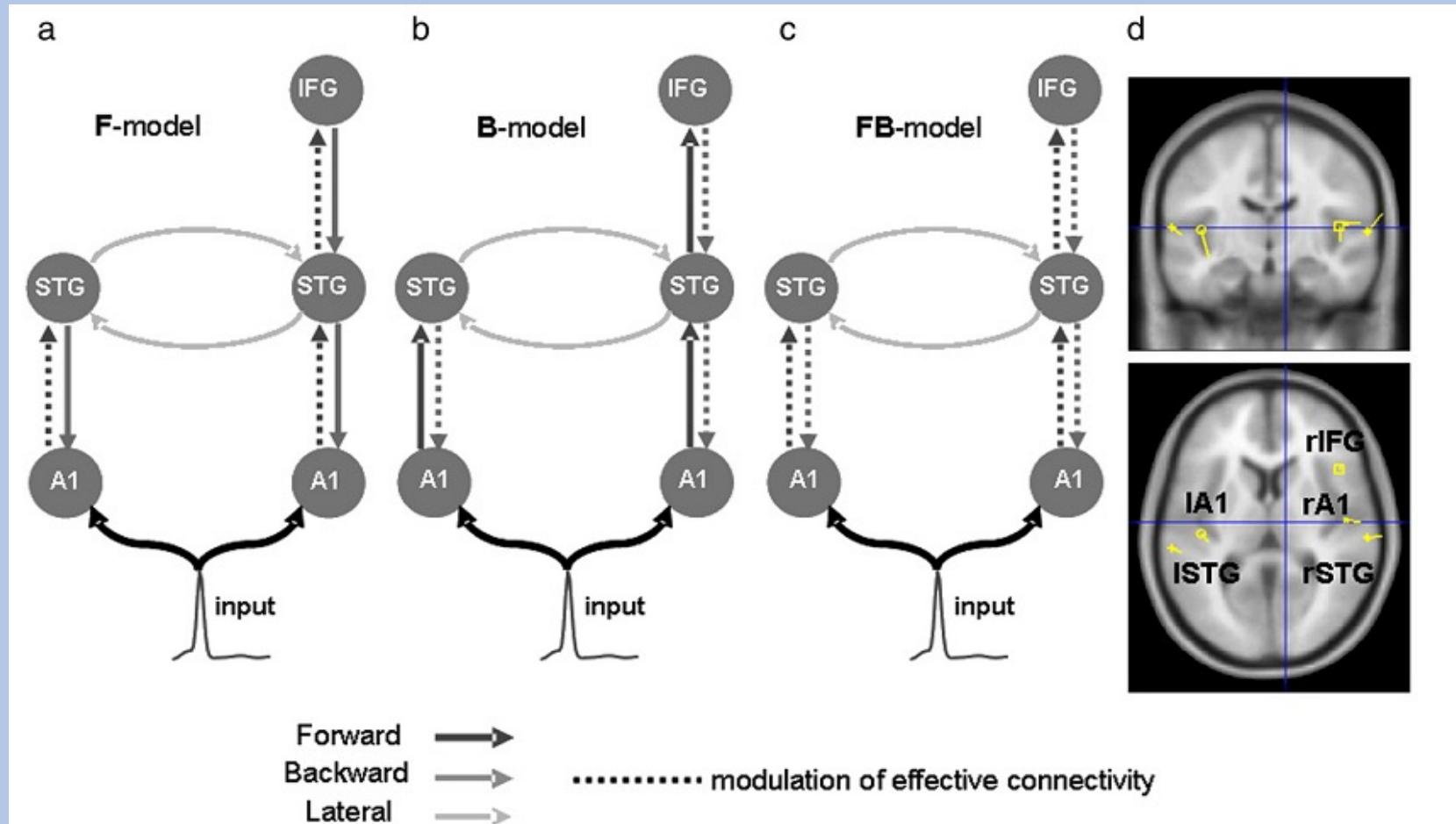
Andrea Mechelli, Cathy J. Price, Uta Noppeney, and Karl J. Friston

Category effects may be bottom-up!



