Brain wiring dictates signaling. But also: brain signaling dictates wiring

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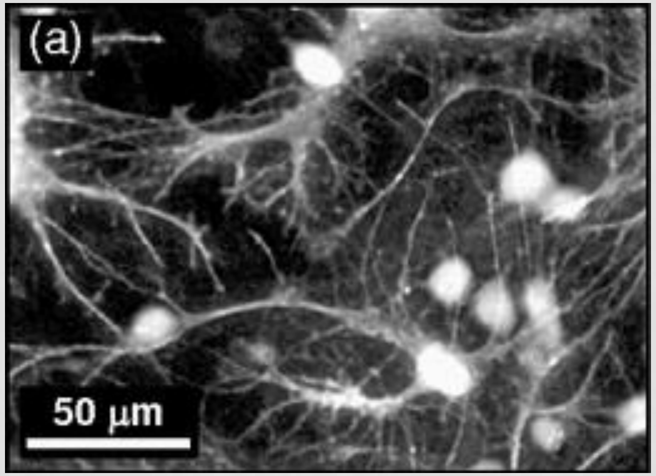
The brain is a network of neurons and synapses

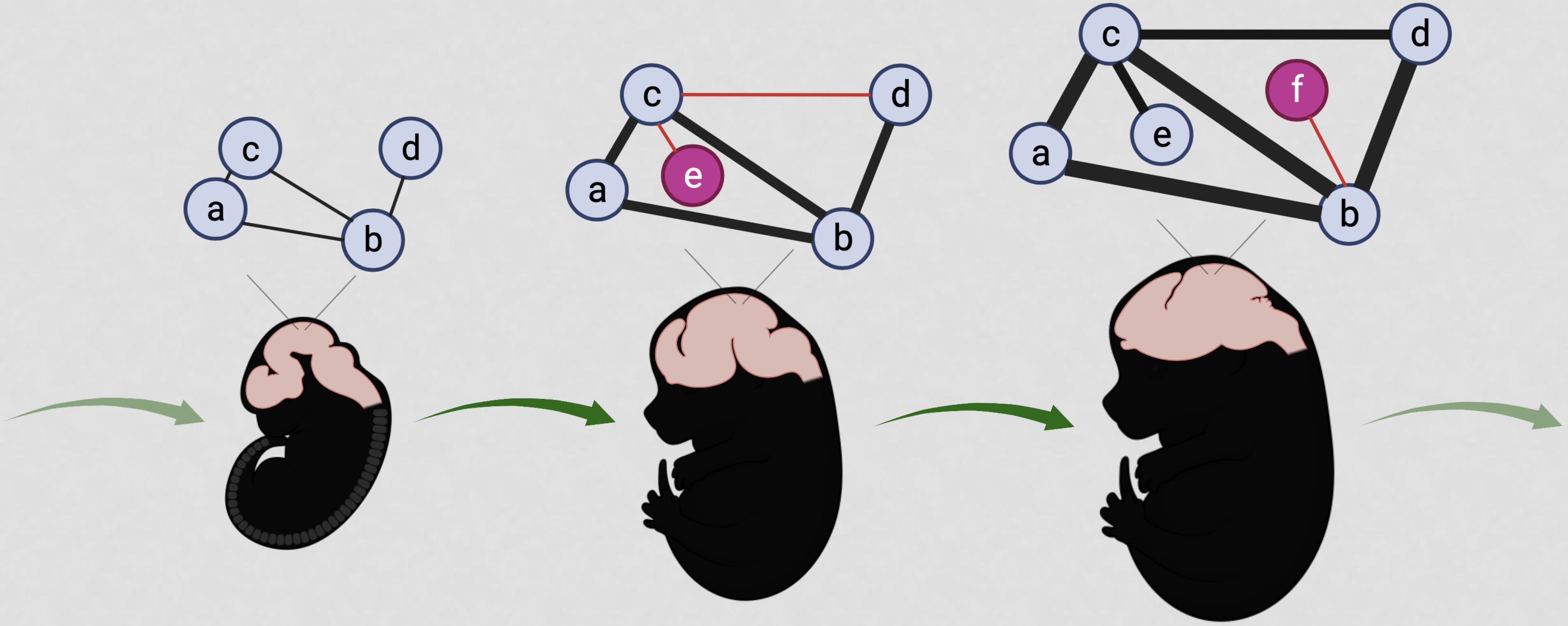
Brainline.org



Breskin et al. (2006)

- 86 billion neurons
- ~100 trillion synapses

Part 1) How do neurons grow into a fully connected brain?

