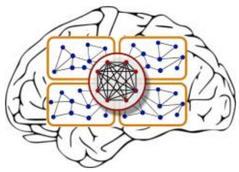
Complex structure and dynamics in neural systems



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Cambridge MPhil in Computational Biology
University of Cambridge
February 2019

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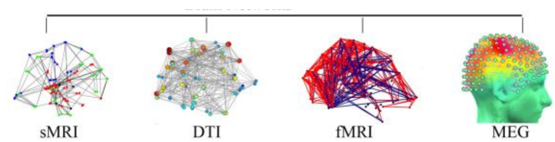
Structural Connectivity	Functional connectivity
Anatomical links	Correlational links
Electron or light microscopy MRI	Multielectrode array recordings, MRI, EEG/MEG
Manual or automated reconstruction	Correlation, synchronization
Positively weighted connections	Positive and negatively weighted connections

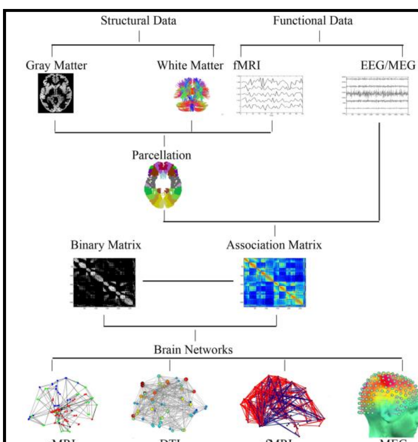
2

Complex networks are a universal framework for representation of multimodal brain connectivity



Bassett and Bullmore, Curr Opin Neurol 2009

3



Bassett and Bullmore, Curr Opin Neurol 2009

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Complexity is not easy to define

- Complexity
  - The quality or state of not being simple: the quality or state of being complex
  - The state or quality of being intricate or complex
  - Something with many parts where those parts interact with each other in multiple ways
- Complex
  - Involving a lot of different but related parts
  - The complexity of a physical system or a dynamical process expresses the degree to which components engage in organized structured interactions

5

There are three distinct notions of complexity

1st notion: Difficulty of “creation”

- Computational complexity.
- Wiring cost (although it’s not usual to describe wiring cost in these terms).

Thanks to Seth Lloyd; MIT

6

There are three distinct notions of complexity

2nd notion: Difficulty of “description”

- Kolmogorov complexity, entropy.
  - Lowest for ordered organizations:
    - E.g. abababababababa
  - Highest for random organizations.
    - E.g 4c1j5b2p0cv4w1x8rx2y

Thanks to Seth Lloyd; MIT

7

There are three distinct notions of complexity

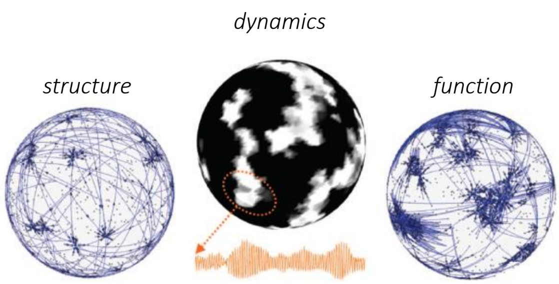
3rd notion: “Richness” of organization.

- Low for ordered organizations,
  High between order and randomness
  Low for random organizations

Thanks to Seth Lloyd; MIT

8

We are interested in structural, dynamical (and functional) complexity of this third kind.



Sporns and Honey, 2006

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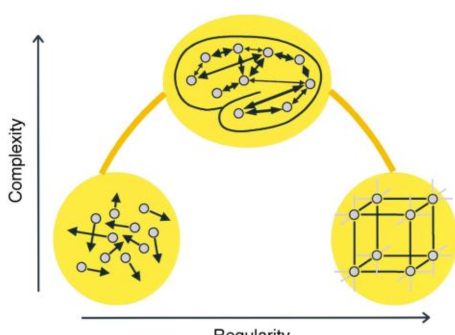
"Richness" of organization



Tononi, Sporns, Edelman, 1998

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Overview

Structure: Complex topology of brain-wiring diagrams

small-worldness

Dynamics: Complex brain activity

multistability

neuronal avalanches

Are Brain networks meaningful objects?

11

STRUCTURE: COMPLEX TOPOLOGY OF BRAIN-WIRING DIAGRAMS

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Review

The Human Connectome: A Structural Description of the Human Brain

Olaf Sporns*, Giulio Tononi, Rolf Kötter

To understand the functioning of a network, one must know its elements and their interconnections. The purpose of this article is to discuss research strategies aimed at a comprehensive structural description of the network of elements and connections forming the human brain. We propose to call this dataset the human "connectome," and we argue that it is fundamentally important in cognitive neuroscience and neuropsychology. The connectome will

Sporns et al., 2005.