*J Cognitive Neurosci, 2003*

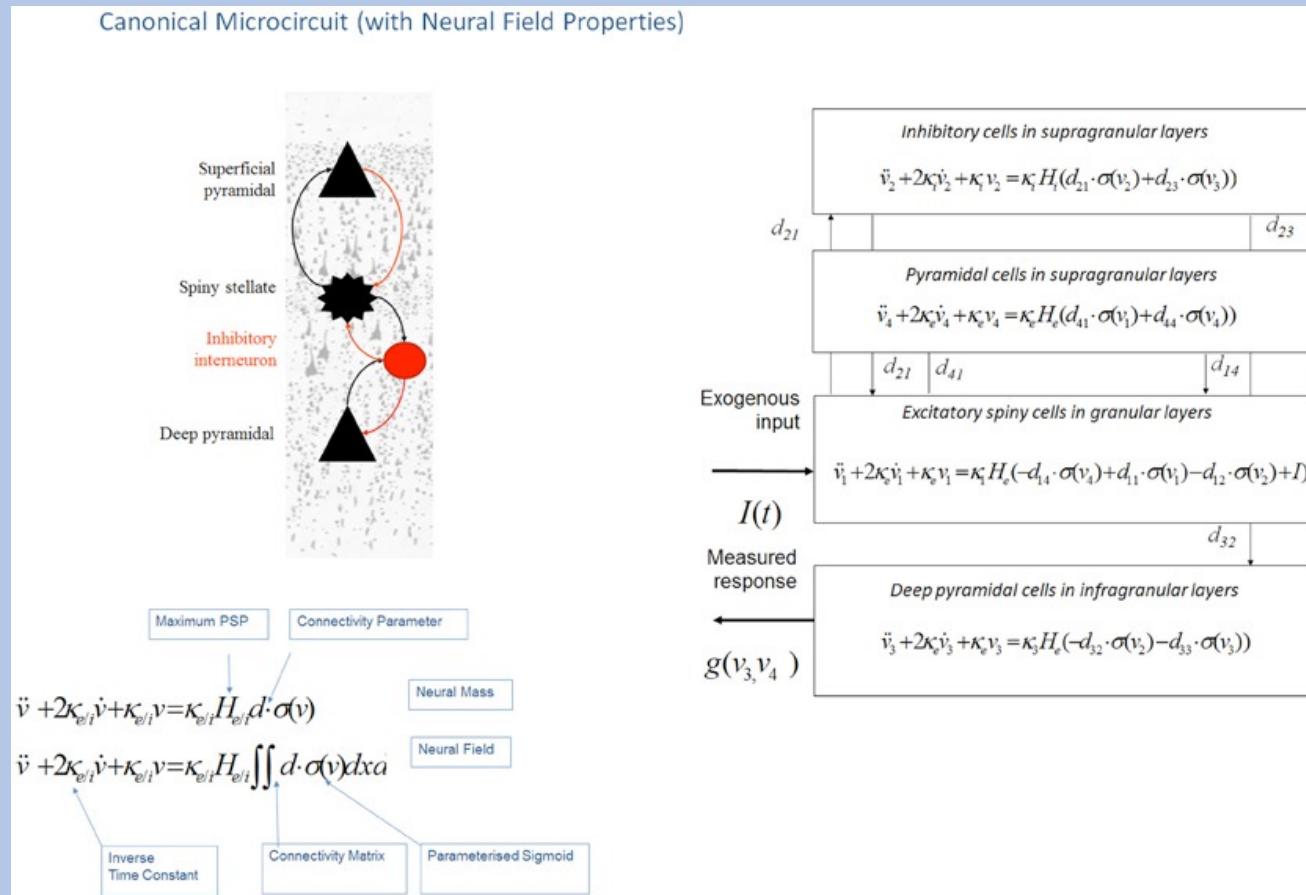
# DCM for EEG/MEG Hierarchical Neural Mass Model



Garrido, et al, Neuroimage, 2008

# Neural masses and fields in dynamic causal modeling

Rosalyn Moran<sup>1,2,3\*</sup>, Dimitris A. Pinotsis<sup>1†</sup> and Karl Friston<sup>1</sup>