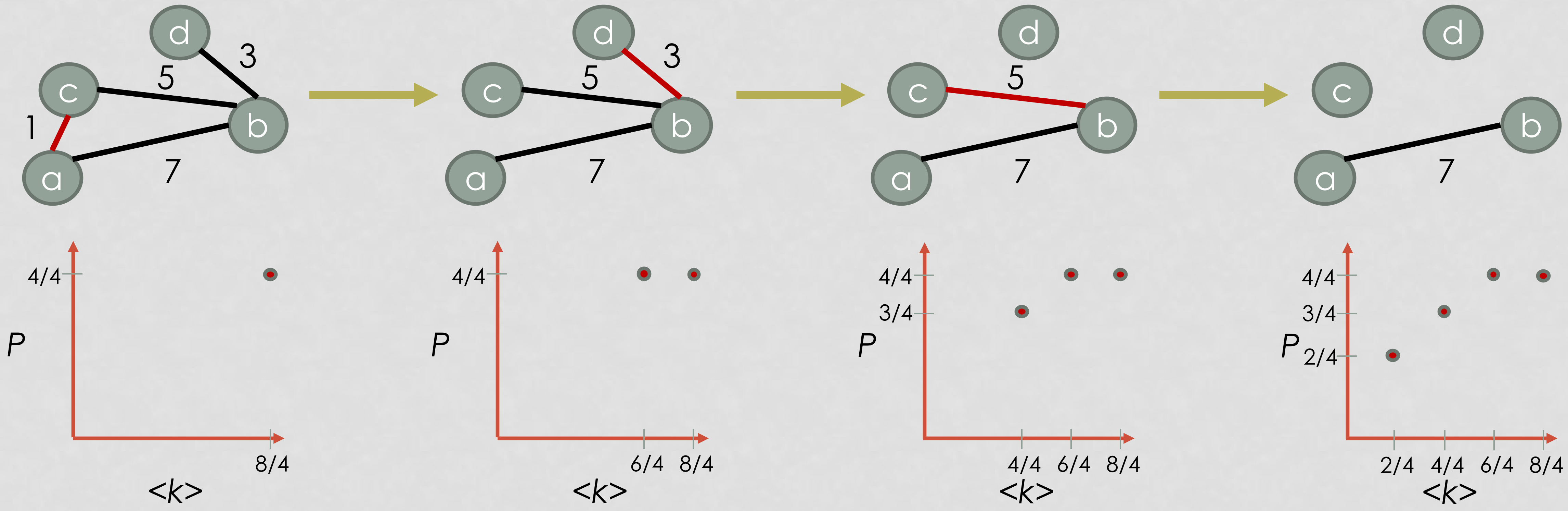


How do neurons grow into a fully connected brain?

