A DIDACTIC INTRODUCTION TO NETWORK NEUROSCIENCE FOR COMPUTATIONAL PSYCHIATRY

WHERE WE ARE AND WHERE WE COULD GO

SOBP
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Brief Outline

I. Introduction to and background for the computational framework

II. Case study of one form of its application

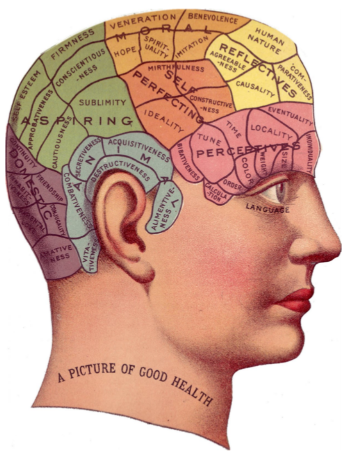
III. Short description of other uses

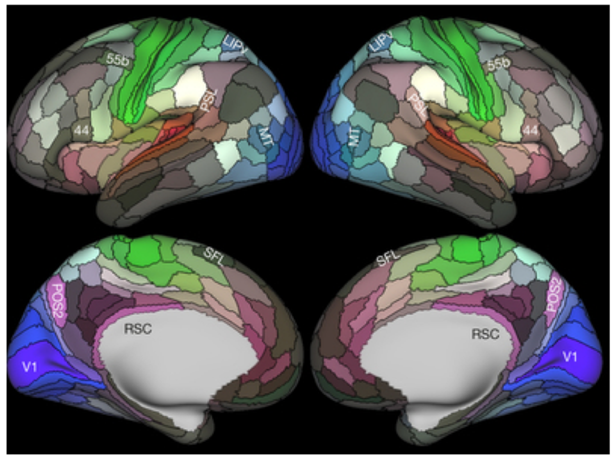
IV. Limitations of the technique, rules of the road problems, perils

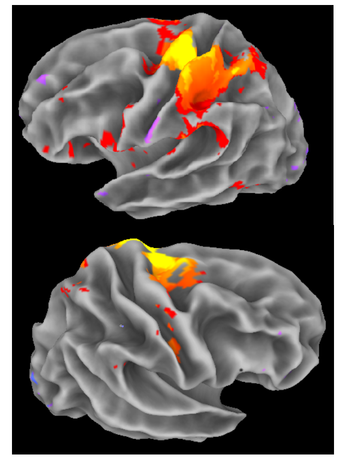
V. Options

VI. Summary

I. The challenge of distilling rules & mechanisms in brain







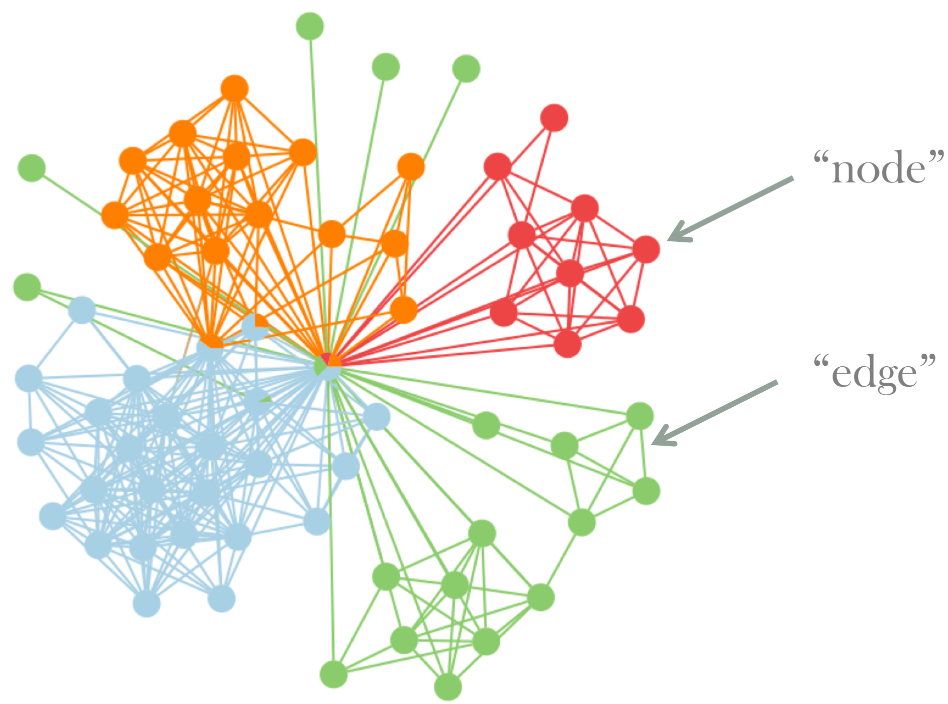
In general, psychiatric conditions are not associated with alterations in a single brain region. Instead, there is a constellation of brain regions and their (structural or functional) connections that are altered.

This complexity produces complex changes in cognition and behavior, and significantly hinders progress in understanding and in the development of effective interventions.

Network Science

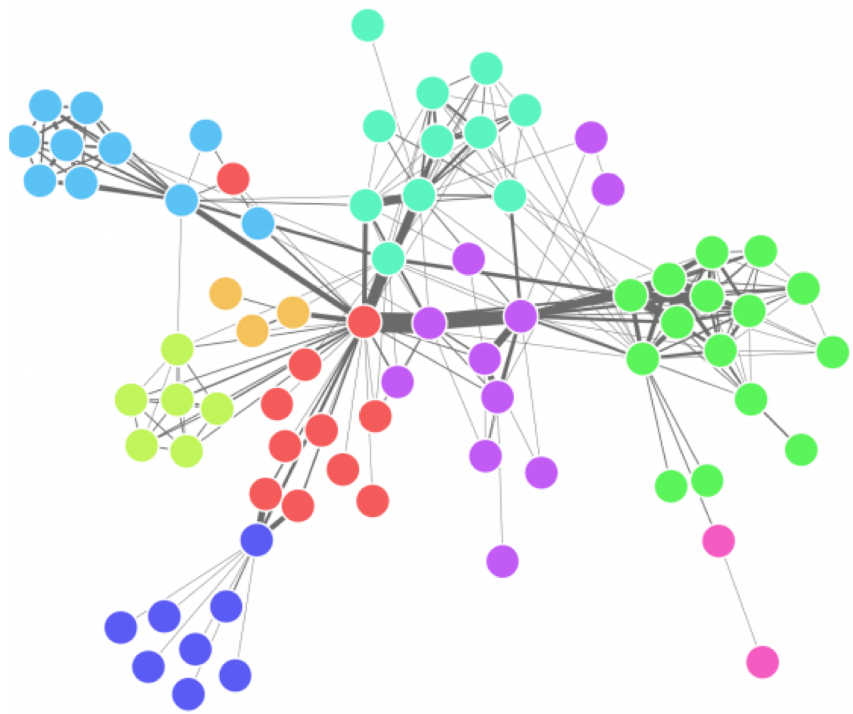
Network science is a natural language in which to frame complex constellations of regions and their connections.

Network science is an emerging academic field that studies *complex networks*, considering distinct elements represented by nodes and the connections between the elements as edges.



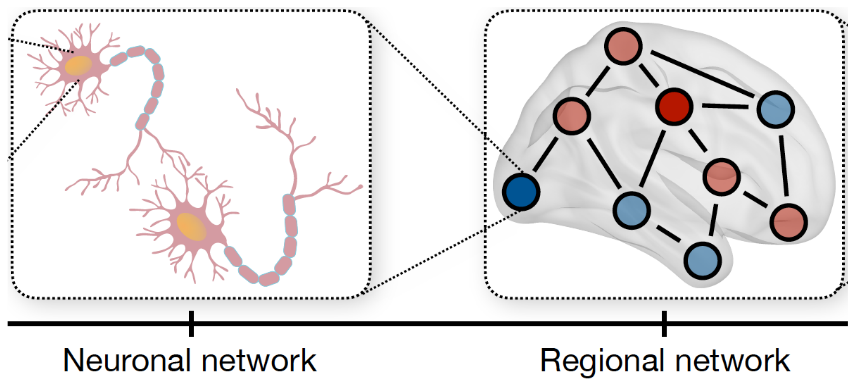
Strengths of the network science approach

- **Flexible framework** that is applicable to many data types, and useful for testing scientific hypotheses in different domains.



Multiscale, multilayer, multiplex networks

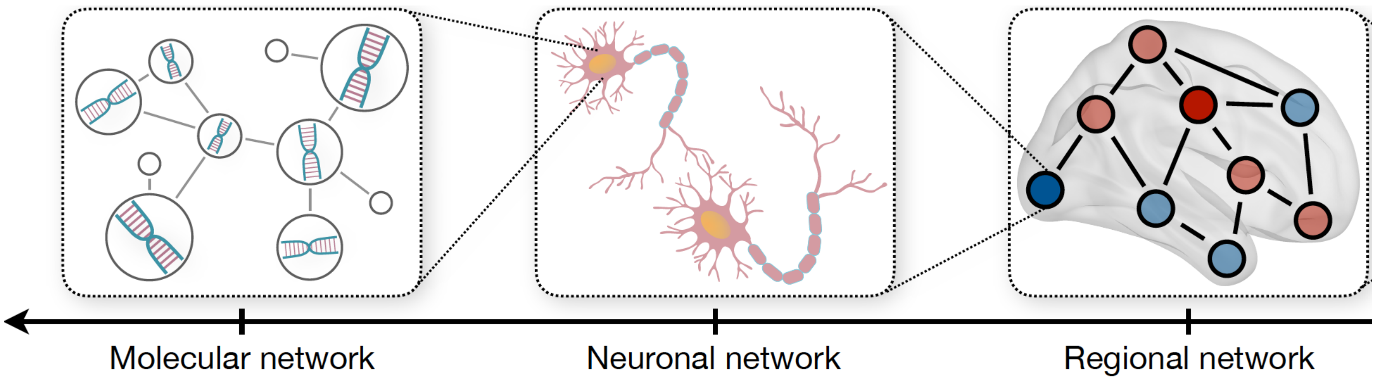
Large-scale brain activity provides a coarse-grained encoding of neural processes, and the map from cellular dynamics to regional dynamics reflects rules of system function.



How do cellular processes shape circuit behavior?