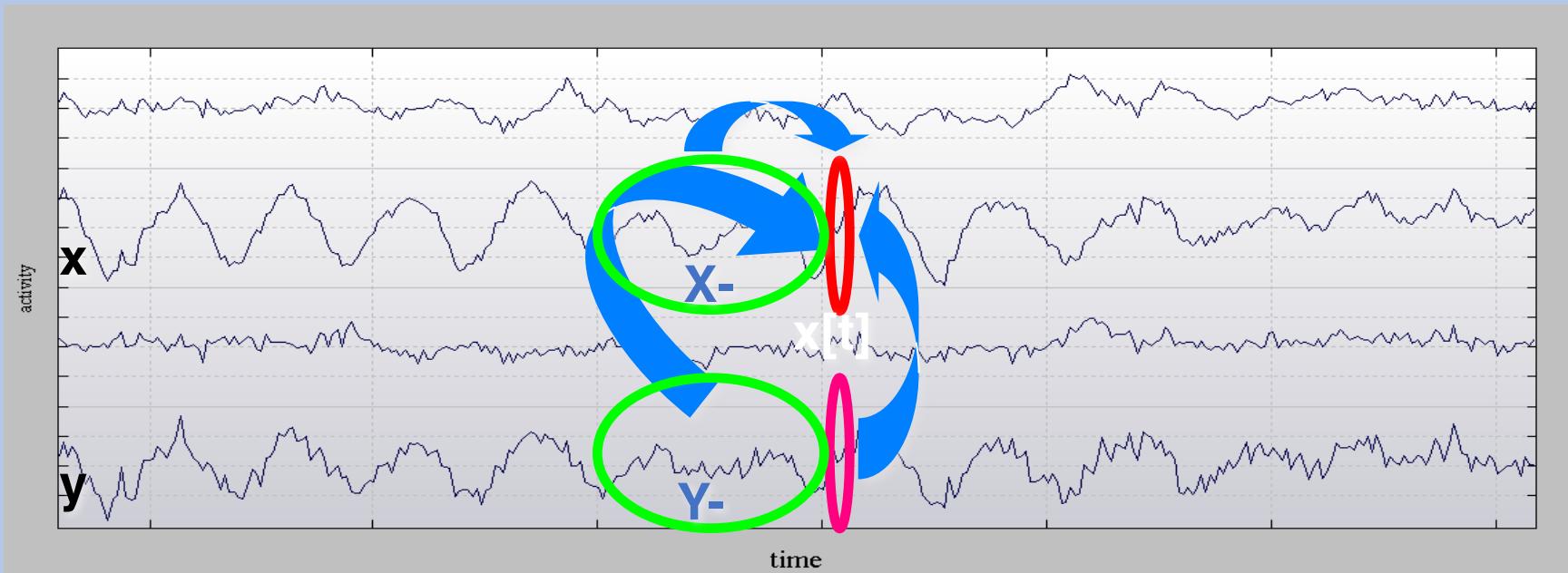


Emphasizes the generative model feature of DCM where inferences are focused at the biophysical level about those causes that generate the observed data