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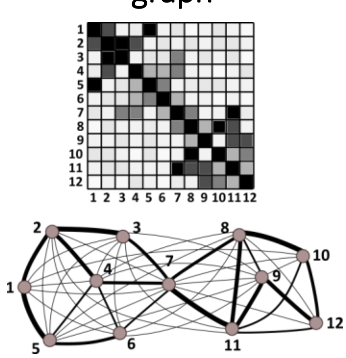
Connectivity matrix represents a graph



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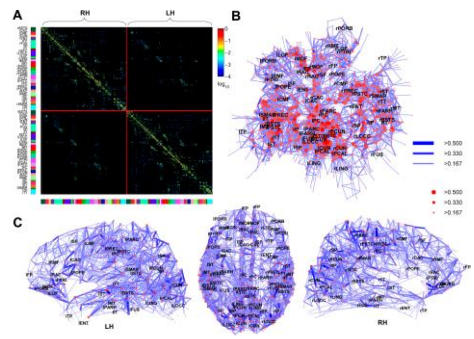
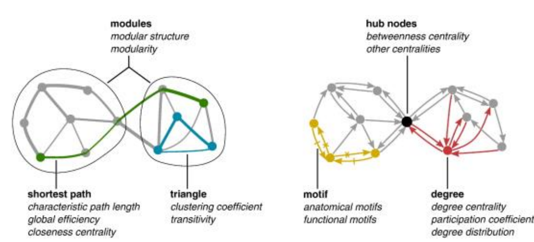
Topological complexity of brain-wiring diagrams



Hagmann et al., 2008

15

Topological complexity of brain-wiring diagrams



Rubinov and Sporns, 2010

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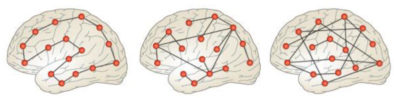
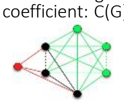
Measures of network macroscale summarize properties of the whole network in a single statistic



Clustering coefficient: C(G)



$C_{red} = \frac{2*2}{3*(3-1)} = 0.66$

Path length: L(G)

Small-world: σ(G)

$$\sigma(G) = \frac{C(G)}{L(G)}$$

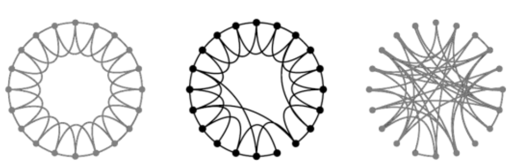
Bullmore and Sporns, 2012.

17

Small-worldness is a simple measure of topological complexity: the combination of high clustering and low path length

$$\sigma(G) = \frac{C(G)}{L(G)}$$

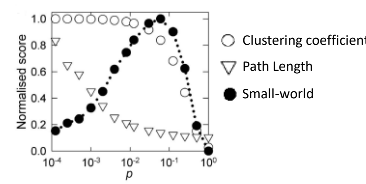
Lattice	Small-world	Random
High clustering	High clustering	Low clustering
High path length	Low path length	Low path length



Watts and Strogatz, Nature 1998

18

Small-worldness is a simple (simplistic) measure of topological complexity



Humphreys and Gurney, 2008

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DYNAMICS:
COMPLEX BRAIN ACTIVITY

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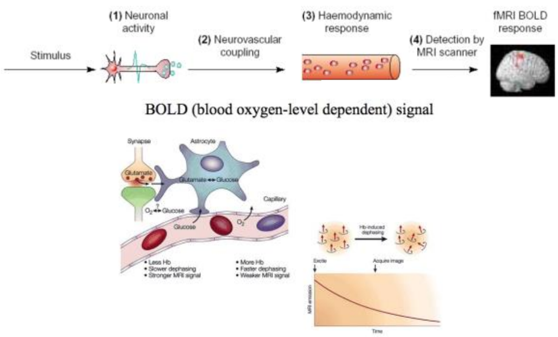
Functional Magnetic Resonance imaging (fMRI)



Arthurs & Boniface, 2002

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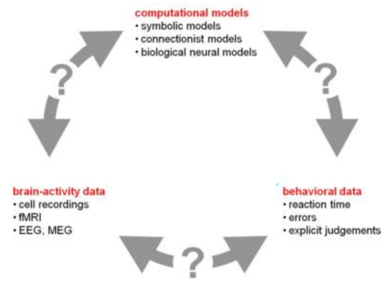
Functional imaging reveals physiological activity to better understand neural mechanism mediating cognition and behavior



Kriegeskarte et al. 2008
Diani et al. 2007

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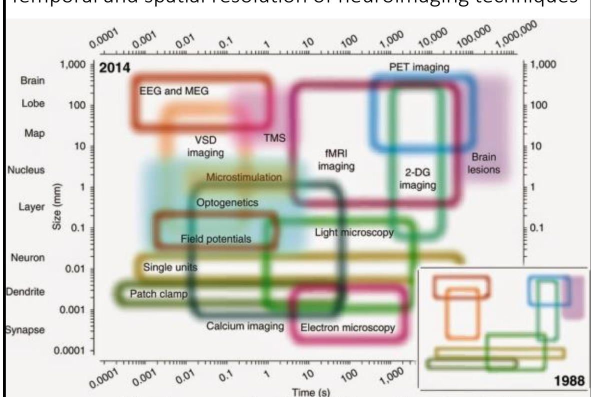
Temporal and spatial resolution of neuroimaging techniques



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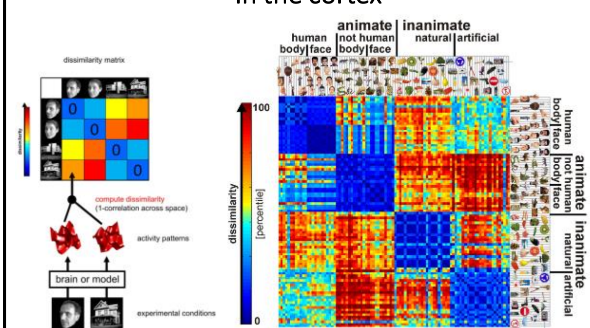
Similar visual stimuli evoke similar activity patter in the cortex