A. Random graph?
B. Preferential attachment?
C. Small-world network?
D. Or something else??

Targeted Attack can generate development trajectory

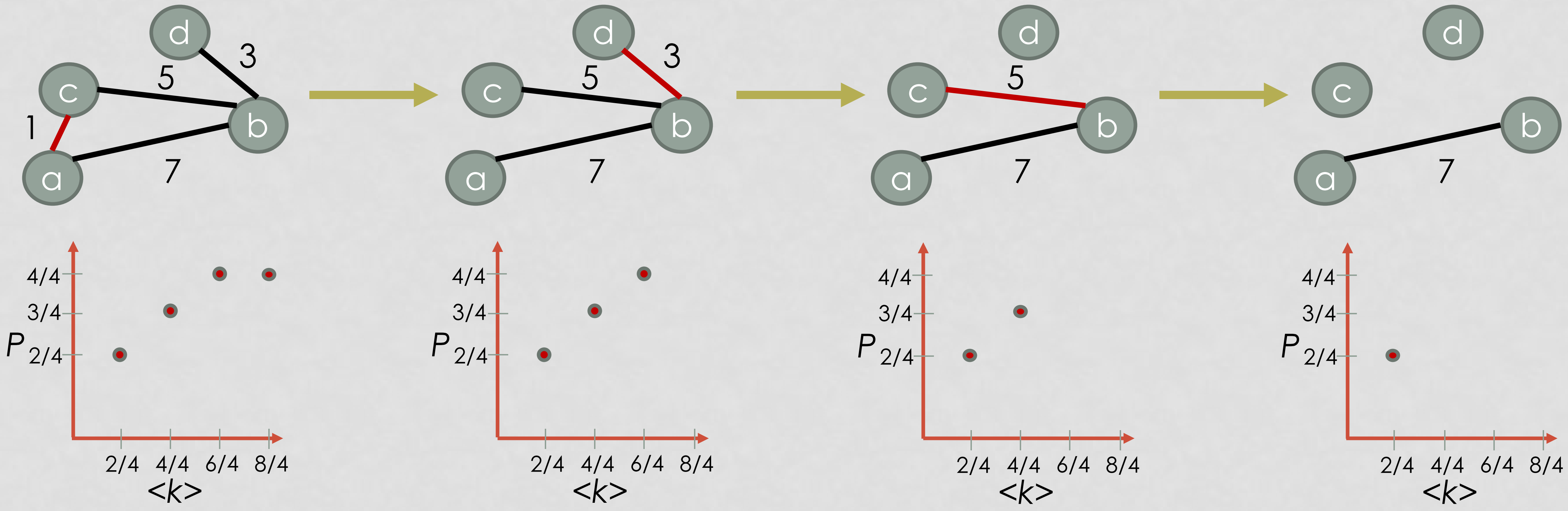
Example: targeted attack procedure on increasing tract lengths



P = probability in giant cluster; $<k>$ = average degree

Targeted Attack can generate development trajectory

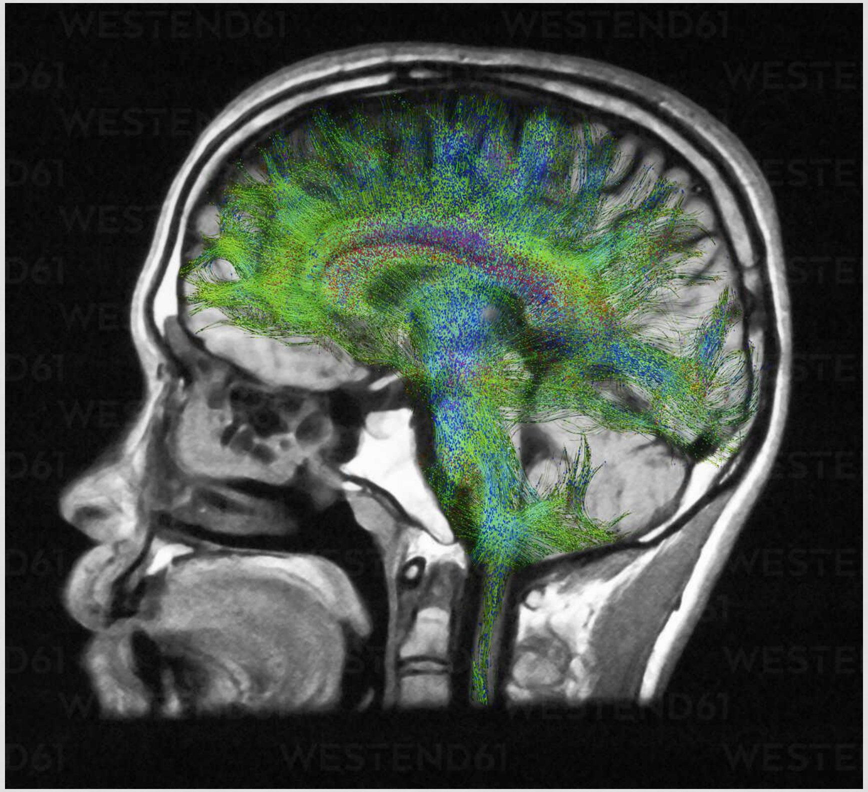
Example: targeted attack procedure on increasing tract lengths



P = probability in giant cluster; $\langle k \rangle$ = average degree

Diffusion MRI measures white matter tracts (bundles of axons) between brain regions