# Effective Connectivity Estimation Using Granger Causality

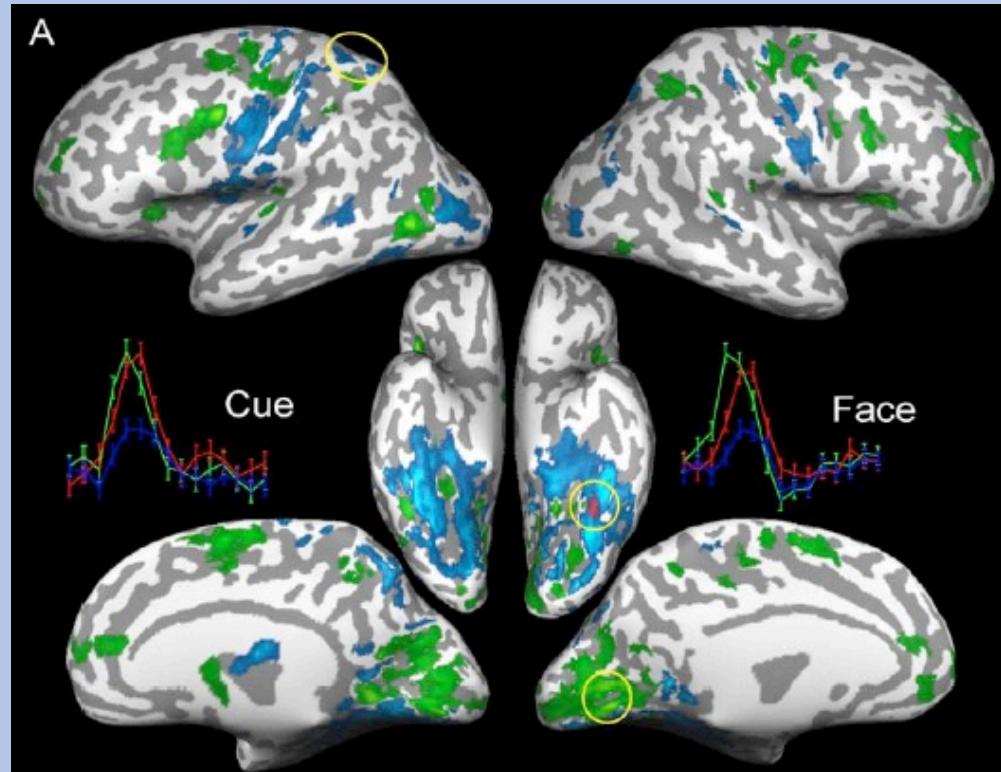
- Explicit use of time series information
- How well does variation in time series "Y" predict variation in time series "X"?
- Previously applied to neuro-physiological data to detect neuronal interactions:
  - Bernasconi & König (1999), LFP-data.
  - Freiwald et al., (1999), LFP-data.
  - Kaminski et 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