Kriegeskarte et al. 2008
Diani et al. 2007

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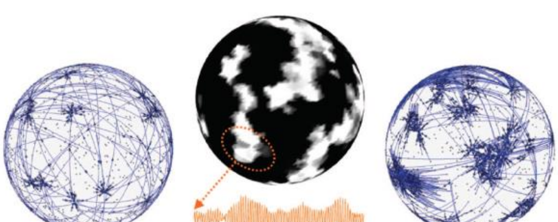
Reconstruction of visual images from human brain activity measured by fMRI

Shen et al. 2017 Biorxiv

25

Dynamics are less significantly constrained by anatomical connectivity on short time-scales.

Dynamics are more significantly constrained by anatomical connectivity on long time-scales.



Sporns and Honey, 2006

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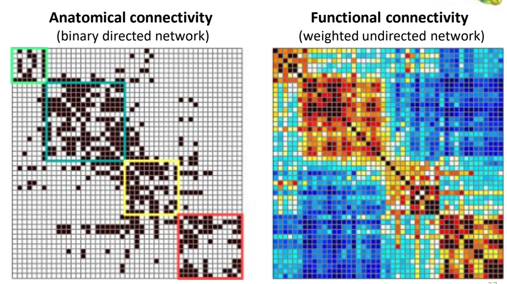
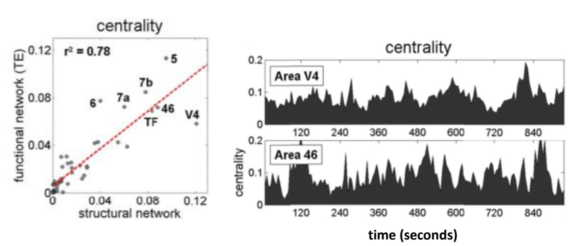
Dynamics/functional connectivity is significantly constrained by anatomical connectivity on long time-scales.



Rubinov and Sporns, 2010

27

Dynamics/functional connectivity is less constrained by anatomical connectivity and is more variable on short time-scales.



Honey et al., 2007

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We consider three popular notions of dynamical complexity

1. MULTISTABILITY
2. THE ENTROPIC BRAIN HYPOTHESIS
3. AVALANCHE DYNAMICS

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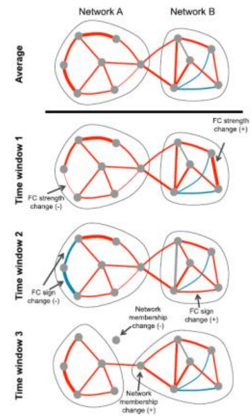
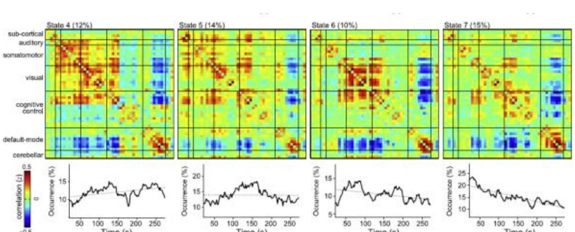


Hutchison et al., 2013

31

1. Multistability is the repeated exploration of distinct dynamical states



Hutchison et al., 2013

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Real-time spontaneous brain activity in the mouse

Voltage sensitive dye imaging of spontaneous activity in isoflurane anesthetized mouse

Mohajerani et al., 2013.

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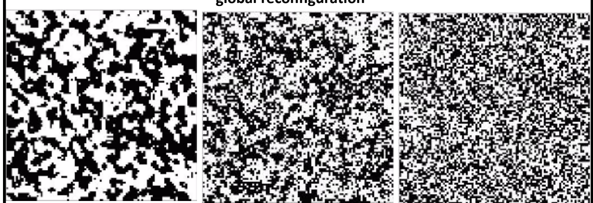
Cortical networks operate near a critical point

Dynamic based on local coupling | Dynamic based on local coupling and global reconfiguration | Dynamic based on global reconfiguration



Beggs and Timme , 2012

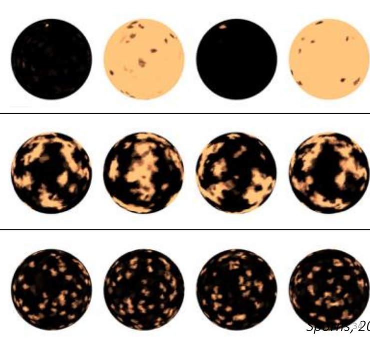
33

Multistability lies between order and randomness

Ordered
Monostable
low complexity

Intermediate
Multistable
high complexity

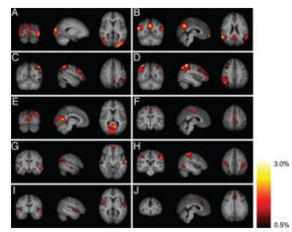
Random
Unstable
low complexity



Sporns, 2007

34

Multistability: alternating between temporality stable states provides a fast response to any stimulus