Brain image



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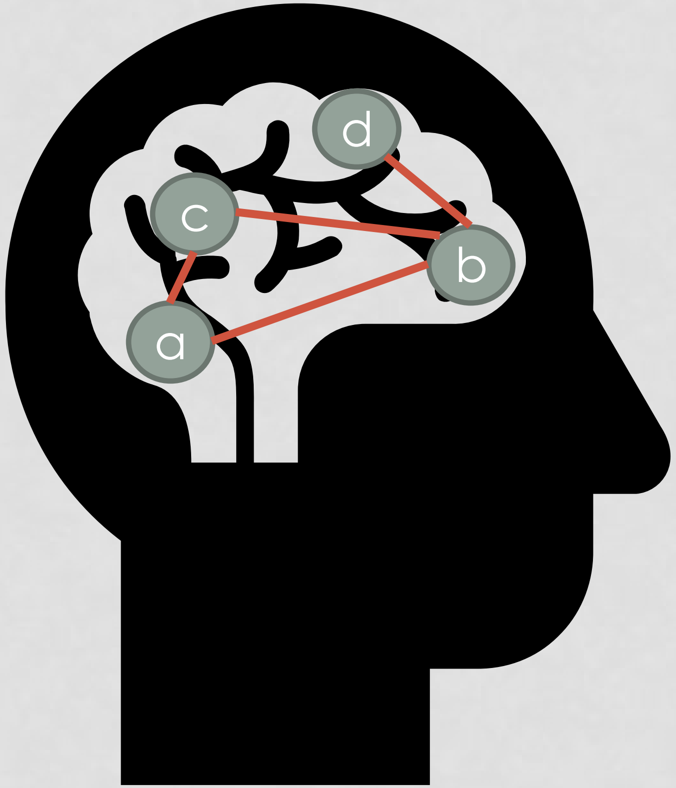
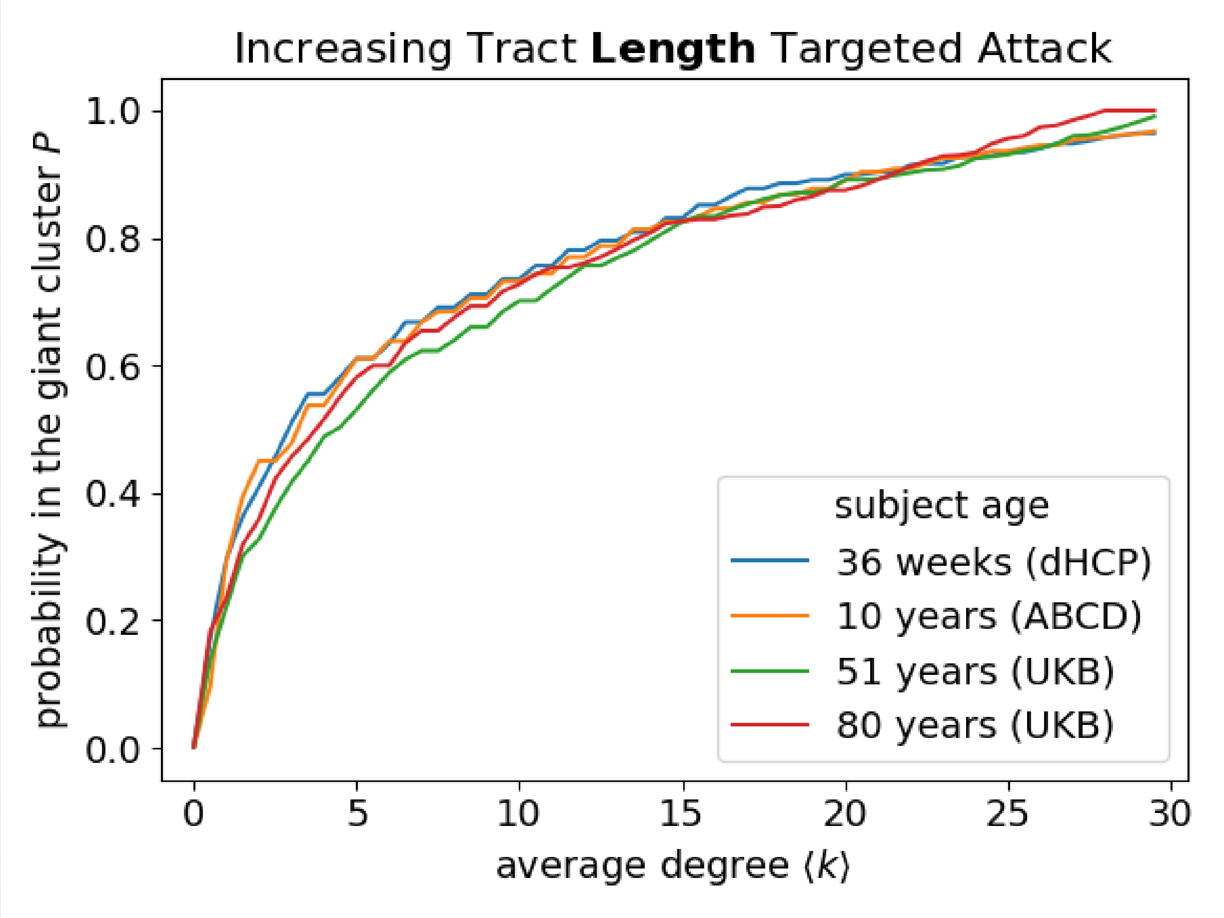
Connectivity matrix