Multiscale, multilayer, multiplex networks

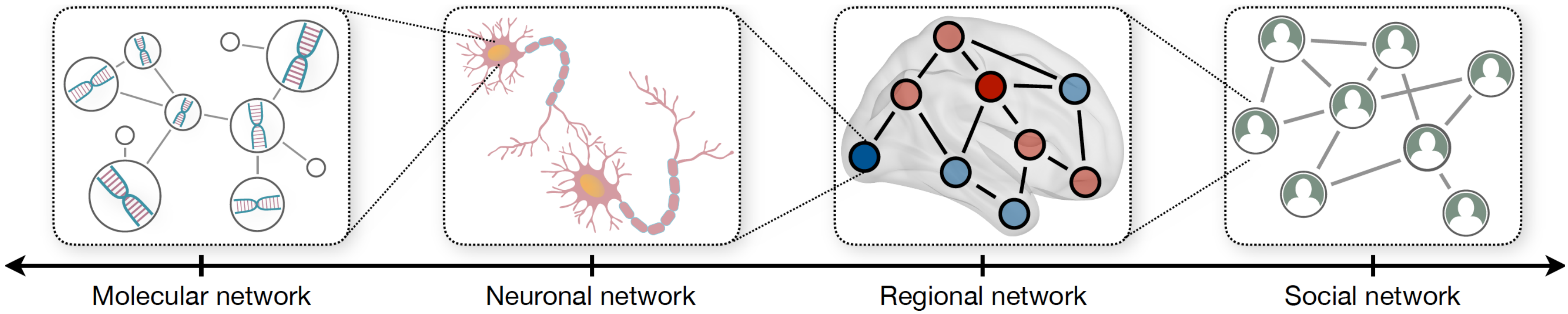
Understanding how molecular mechanisms affect large-scale brain network function is critical for the development of effective pharmacological interventions.



How do genetic material and epigenetic drivers shape circuit behavior across spatial scales?

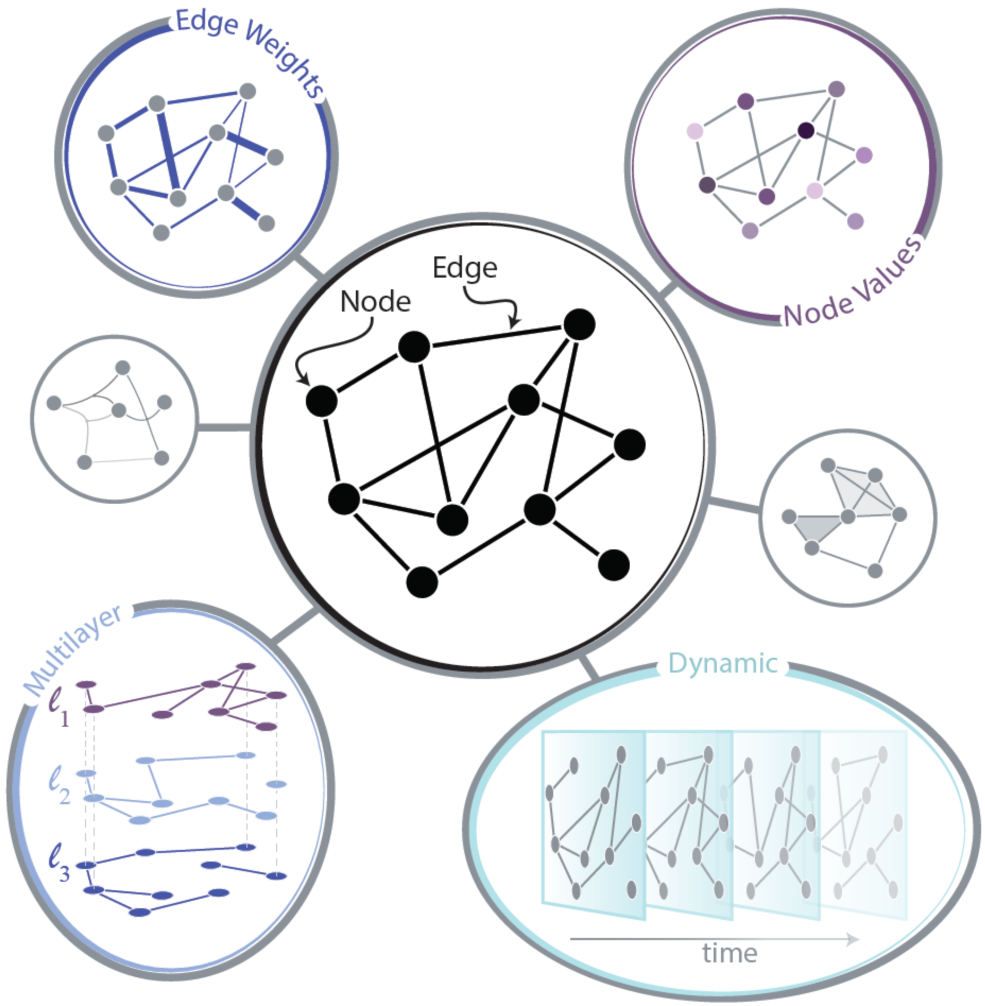
Multiscale, multilayer, multiplex networks

While brain activity and structure offer biological mechanisms for human behaviors, social networks offer external inducers or modulators of those behaviors.



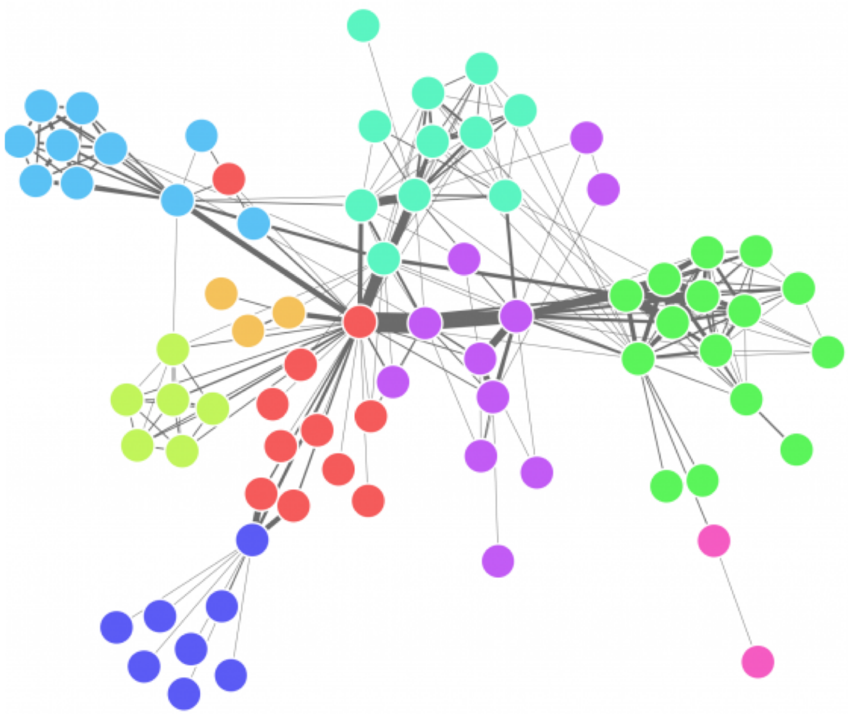
How do brains shape social networks?
How do social ties shape the brain?

Encoding different sorts of network models



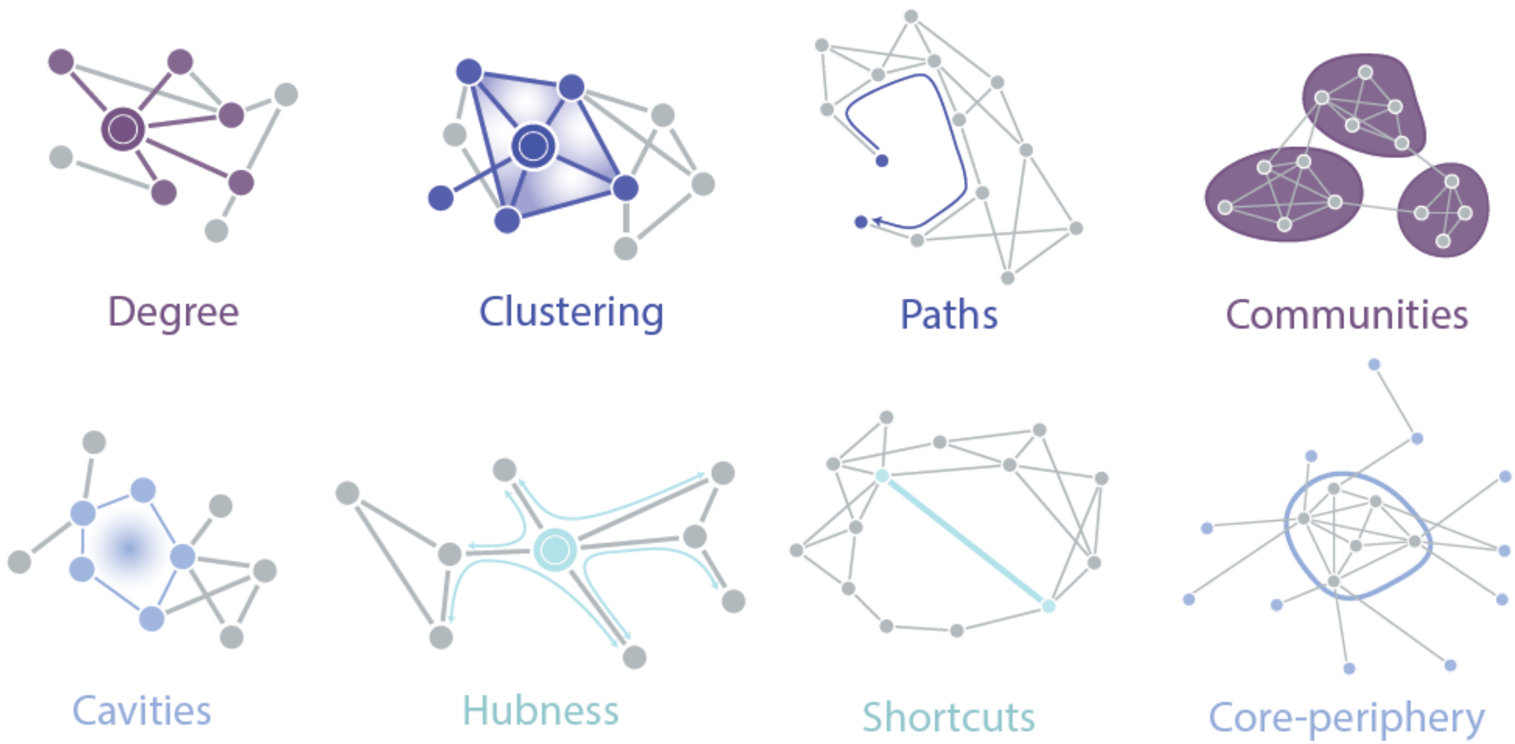
Strengths of the network science approach

- **Flexible framework** that is applicable to many data types, and useful for testing scientific hypotheses in different domains.
- Provides a **rich set of statistical tools**, computational **algorithms**, and **theories** developed in math, physics, engineering, and computer science.