Damoiseaux et al., PNAS 2006

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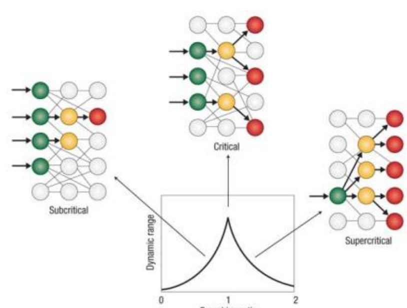
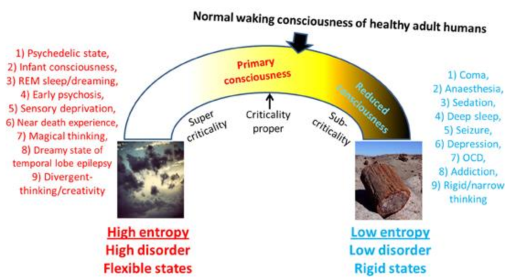
Such scaling is associated with functional benefits such as maximized dynamic range



Chialvo et al., 2006

36

2. The entropic brain hypothesis



Carhart-Harris et al. 2014

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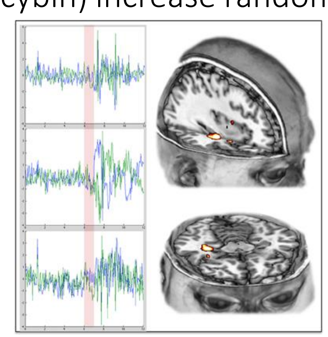
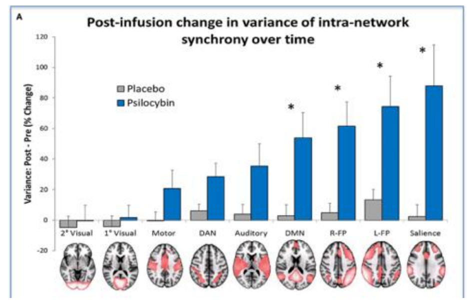
Administration of psychedelic drugs (psilocybin) increase randomness



Carhart-Harris et al. 2014

38

Changes in network metastability and entropy post-infusion of psilocybin



Carhart-Harris et al. 2014

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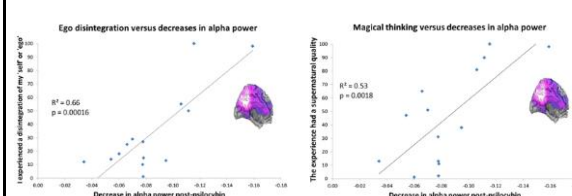
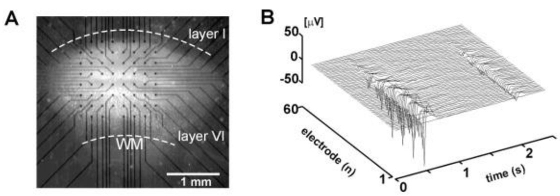
Brain randomization is associated to ego dissolution and magical thinking



Carhart-Harris et al. 2014

40

3. Neuronal avalanches are discrete spatio-temporal patterns of spontaneous activity



Beggs and Plenz, 2003

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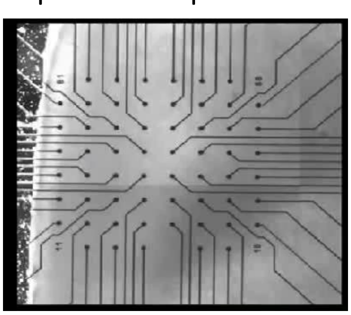
Neuronal avalanches are discrete spatio-temporal patterns of spontaneous activity



Dietmar Plenz Lab, NIH

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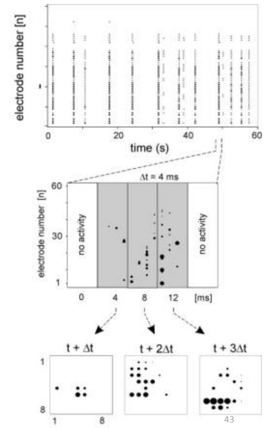
Neuronal avalanches are discrete spatio-temporal patterns of spontaneous activity



Beggs and Plenz, 2003

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Are Brain networks meaningful objects?

- Brain networks are…
  1. Consistent across subjects
  2. Heritable
  3. Related to cognition
  4. Can predict behaviour
  5. Affected by disease
  6. Affected by drugs

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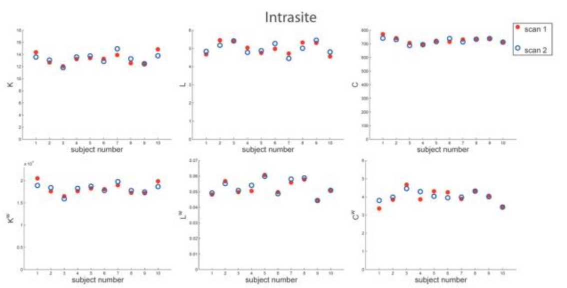
1. Brain networks are **consistent across subjects**



Owen et al., 2012

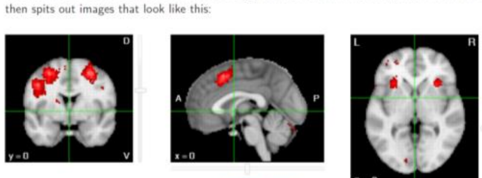
45

1. Brain networks are **consistent across subjects:** Neurosynth

neurosynth.org

Neurosynth is a platform for large-scale, automated synthesis of functional magnetic resonance imaging (fMRI) data.