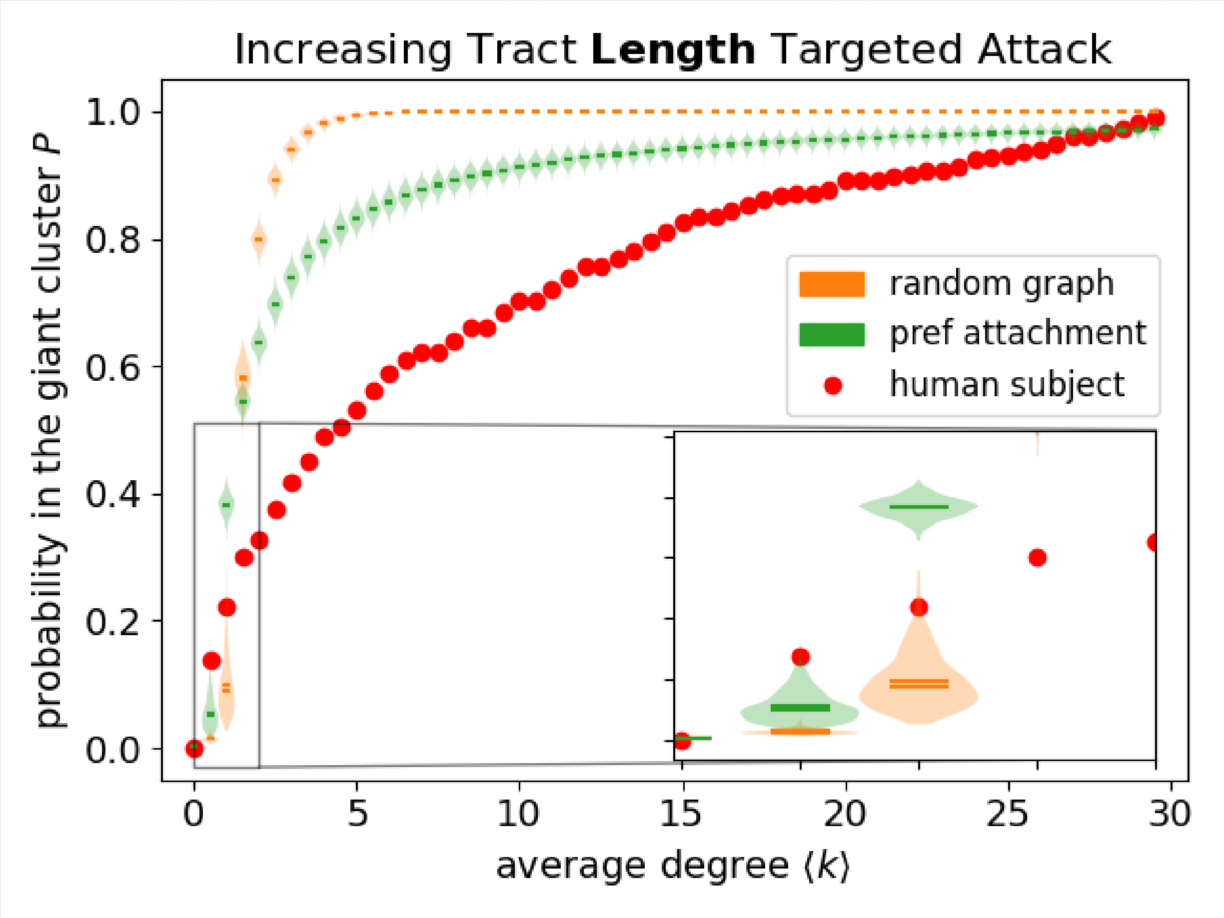


Increasing length targeted attack reflects