Statistical tools to probe network architecture

Network statistics allow us to quantitatively characterize neural circuits, behaviors, and symptoms characteristic of psychiatric disorders, and to distinguish between groups of subjects either within the disorder or between disorders.



Bassett, Zurn, Gold, 2018 *Nat Rev Neurosci*

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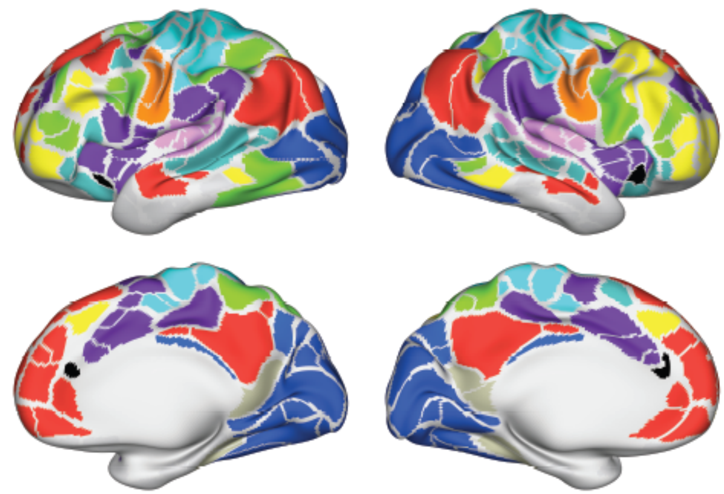
II. Case Study



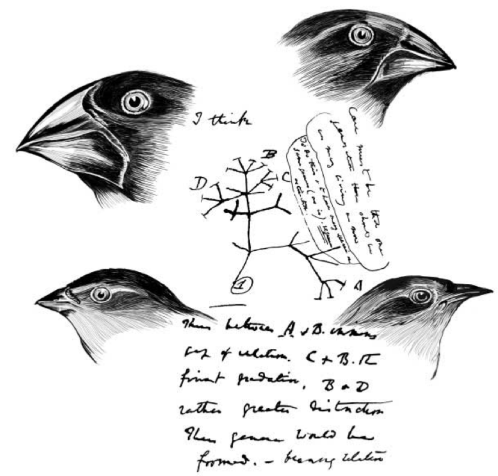
Structural or functional connections between diverse brain areas.

The latter estimated either at rest or during the performance of tasks thought to activate circuits relevant for psychiatry.

Goal: to understand the architecture of structural or functional circuitry underlying cognitive deficits in disorders of mental health.

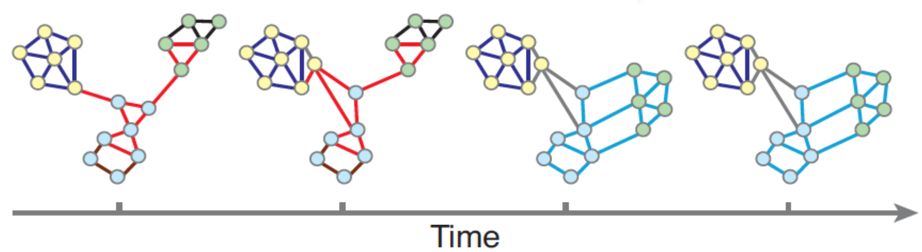
Network substrates for adaptation & learning

Modularity of structure
& morphology



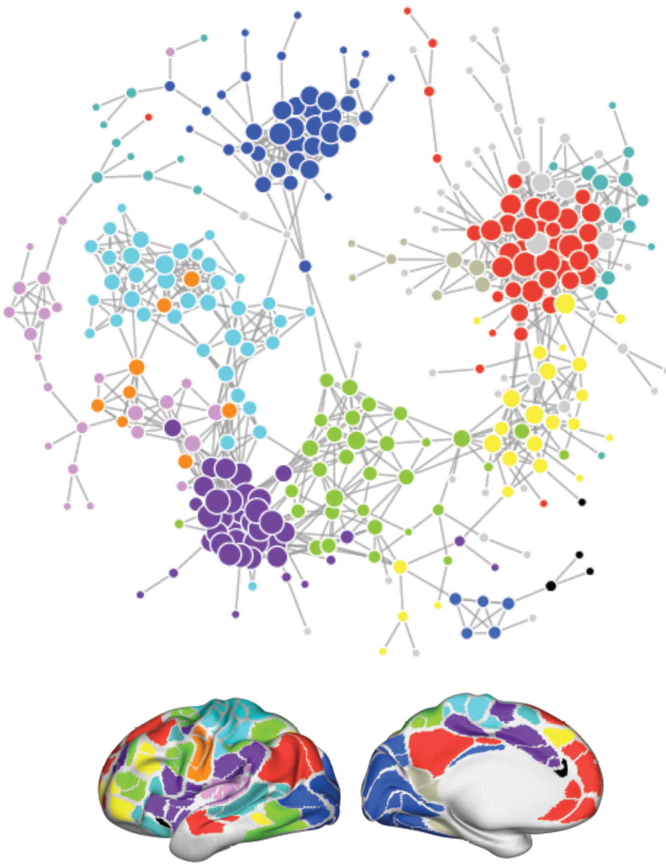
Modularity of mind

Modularity of networks



- Are brain networks modular? Does modularity help us to understand large-scale neural signatures of adaptation and learning?

Theoretical & Computational Challenges



Challenge: Parsimoniously representing and describing complex connectivity patterns.

- Network models
  - Bassett, Zurn, Gold (2018) *Nat Rev Neuro*

Challenge: Detecting modular structure in network models of brain connectivity.

- Modularity maximization (NP Hard)
  - Meunier et al. (2009) *NeuroImage*

$$Q = \sum_{ij} [A_{ij} - P_{ij}] \delta(\sigma_i \sigma_j)$$

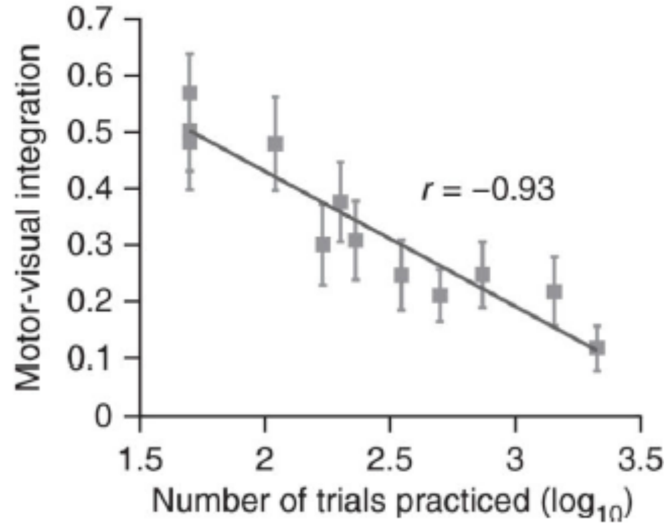
Challenge: Detecting evolving modules.

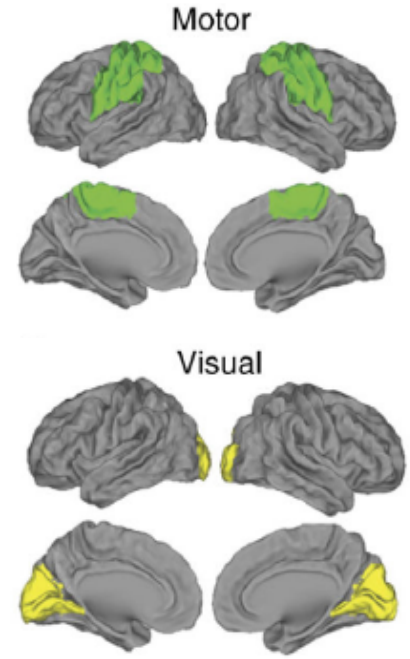
- Multilayer modularity maximization
  - Mucha et al. (2010) *Science*

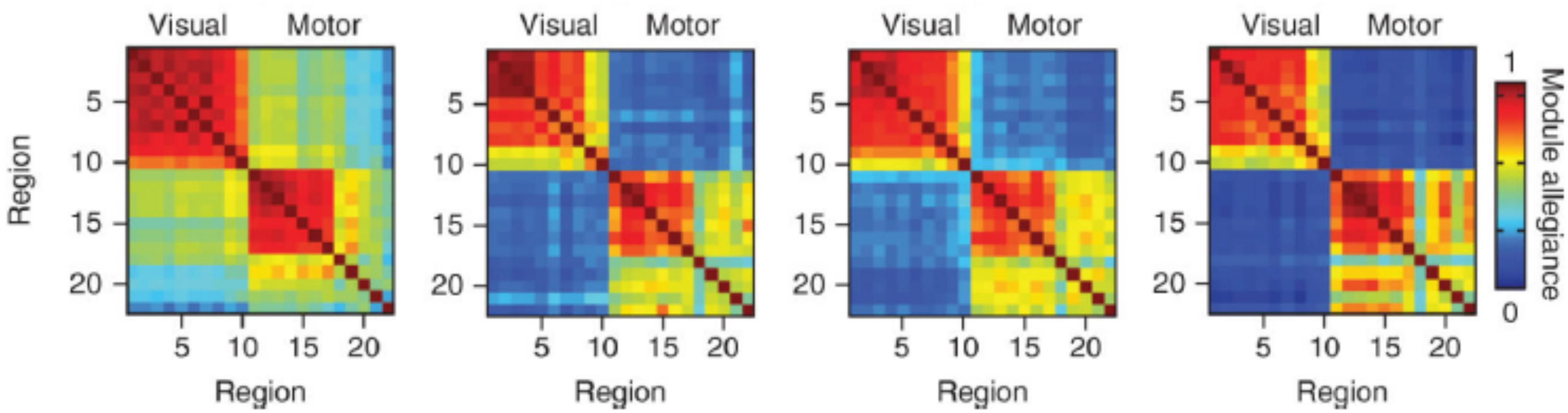
$$Q_{multi} = \frac{1}{2\mu} \sum_{ijls} [(\mathcal{A}_{ijl} - \gamma_l \mathcal{P}_{ijl})\delta_{lm} + \omega_{jlm}\delta_{ij}]\delta(c_{il}, c_{jm})$$