It takes thousands of published articles reporting the results of fMRI studies, chews on them for a bit, and then spits out images that look like this:



An automated meta-analysis of 901 studies of working memory

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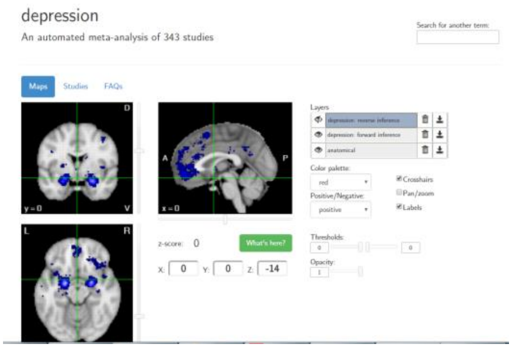
1. Brain networks are **consistent across subjects:** Neurosynth Meta-analyses



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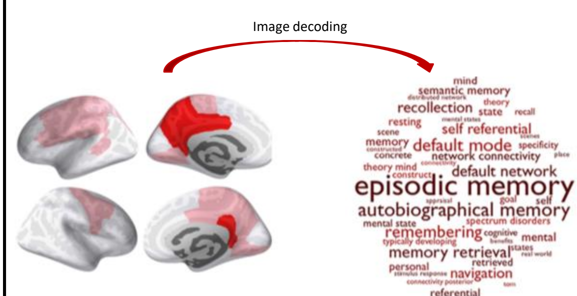
1. Brain networks are **consistent across subjects:** Neurosynth decoder



Romero-Garcia et al., Unpublished data

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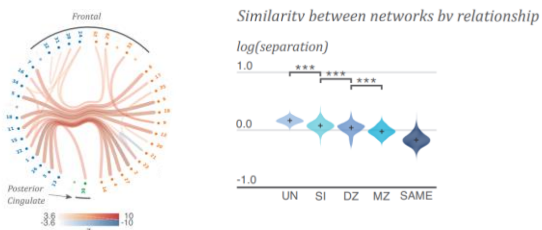
2. Brain networks are **heritable**



UN - Unrelated
SI - Siblings
DZ - Dizygotic twins
MZ - Monozygotic twins

Colclough et al., 2017

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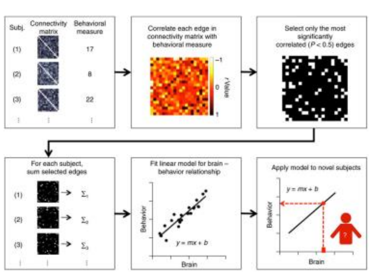
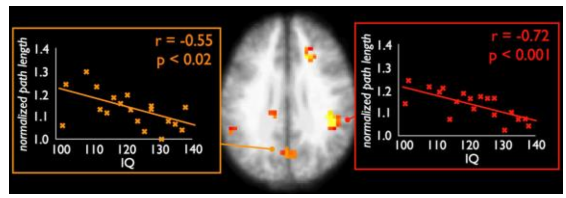
3. Brain networks can **predict behaviour**



Shen et al., Nature protocols 2017

50

4. Brain networks are **related to cognition**



van den Heuvel et al., J Neurosci 2009

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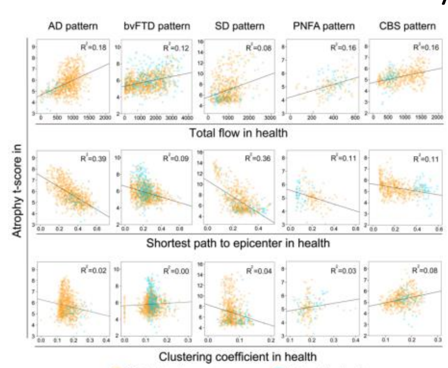
5. Brain networks are **affected by disease**



Zhou et al., Neuron 2012

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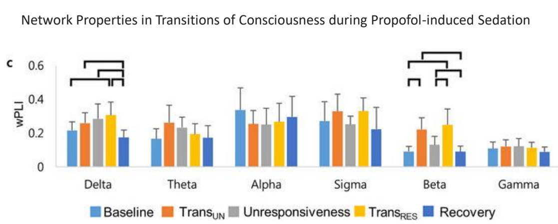
6. Brain networks are **affected by drugs**



Lee et al., Scientific Reports 2017

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Some take home thoughts

- Relevant complexity of neural systems captures a "rich" organization between order and randomness.
- Brain dynamic is multistable and it operates in a critical point.
- Brain networks are consistent, heritable, related to cognition and behavior, and affected by diseases and drugs.