fetal development

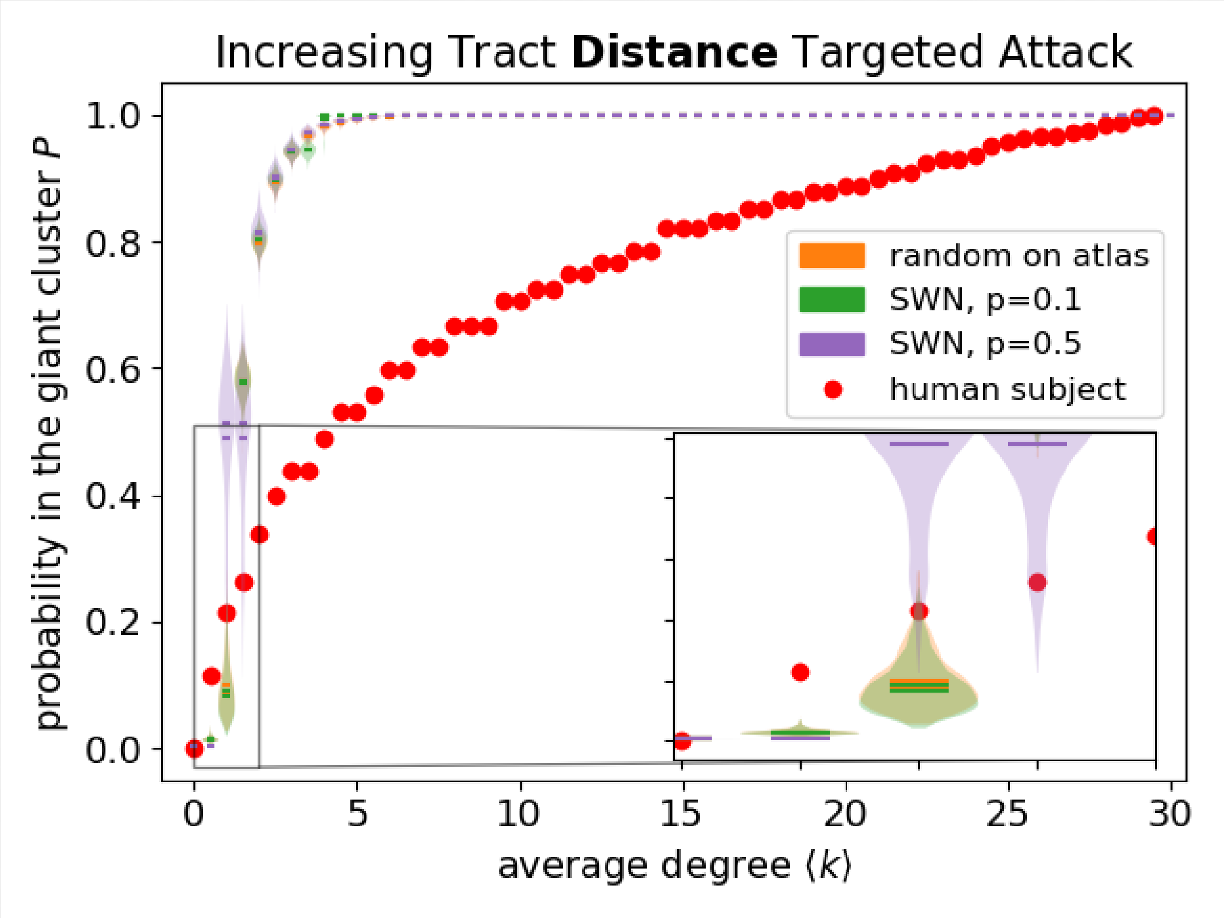


RR et al. (2023)