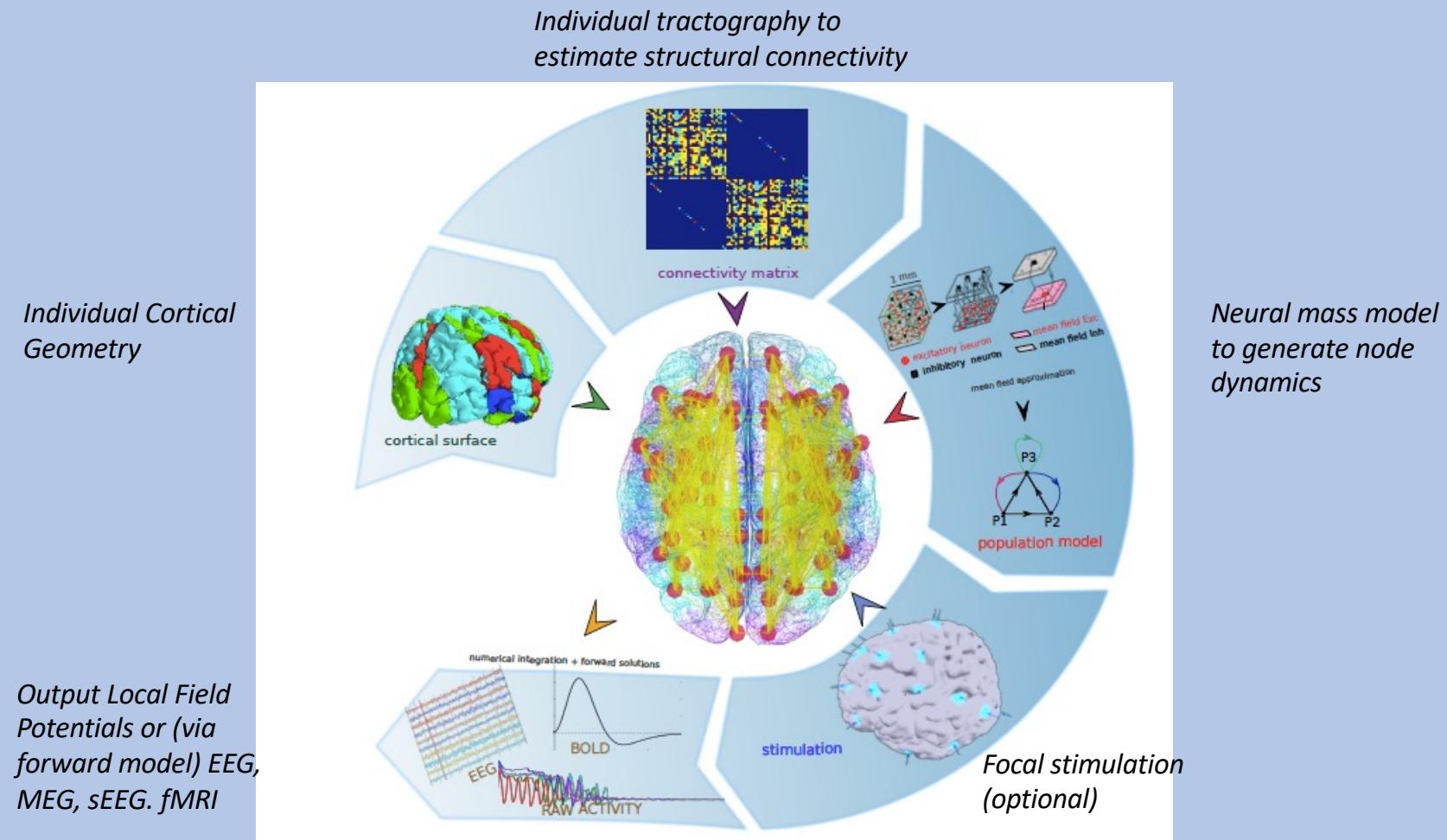
## GENERATIVE

- 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



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



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**Delivering practical results. For novel clinical applications.**

**For over 20 years, bright minds and ambitious projects have attempted to emulate the human brain across various scales of organization. Despite impressive efforts to bring in the latest and greatest computing power of massively parallel hardware, success hasn't yielded practical applications yet.**

To get practicality sooner, The Virtual Brain takes a network approach on the largest scale: By manipulating network parameters, in particular the brain's connectivity, The Virtual Brain simulates its behavior as it is commonly observed in clinical scanners (e.g. EEG, MEG, fMRI).

Though The Virtual Brain incorporates the complex world of neuro-chemistry only to a small degree, it gains a lot by not becoming as complex as the brain itself.

Instead, The Virtual Brain embraces and extends novel concepts from computational, cognitive and clinical neuroscience in order to drastically reduce the model's complexity while still keeping it sufficiently realistic – and delivering the same output as clinical brain-scanners.

**Past events**

- AUG 31** Workshop: TVB Node#9 Warsaw, Poland : 1 DAY WORKSHOP :: AUGUST 31, 2019 Get up to speed about the fundamental principles of full brain network modeling using
- JUL 16** CNS\*2019 Workshop in Barcelona Barcelona, Spain : We introduce here VirtualBrainCloud - a EU project - that integrates existing software tools and platforms to provide access