Module Autonomy in Sequence Learning

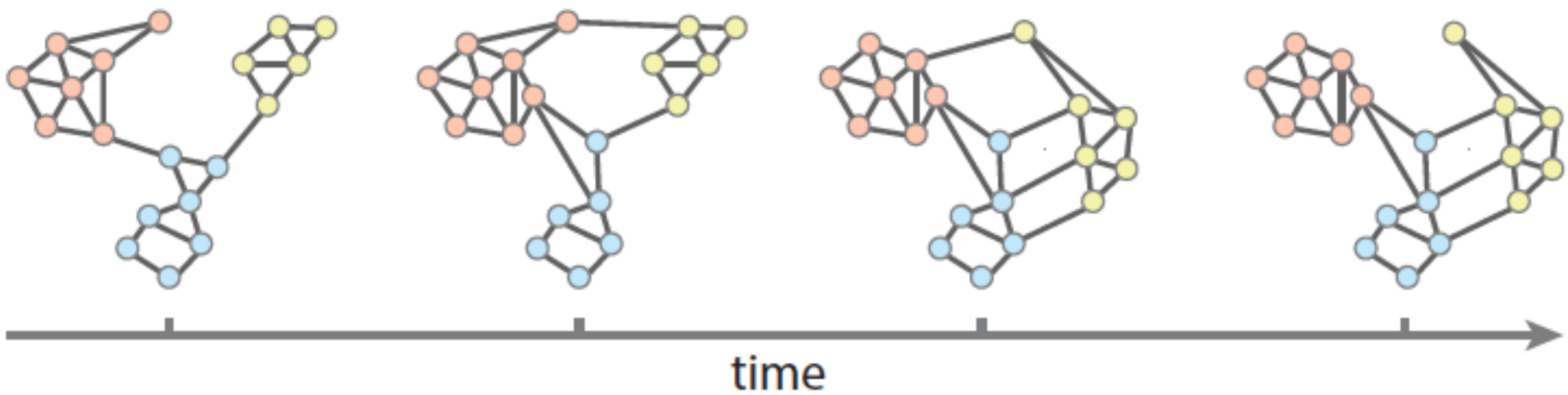
The coherence between motor and visual modules decreased markedly with training, suggesting a growing autonomy.







Flexible modularity supports executive functioning



Flexibility in network modules is predicts individual differences in:

Visuo-motor learning (Bassett et al. 2011 *PNAS*)

Future learning (Mattar et al. 2018 *NeuroImage*)

Learning rate (Gerraty et al., 2018, *J Neurosci*)

Cognitive flexibility (Braun et al. 2015 *PNAS*)

Working memory (Braun et al. 2015 *PNAS*)

(Shine et al. 2016 *Neuron*)

Planning & reasoning (Pedersen et al. 2018 PNAS)

Intermediate Phenotype for Schizophrenia (Braun et al. 2016, *PNAS*)

Medication (Braun et al. 2016, *PNAS*)

Mood (Betzel et al. 2017 *Sci Rep*)

Intervention-related plasticity (Gallen & D'Esposito 2019 TICS)

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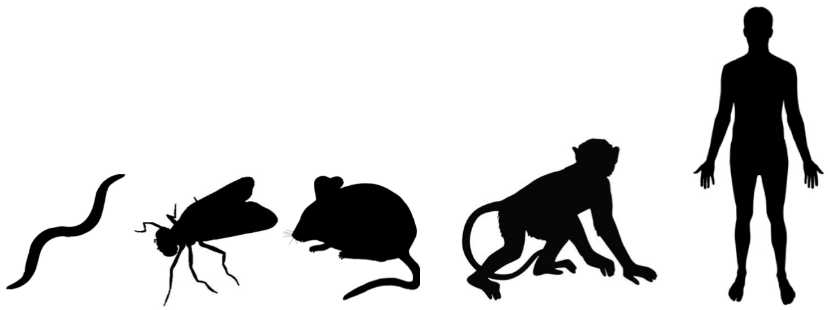
III. Other Uses



1. Neural systems & genetics across species & scales

   Betzel & Bassett Multiscale brain networks (2017) NeuroImage

   Van den Heuvel et al. Comparative connectomics (2016) TICS

   Fornito et al. Connectome & transcriptome (2019) TICS

2. Behavior

   Kahn et al. Network constraints on learnability

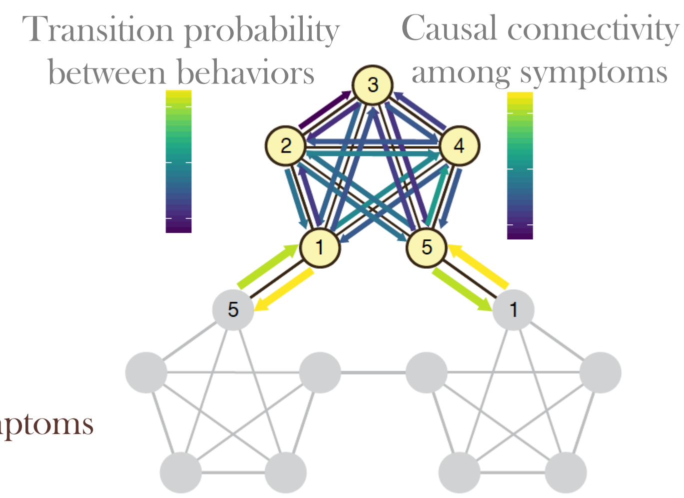
   .... (2018) *Nature Human Behavior*

   Stereotypies, risk-taking, substance use, …

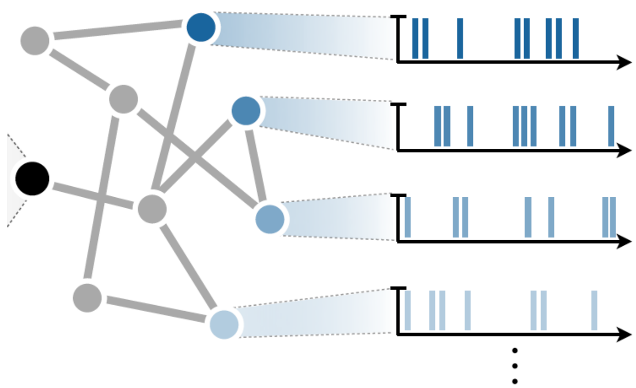
3. Symptoms

   Yang et al. Socioemotional dynamics … of depressive symptoms (2018) *Complexity*

   Anger, anxiety, depressed mood, difficulty concentrating, sleep problems, restlessness …

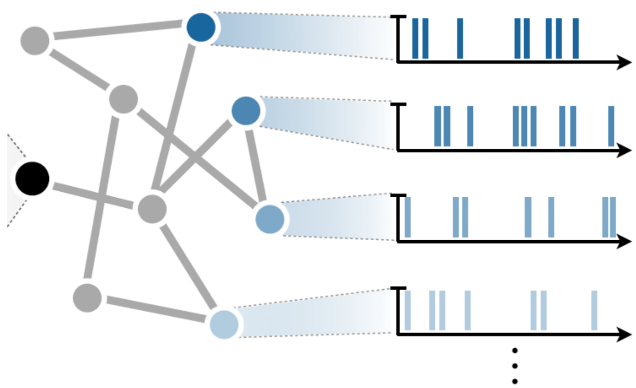


Network Computation



Denk et al. 2012 Nature Reviews Neuroscience

Network Computation

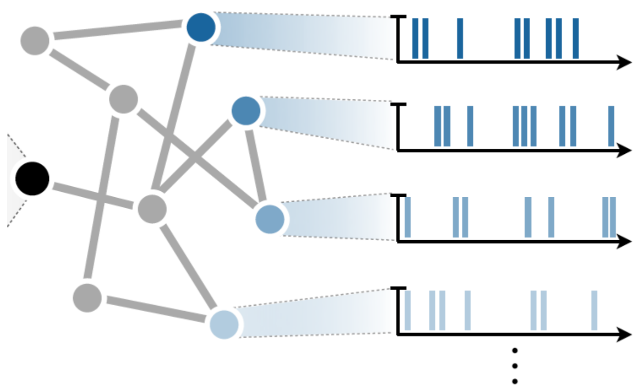


Denk et al. 2012 Nature Reviews Neuroscience

Network Development

Di Martino et al. 2014 Neuron

Network Computation



Denk et al. 2012 Nature Reviews Neuroscience

Network Development

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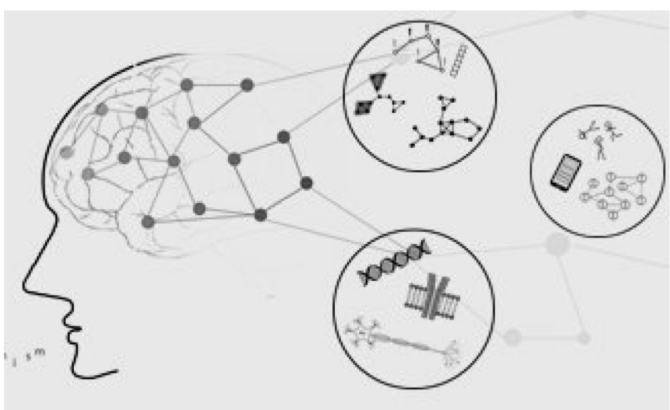
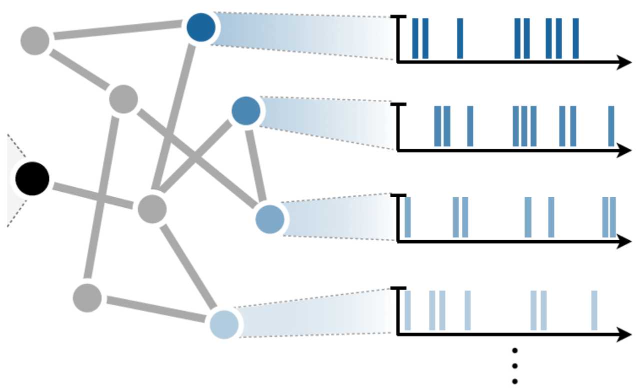
Network Pathology