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XKCD

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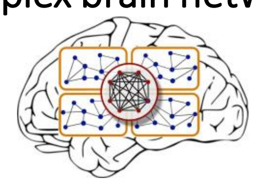
Generative and null models of complex brain networks



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Cambridge MPhil in Computational Biology
University of Cambridge
February 2016

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Ramón y Cajal on the need for generative models

"That apparent disorder of the cerebral jungle conceals a profound organization of the utmost subtility which is at present inaccessible"

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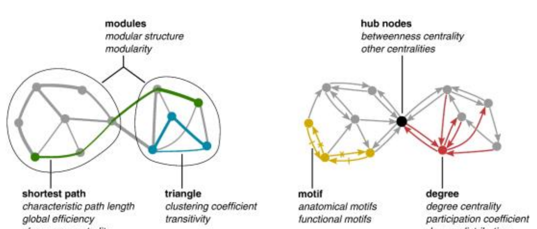
Generative and null models aim to 1) describe and 2) explain topological complexity of brain-wiring diagrams



Rubinov and Sporns, 2010

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Overview

Generative models of brain networks

- Principle of brain economy

Null models of brain networks

- Random networks

Brain networks in schizophrenia

Neuroimaging and connectomics in Brain Tumours

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GENERATIVE MODELS

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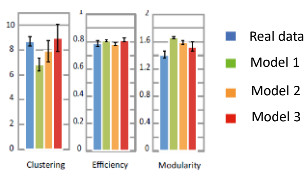
A generative model is a rule, mechanism or equation ('proto-theory') for generating a class of networks

Generative models should preferably:

1. Reproduce a sufficient degree of observed structural complexity



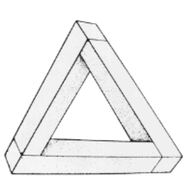
Vertes et al., PNAS 2012

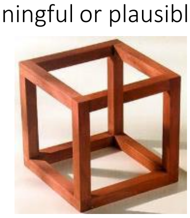
61

A generative model is a rule, mechanism or equation ('proto-theory') for generating a class of networks

Generative models should preferably:

2. Be biologically meaningful or plausible





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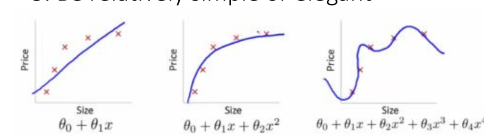
A generative model is a rule, mechanism or equation ('proto-theory') for generating a class of networks

Generative models should preferably:

3. Be relatively simple or elegant



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Preferential attachment rule (Barabási-Albert model) rule generates networks with power-law degree distributions

The probability p_i that the new node is connected to node *i* is :

$$p_i = \frac{k_i}{\sum_j k_j},$$

Where k_i is the degree of node *i* and the sum is made over all pre-existing nodes *j*

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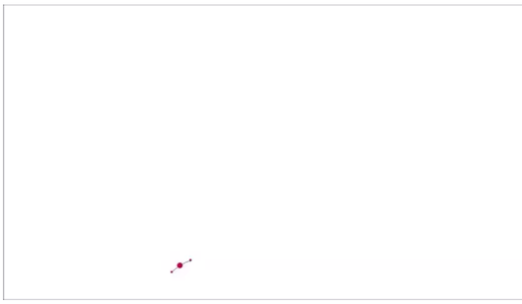
Preferential attachment rule (Barabási-Albert model) rule generates networks with power-law degree distributions



Edwin Grappin, Centre de Recherche en Economie et Statistique

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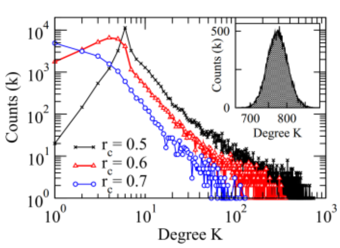
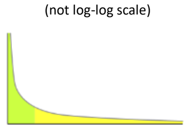
Example 1: Preferential attachment model



Theoretical Power-law graph
(not log-log scale)



Barabasi and Albert, 1999; Eguiluz et al., 2005

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Preferential attachment rule as a generative model of brain networks.

- Reproduces a sufficient degree of observed structural complexity ☹
- Is biologically meaningful or plausible ☹
- Is relatively simple or elegant ☺

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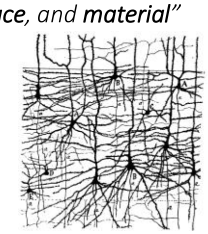
Ramón y Cajal's principle of economy as generative model

*"all of the various conformations of the neuron and its various components are simply morphological adaptations governed by laws of conservation for **time**, **space**, and **material**"*



Ramón y Cajal, 1899

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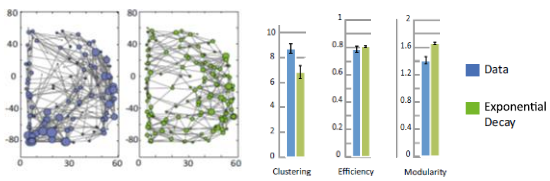
Recently, investigators report a exponential decay with distance as a good generative model of the brain



Vertes et al., PNAS 2012

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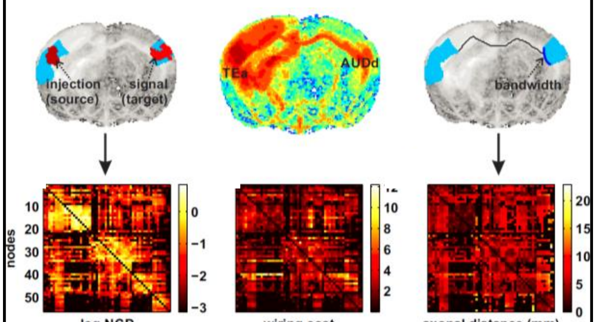
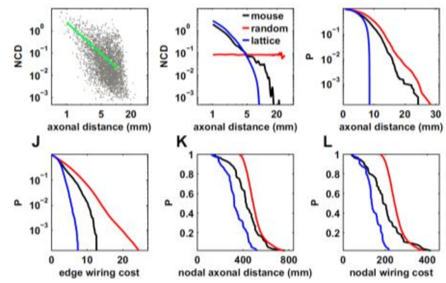
We evaluated this model in a new mouse brain dataset



Rubinov, Ypma, Watson, Bullmore, 2015.