- JUN 15** Long Night of Sciences 2019 Berlin, Germany : The Long Night of Sciences (in German: Lange Nacht der Wissenschaften (LNDW)) is an annual event in Berlin celebrating the
- MAY 20** Workshop: TVB:Node#8 Marseille, France : 2 DAY WORKSHOP :: MAY 20-21, 2019 Get up to speed about the fundamental principles of full brain network modeling
- NOV 4** See TVB live at SIN 2018! San Diego, USA : The Virtual Brain team will exhibit at the Annual Meeting of the Society for Neuroscience in San Diego, USA. This is your
- AUG 7** Workshop: TVB:Node#7 Montréal, QC, Canada : 2 DAY WORKSHOP :: AUGUST 7-8, 2019 Get up to speed about the fundamental principles of full brain network modeling

**Latest publications**

- Modeling brain dynamics after tumor resection using The Virtual Brain *bioRxiv*
- A macaque connectome for large-scale network simulations in The Virtual Brain *Nature Scientific Data*
- Linking molecular pathways and large-scale computational modeling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer's disease *Frontiers Computational Neuroscience*

**New developments**

Lecture on The Virtual Brain at HEIBRIDS Berlin January 6- Dr. Petra Ritter



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**Software Downloads** **System Requirements** **Import & Export data** **Getting Help & Support** **Screenshots**

**Download The Virtual Brain for free! For Windows, Mac and Linux.**

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**What you are getting**

We offer ready-made packages which were tested for all major, 64-bit desktop platforms. If you wish to install a 32-bit version of TVB, you can still do so from the → source code on GitHub.