Stam 2014 Nature Reviews Neuroscience
Braun et al. 2018 Neuron

Network Computation



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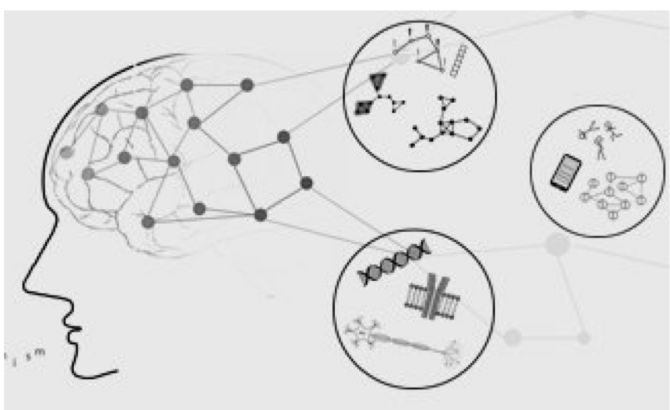
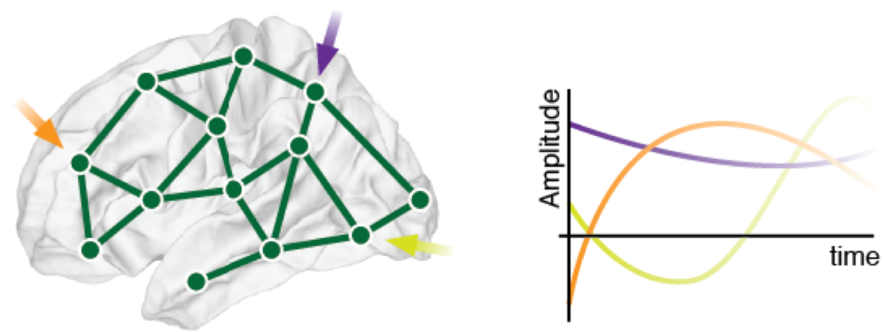


Stam 2014 Nature Reviews Neuroscience
Braun et al. 2018 Neuron

Network Intervention



Tang et al. 2018 Review of Modern Physics

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IV. Models make assumptions

Network science is a modeling assumptions.

Assumption 1: You can separate the system into cleanly delineated units.

Assumption 2: You can define the most salient relations or connections between units.

Assumption 3: From the structure of the connectivity pattern, one can learn about a system's organization, make educated guesses about its function, and build models of its development, growth, or evolution

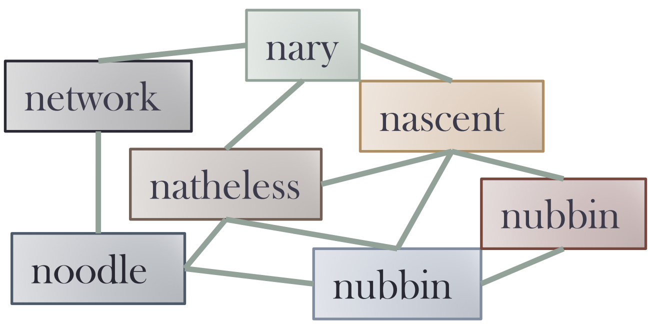
Example violations of assumptions

Ocean currents

Fluid dynamics

Orchestra

Music Theory



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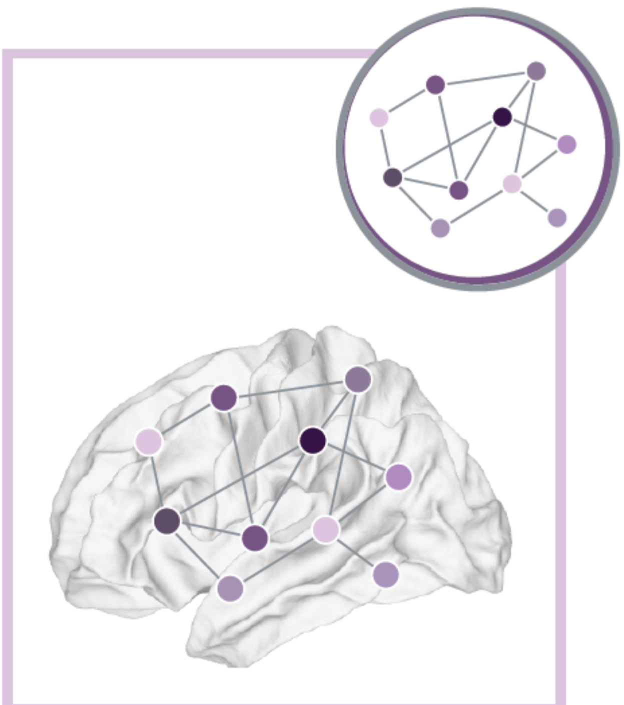
Evaluating and testing the validity of network models

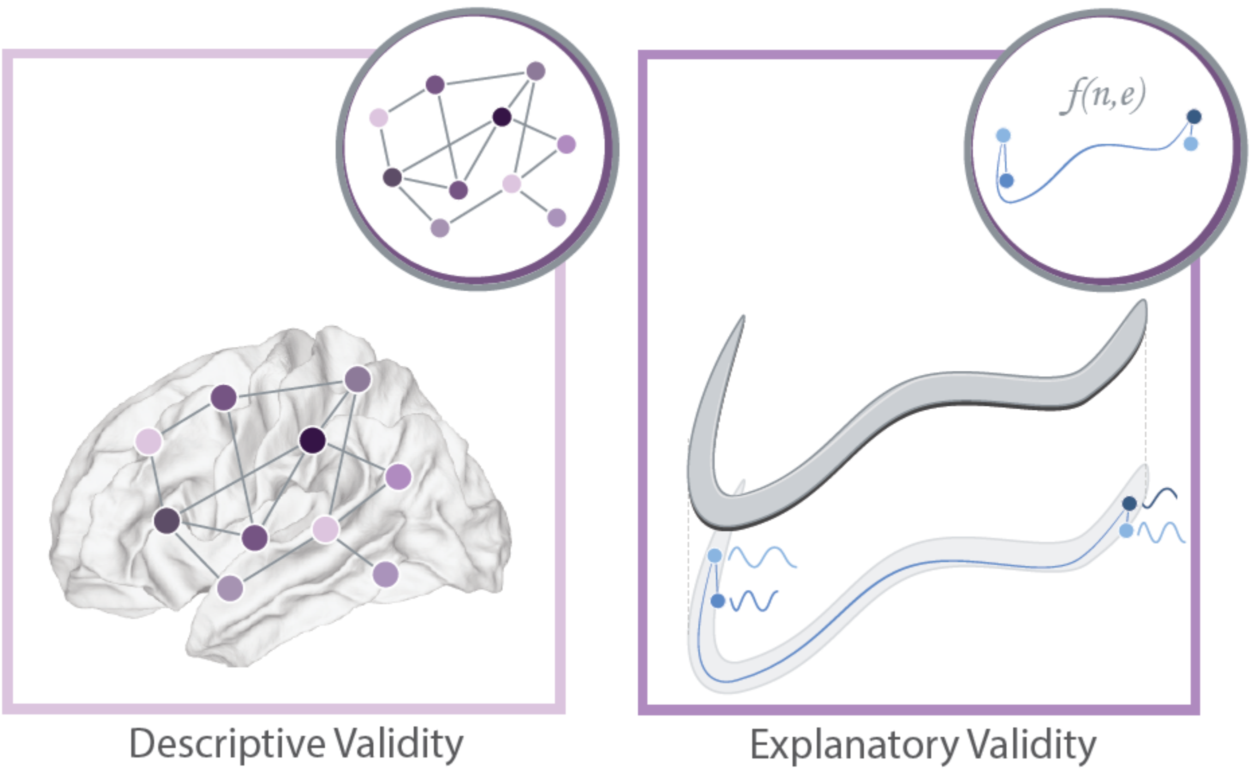


Descriptive Validity

The validity of a particular network model depends on the goals of its use and the domains of its application.

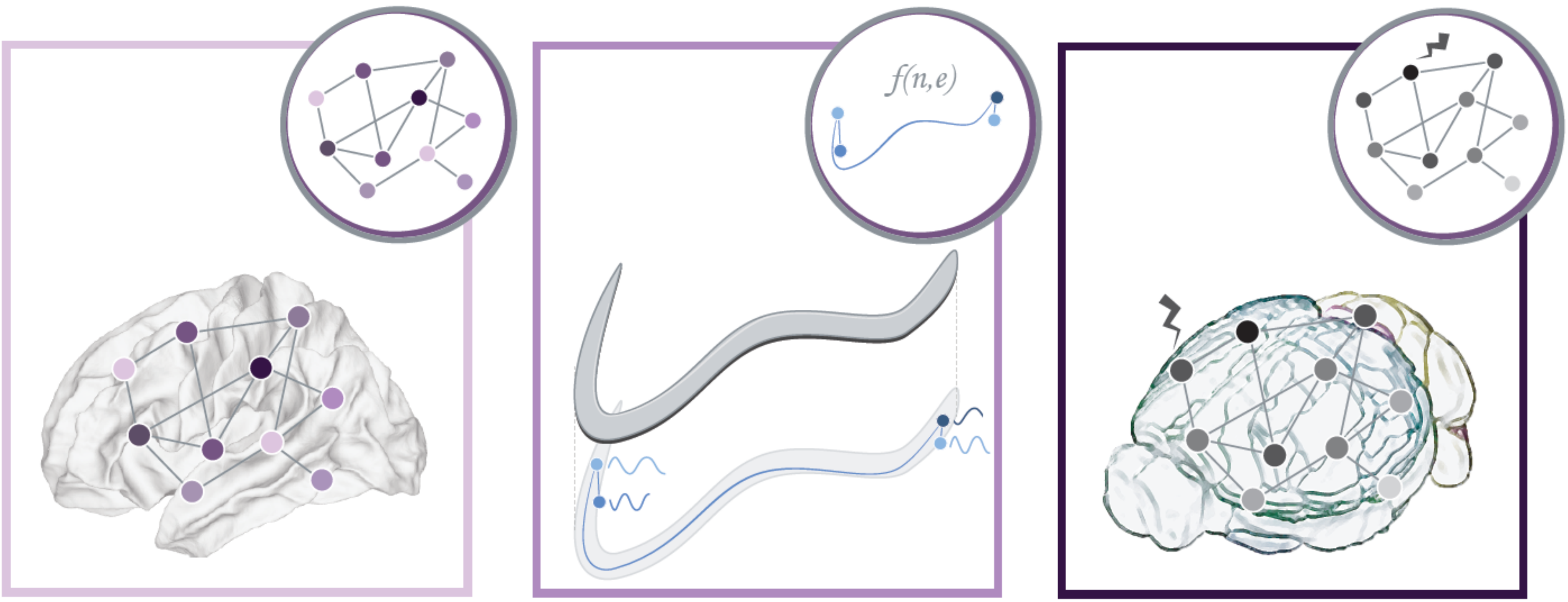
Descriptive validity addresses the question of whether the model resembles in some key way(s) the system it is constructed to model. It aligns with questions about how well the specific patterns of nodes and edges matches the anatomical and/or functional data that it represents.