70

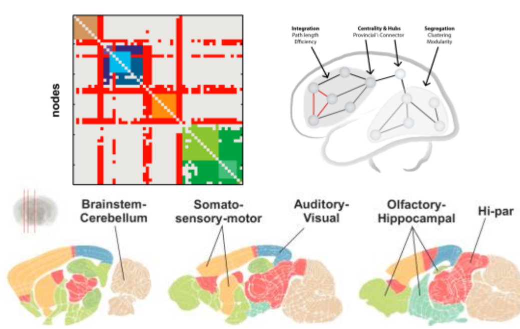
Our results argue against distance minimization as an accurate generative model of the mouse brain connectome.



Rubinov, Ypma, Watson, Bullmore, 2015.

71

We decompose the mouse brain into modules and hubs



Rubinov, Ypma, Watson, Bullmore, 2015.

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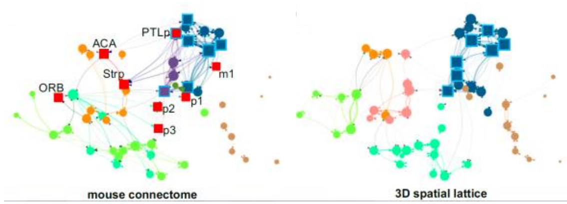
The distance minimization model reproduces the modules but not the hubs



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How good is Ramón y Cajal's principle of economy as a generative model?

<u>Economy of space and material</u>

- Reproduces a sufficient degree of observed structural complexity ☹
- Is biologically meaningful or plausible ☺
- Is relatively simple or elegant ☺

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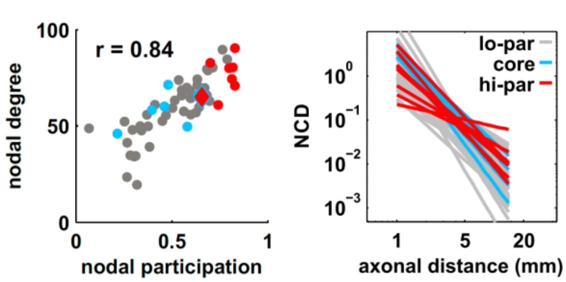
Hi-par nodes a higher distance than would be expected with distance minimization.



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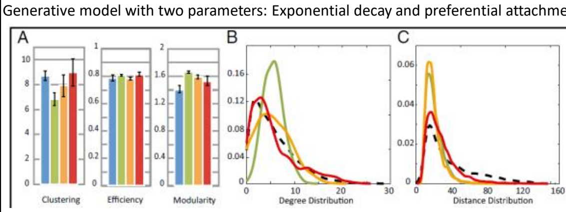
Generative model with two parameters: Exponential decay and preferential attachment



Vertes et al., PNAS 2012

Colour Legend:

- ■ ■ ■ Data
- Data
- Exponential Decay $P_{i,j} \propto \exp(-\eta d_{i,j})$, where d_{ij} is the anatomical distance between regions i and j, and η is the only parameter of the model.
- Economical Preferential Attachment $P_{i,j} \propto (k_i k_j)^{\gamma}(d_{i,j})^{-\eta}$, k_i and k_j represent nodal degree, η is the parameter of distance penalization,
- Economical Clustering $P_{i,j} \propto (k_{i,j})^{\gamma}(d_{i,j})^{-\eta}$, k_{ij} is the number of nearest neighbors in common between nodes i and j

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How good is the economical clustering as a generative model?

Economy of space and material

- Reproduces a sufficient degree of observed structural complexity ☹
- Is biologically meaningful or plausible ☺
- Is relatively simple or elegant ☺

77

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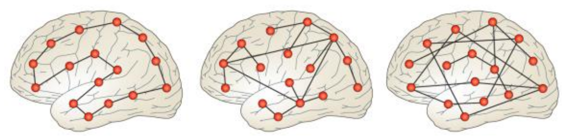
Nontrivial properties of network topology can only be claimed through comparisons with "null model" networks



Watts and Strogatz, Nature 1998

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NULL MODELS

78

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Null models are networks which preserve "trivial" properties of empirical networks

A good null model should preserve

- all the "trivial" properties and
- none of the "nontrivial" properties

of the original empirical network

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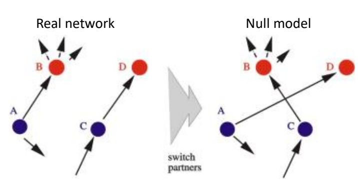
Null models are networks which preserve "trivial" properties of empirical networks

Algorithms to create null models
- should sample the space of all possible null models in an unbiased way
- should run in reasonable time
- do not need to be biological or elegant

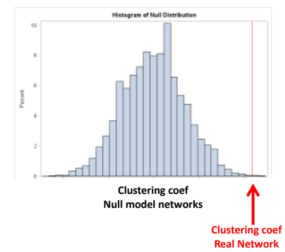
Edge permutation as a null Model

Permuting edges to create null models preserve the number of nodes, edges (and degree distribution)



Maslov, 2002

In general these null models are overly simplistic and too easy to "reject"



Robinson et al., 2009

Some take home thoughts

- Generative models are akin to 'proto-theories' of brain-network organization.
- Null models are akin to 'null hypotheses' of brain-network organization.