These packages work equally well for new installations or for updating existing installations. After unpacking, it's a good idea to look into the included README and Tutorial files, as well as our extensive → documentation website. Besides that, we provide ample → help and support for the software.

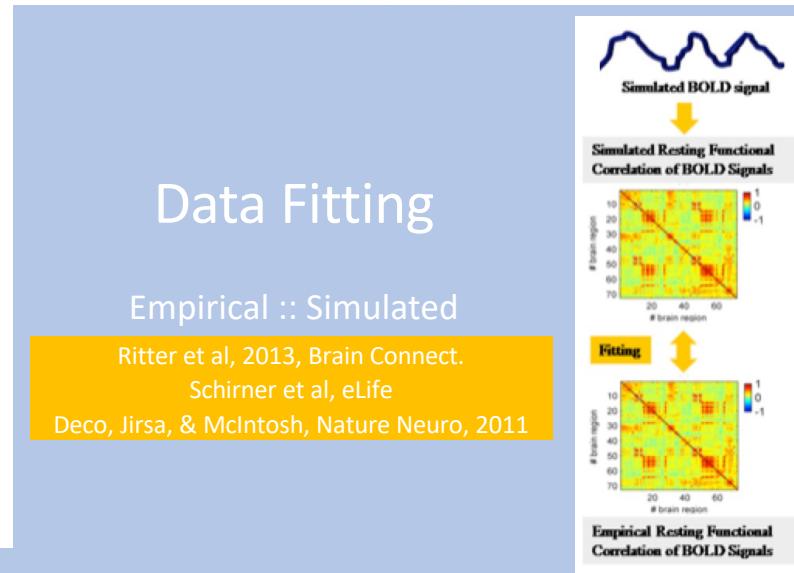
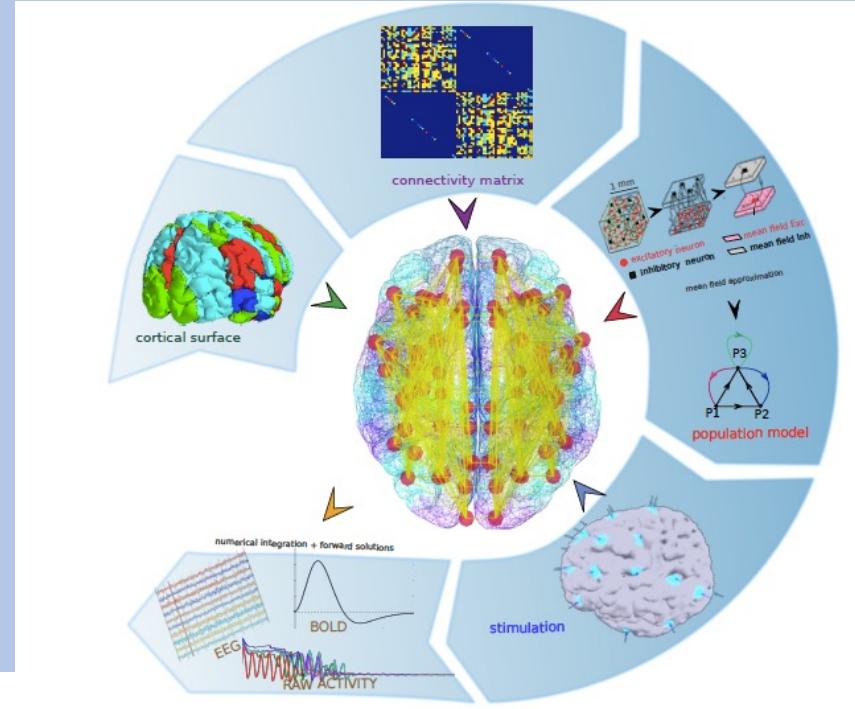
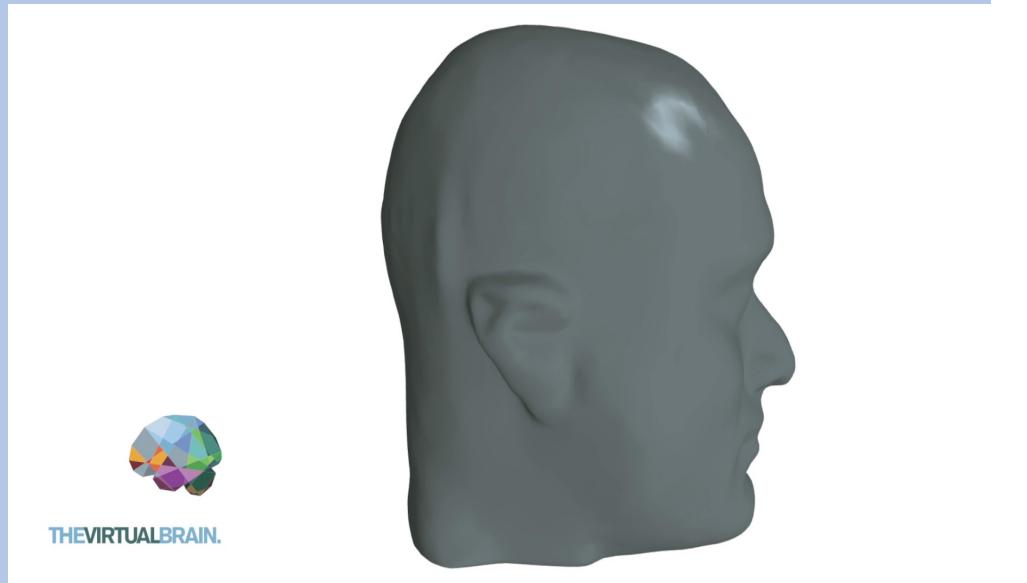
Our brain simulator software requires modern hardware, operating systems and web browsers. Please see our → technical requirements for details. While the TVB software itself is open source with a → GPLv3 license, we include some → 3rd party packages with different licenses.