Validity of network models



Explanatory validity focuses on a theoretical construct used to develop statistical tests and support conclusions drawn from the use of the model. It addresses whether a network's architecture can be justified from data and used to test for causal relations to dynamics or behavior based on that architecture.

Validity of network models



Descriptive Validity

Explanatory Validity

Predictive Validity

Predictive validity occurs when there is an organism-model correlation in response to a perturbation, such as a drug, electrical or chemical stimulation, neurofeedback, or training.

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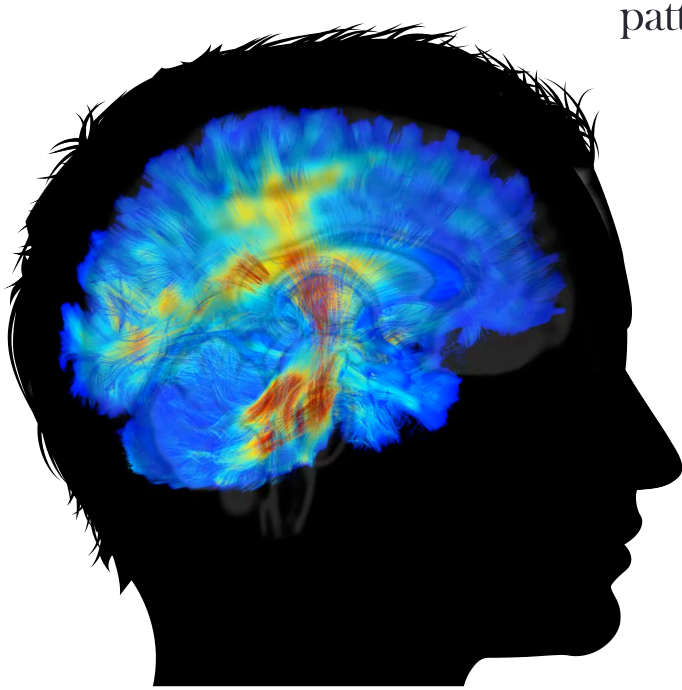
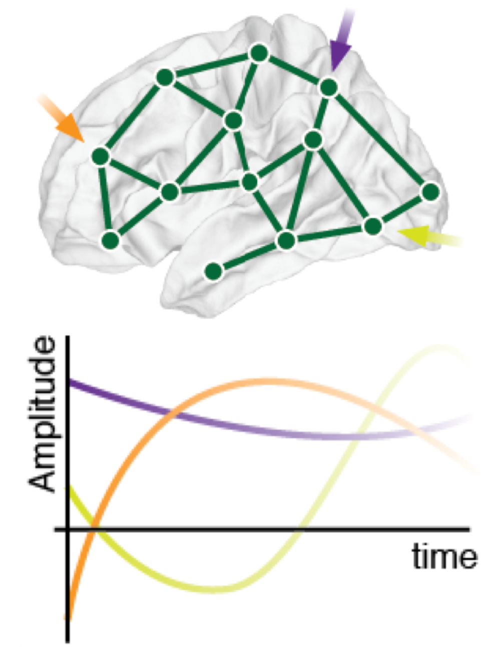
V. Options: Moving closer to predictive validity

First note that the propagation of signals in a networked system depends on the pattern of links.



What we have: A network of structural links empirically measured by neuroimaging.



What we seek: A theory for how a change in activity in one region affects activity in other regions.

Formalizing the Problem of Network Control

- Neural processes can be approximated by linearized generalizations of nonlinear models of cortical circuit activity (Galan 2008; Honey et al. 2009).
- We consider a noise-free linear discrete-time and time-invariant network model:

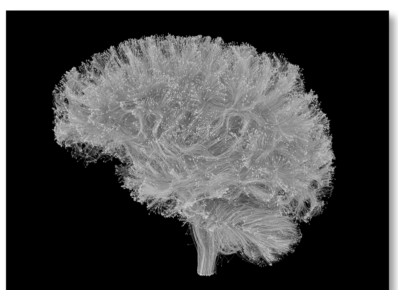
Number of regions being controlled

$$x(t+1) = Ax(t) + B_{\mathcal{K}} u_{\mathcal{K}}(t)$$

State of brain regions over time

Weighted adjacency matrix

Control energy



Gu et al. (2015) *Nature Communications*; Tang et al. (2017) *Nature Communications*

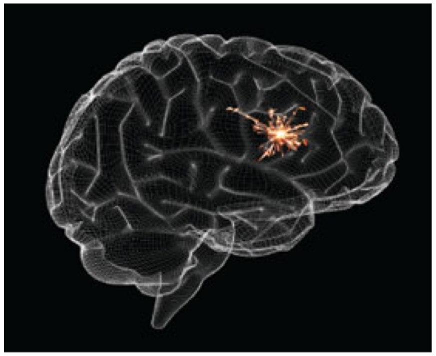
Is the brain theoretically controllable?

How controllable the network is can be estimated using the smallest eigenvalues of the T-steps controllability Gramian:

$$W_{\mathcal{K},T} = \sum_{\tau=0}^{T-1} A^{\tau} B_{\mathcal{K}} B_{\mathcal{K}}^{\mathsf{T}} (A^{\mathsf{T}})^{\tau}$$

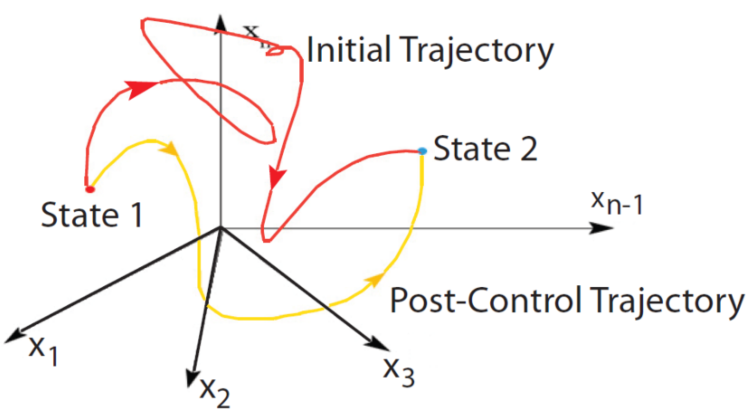
For brain networks, this value was small: 2.5 x 10^(-23)

- Practically extremely hard to control



Types of driver nodes

- Which regions of the brain are most efficient or most difficult to control?

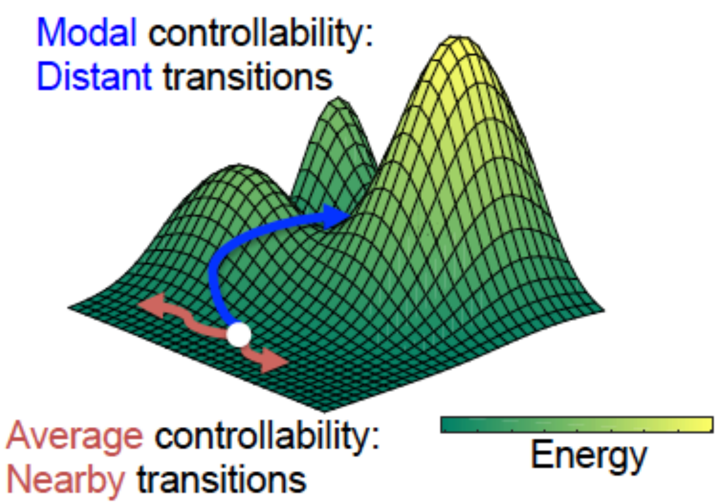


A couple control strategies:

1. **Average Controllability:** Steer to many easily reachable states

2. **Modal Controllability:** Steer to few difficult to reach states

Average and modal control



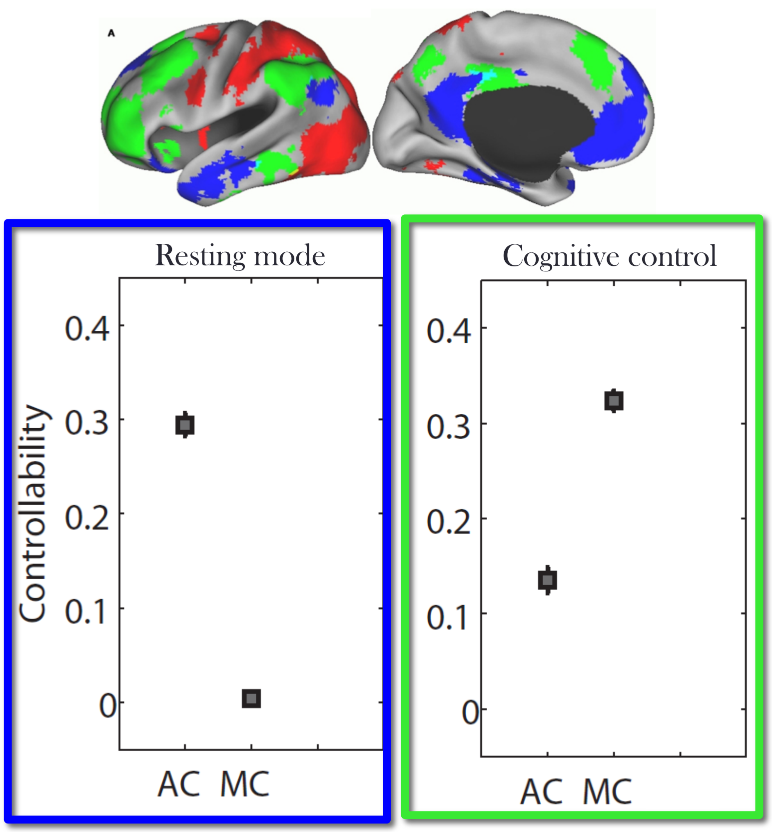
$$x(t+1) = Ax(t) + B_{\mathcal{K}} u_{\mathcal{K}}(t)$$

$$W_{\mathcal{K},T} = \sum_{\tau=0}^{T-1} A^{\tau} B_{\mathcal{K}} B_{\mathcal{K}}^{\mathsf{T}} (A^{\mathsf{T}})^{\tau}$$

Average: Trace(W_K^{-1}))

Modal: Let v_j be the j^{th} eigenvector of A with eigenvalue λ_j. Then if v_{ij} is small, then the j^{th} mode is poorly controllable from node *i*. Define $\phi_i = \sum_{j=1}^{N} (1 - \lambda_j^2(A)) v_{ij}^2$ as a scaled measure of controllability of all *N* modes from region *i*.)