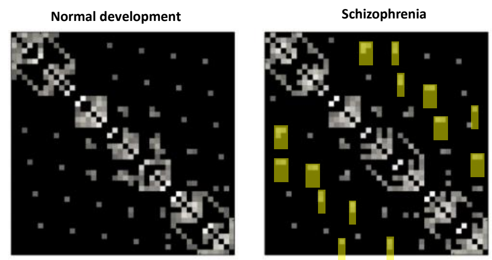
Brain Networks in psychiatric

85

Schizophrenia is a disorder characterized by a mixture of heterogeneous symptoms

86

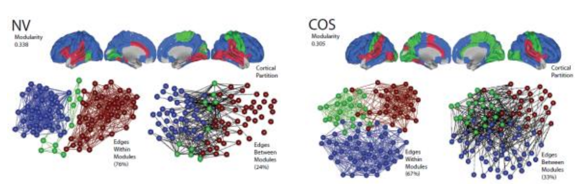
Schizophrenia is associated with a subtle randomization of whole-brain network topology



Rubinov et al., 2009.

87

Schizophrenia is associated with a subtle randomization of whole-brain network topology



Alexander-Bloch et al., Frontiers Syst Neurosci 2011

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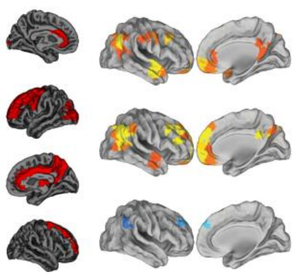
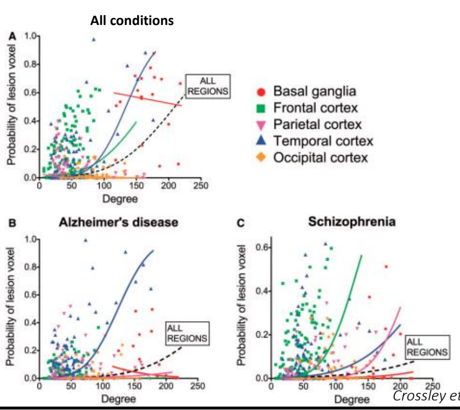
Schizophrenia associates with abnormal association and limbic hubs



Rubinov and Bullmore, 2013.

89

Neither abnormality is specific to schizophrenia



Crossley et al., 2014

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Computational neuropsychiatry

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Some take home thoughts

- Neuropsychiatry disorders are complex phenomenon that cannot be treated by targeting localized areas.
- Computational models based on connectome data can help to better understand the mechanisms associated to neuropsychiatry diseases

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Neuroimaging and connectomics in Brain Tumours

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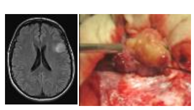
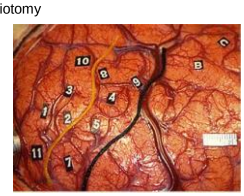
Supporting surgical management of low grade gliomas with structural and functional connectomics

- Brain tumours have a five-year survival rate of only 18.5%
- **Low Grade Gliomas** are slow-growing tumours
  - Resection beyond the abnormality improves prognosis
  - Only worthwhile if brain function can be maintained
  - Motor and somatosensory functions can be assessed using awake craniotomy





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Awake craniotomy

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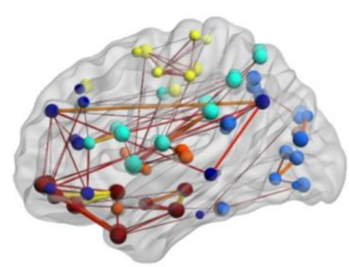
Supporting surgical management of low grade gliomas with structural and functional connectomics



Research hypothesis:

Connectomic-based models can predict post-operative cognitive deficits and can support surgical resection of tumours

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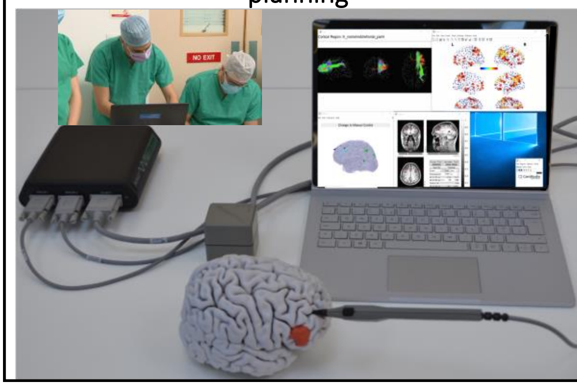
Neuronavigation device in support of surgical planning



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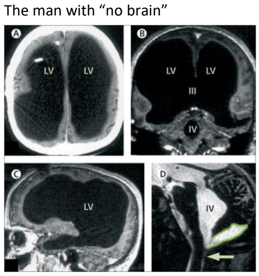
Methodological considerations (I)

- Neuroimaging findings need to be integrated into clinically validated models
- Brain plasticity and compensatory mechanisms difficulties our capability to map cognitive functions into brain regions/circuits in individual subjects.

The man with “no brain”



Feuillet et al. 2007

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Methodological considerations (II)

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Questions?

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