**Release notes**

Date	Version	Changes	Description
OCT 16 2017	Q Version 1.5.4 (build 8430)	58 changes	Improvements in visualizers
2017	Q Version 1.5.4 (build 8253)	58 changes	Improvements in visualizers
2017	Q Version 1.5.4 (build 8247)	58 changes	Improvements in visualizers
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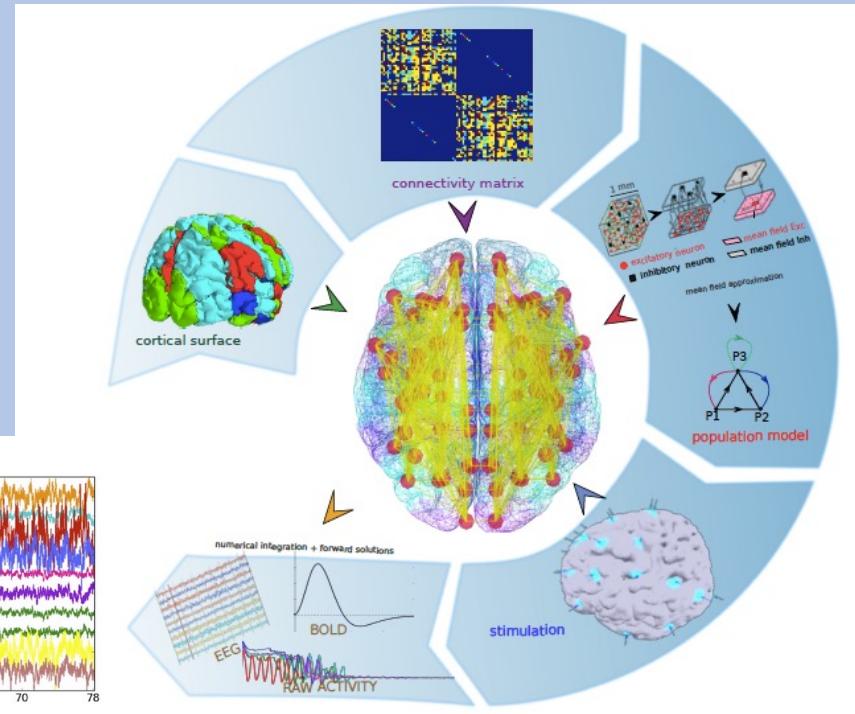
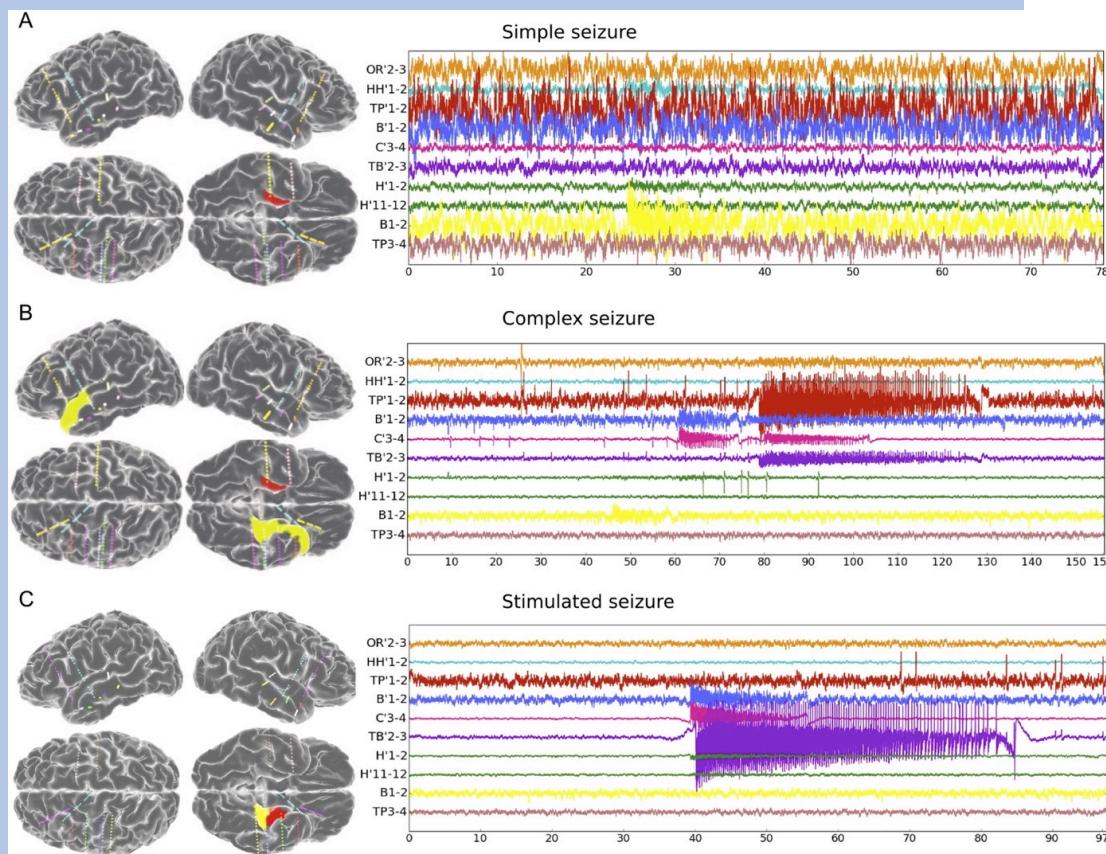
# RESTING STATE

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



# EPILEPSY

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



The Virtual Epileptic Patient  
(EPINOV – National Clinical Trial)

Jirsa et al. 2017 *NeuroImage*

# The elusive concept of brain connectivity

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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>