Controllability profiles differ across brain regions



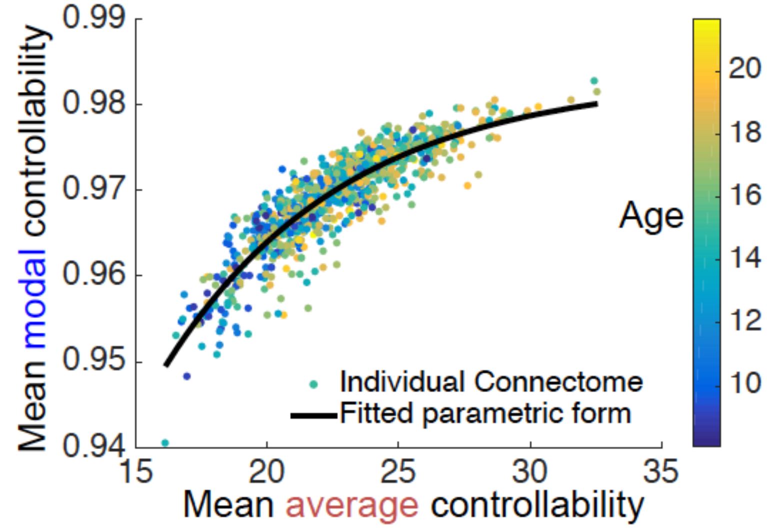
AC = average controllability
MC = modal controllability

Regions known to affect **transient control** of cognition are high in modal controllability, and are therefore structurally predisposed to push the brain to **difficult-to-reach** states.

Regions active at rest show white matter connectivity patterns predicted to effectively drive the brain to **nearby** brain states.

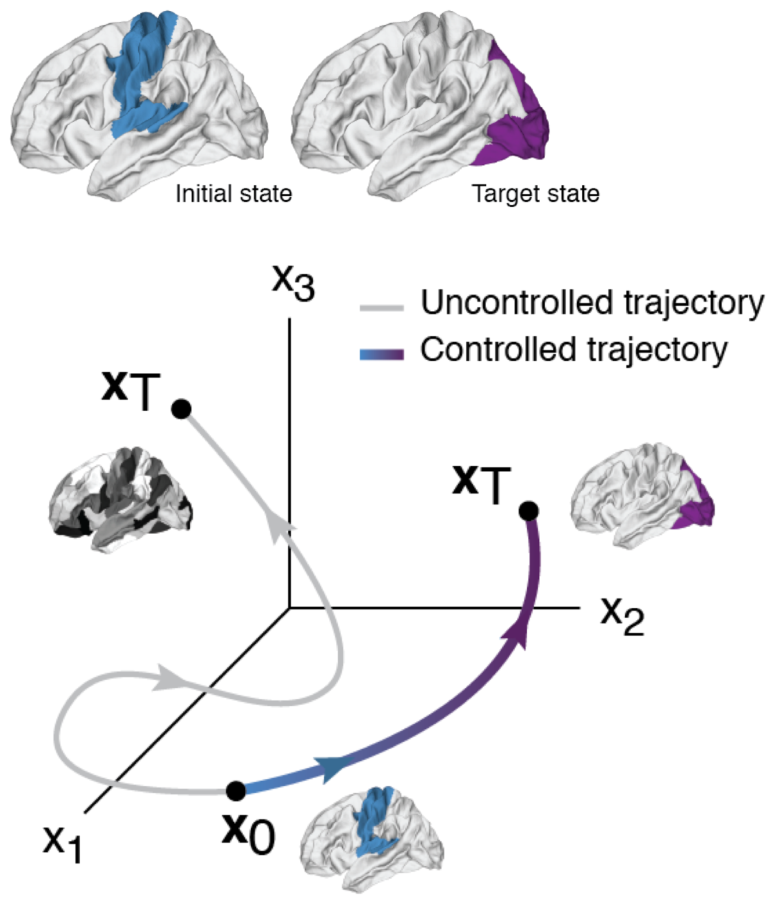
Network control as a mechanism to effect cognition

- Different brain regions have more or less power to alter whole-brain dynamics
  (Gu et al. 2015 *Nature Communications*)
- The capacity for brain regions to change brain dynamics grows as children develop
  (Tang et al. 2017 *Nature Communications*)
- Youth with greater network control also score better on cognitive tasks
  (Cornblath et al. 2018 NeuroImage)



Together, these results suggest that our theory is a useful marker of how the brain enacts control to change network function.

Precise control of specific state transitions



<u>What we want</u>

- Finite time, Finite energy,
- Multi-point control
- Initial state, Target state

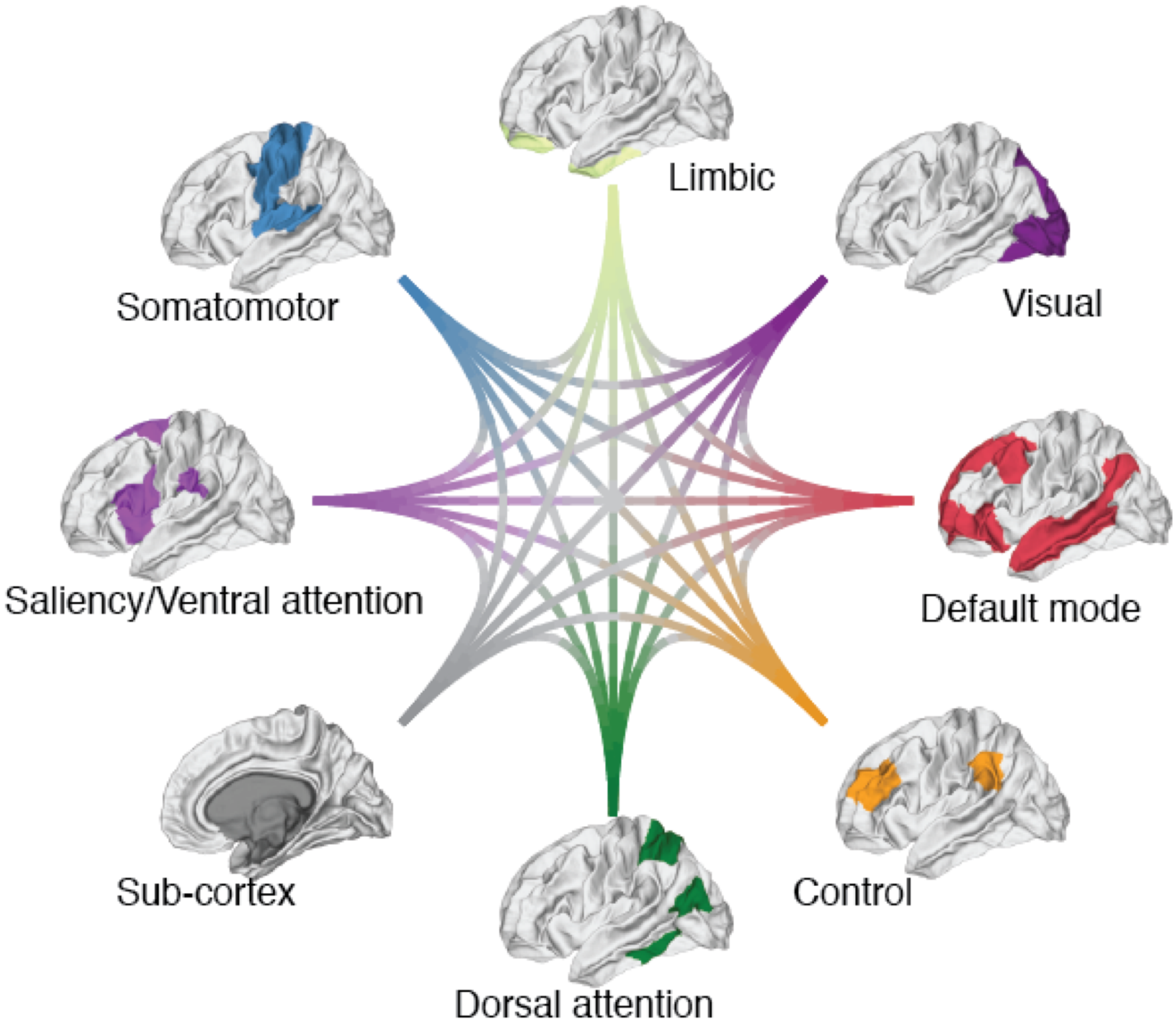
Define model of network dynamics.

$$x(t+1) = Ax(t) + B_{\mathcal{K}} u_{\mathcal{K}}(t)$$

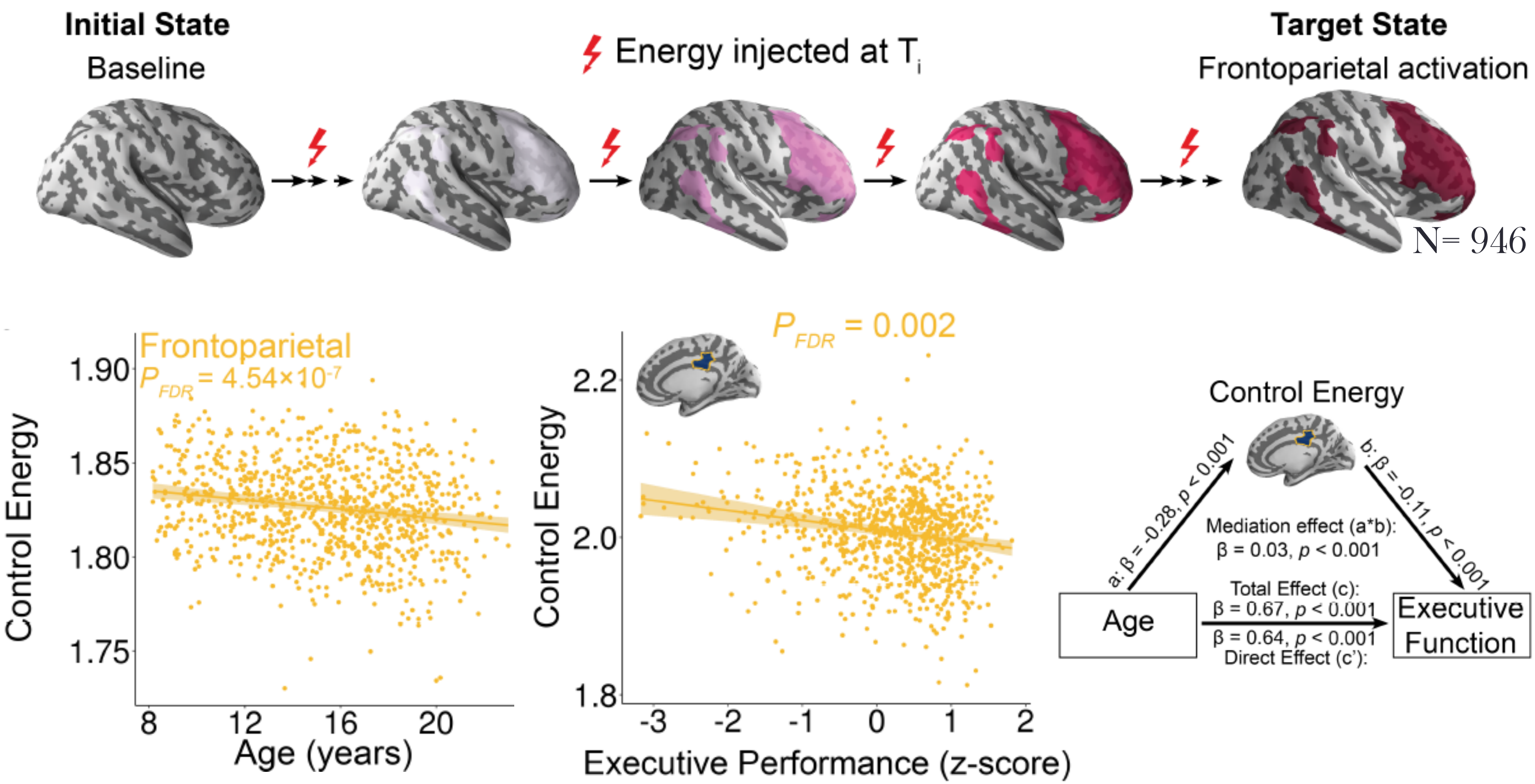
Define a cost function penalizes energy and distance of x(t) from the target state.

$$\min_{\mathbf{u}} \int_0^T (\mathbf{x}_T - \mathbf{x})^T (\mathbf{x}_T - \mathbf{x}) + \rho \mathbf{u}_{\mathcal{K}}^T \mathbf{u}_{\mathcal{K}}$$

Betzel et al. (2016) *Scientific Reports*; Gu et al. (2017) *Neuroimage*

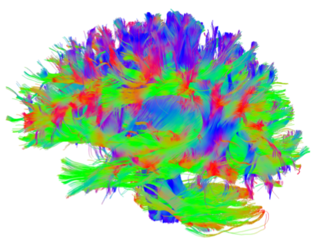

Limbic
Somatomotor
Visual
Saliency/Ventral attention
Default mode
Sub-cortex
Control
Dorsal attention

Probing recruitment of the executive system

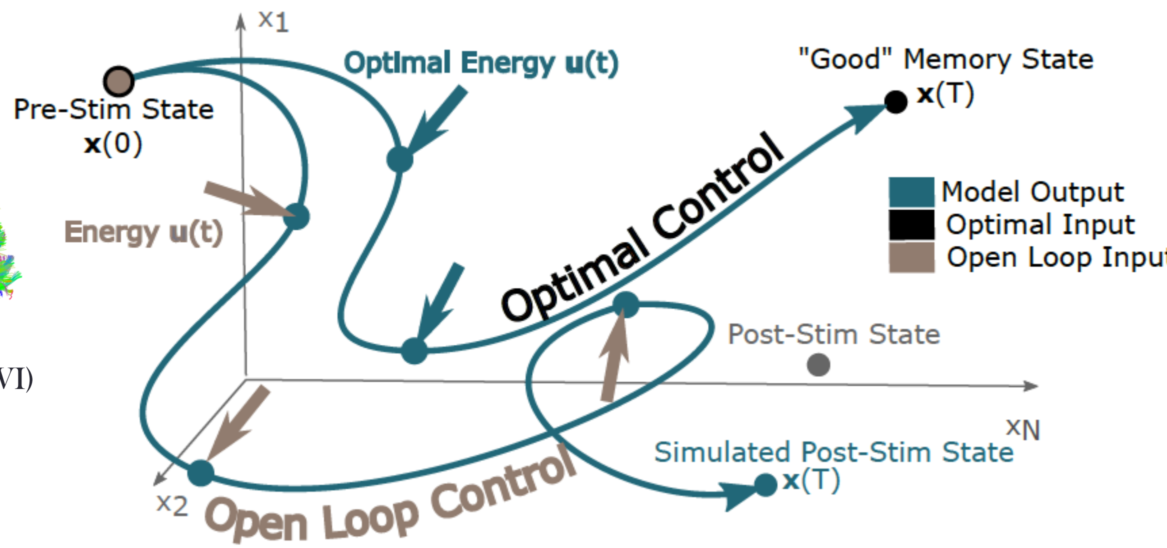


Extending to exogenous control signals

How does white matter network architecture guide direct electrical stimulation through optimal state transitions?

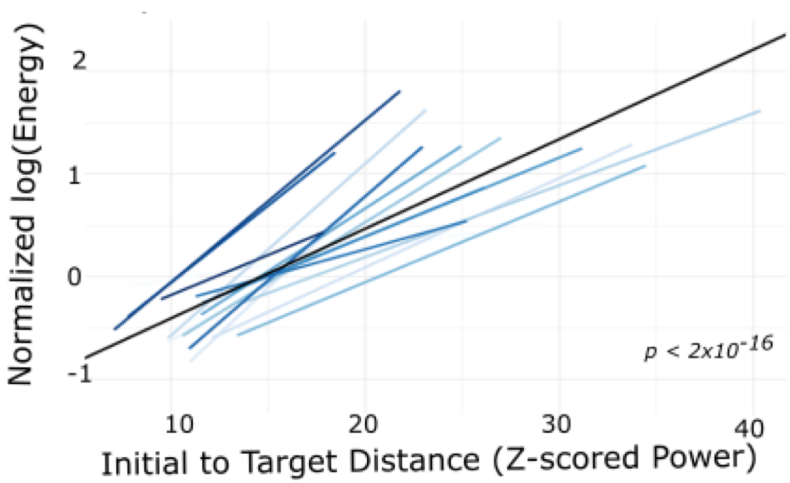


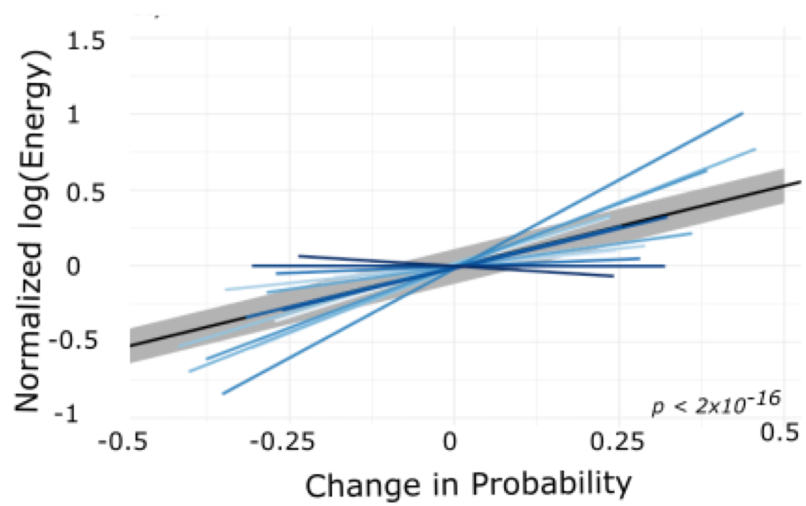
Diffusion Imaging (DWI)



Energy requirement depends on extent of transition

When enacting an optimal control transition from an initial state to a good memory state, the required energy depends on the distance in state space to be traversed …





… and on the differences in cognitive state.

In fact, we can predict with 93.2% accuracy the energy required for a state transition using (i) transition distance, (ii) network topology, (iii) stimulation target.

Stiso et al. 2019 *Cell Reports*

Danielle S. Bassett

Brief Outline

I. Introduction to and background for the computational framework

II. Case study of one form of its application

III. Short description of other uses

IV. Limitations of the technique, rules of the road problems, perils

V. Options

VI. Summary

VI. Summary: Network Neuroscience for Psychiatry

Where we are and where we could go

- Network science is one approach to address the complexity of neurobiological underpinnings of cognition, and its alteration in psychiatric conditions.
- The approach is flexible across data types, and provides statistics that can help us to quantitatively characterize networks representing neural circuits, behavioral transitions, and symptoms.
- It is fundamentally a modeling endeavor, with explicit assumptions. Care must be taken in choosing systems and scientific questions for which those assumptions are not violated.
- When engaging in the modeling endeavor, it behooves us to think carefully about model validation.
- Network control theory offers an option that could push us closer to predictive validity.

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