~~Random graph~~ and ~~preferential attachment~~

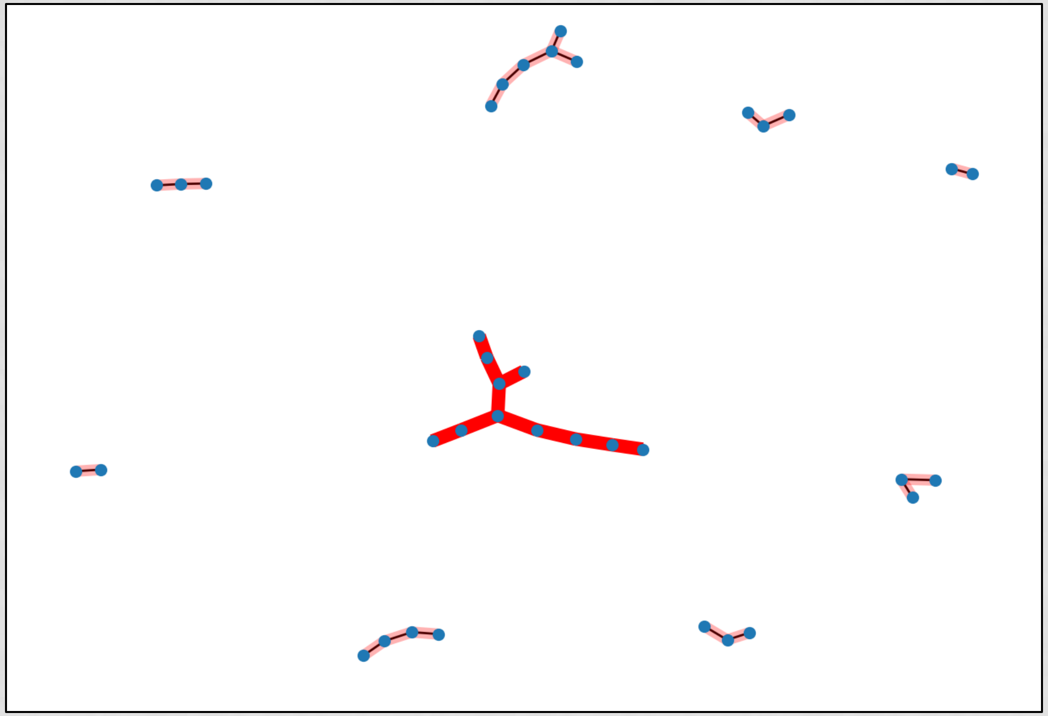


~~Small-world network~~

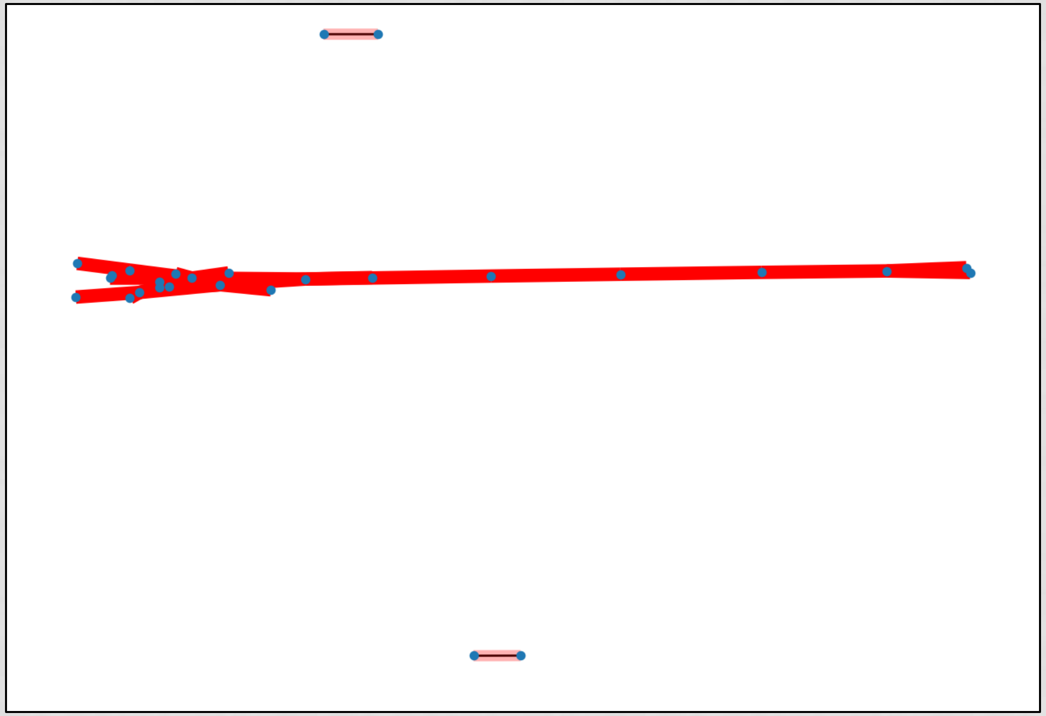


The brain essentially has one cluster

Random graph simulation



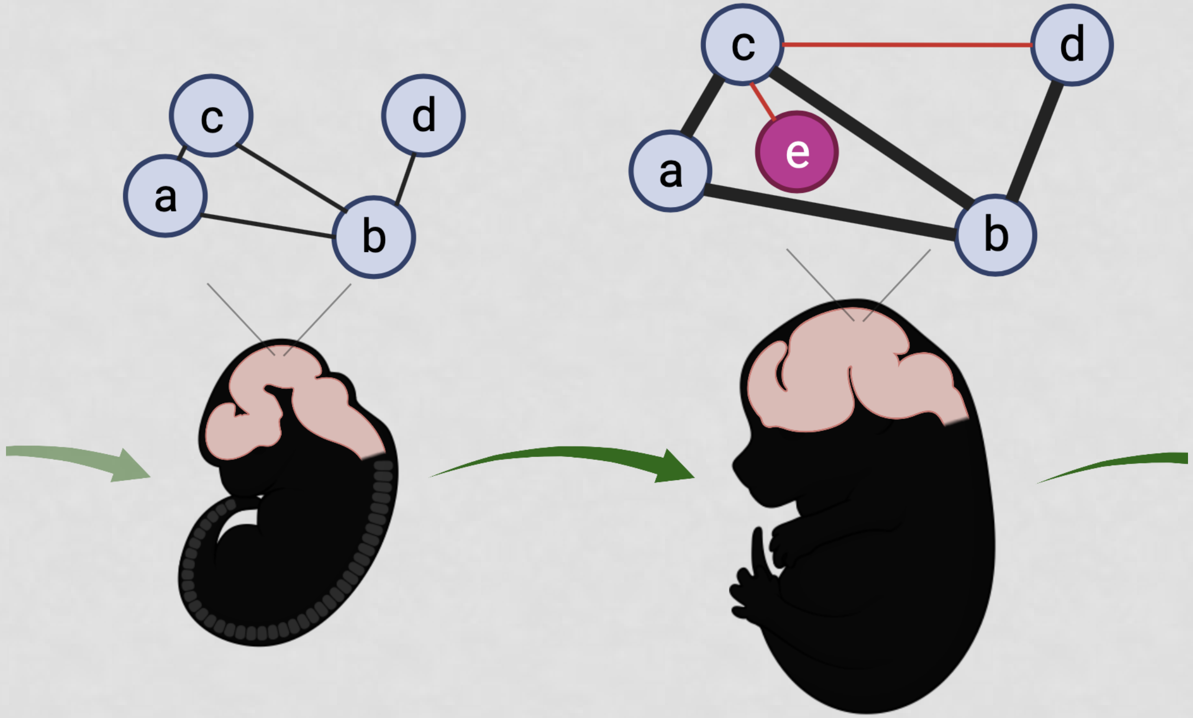
Brain network



Giant Cluster Self Preference theory

- Edge addition can occur:

1. within pre-existing nodes
2. pre-existing node and newly created node



Giant Cluster Self Preference theory

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1. within pre-existing nodes
2. pre-existing node and newly created node

Transition probability to grow *n* nodes and *E* edges:

$$p(n \rightarrow n+1 | E \rightarrow E+1) = \frac{\frac{1}{\alpha}n(N-n)}{\frac{1}{2}n(n-1) - E + \frac{1}{\alpha}n(N-n)}$$

N := number of nodes at end of development

$1/\alpha$:= probability of forming a new node (*fit to experiment)

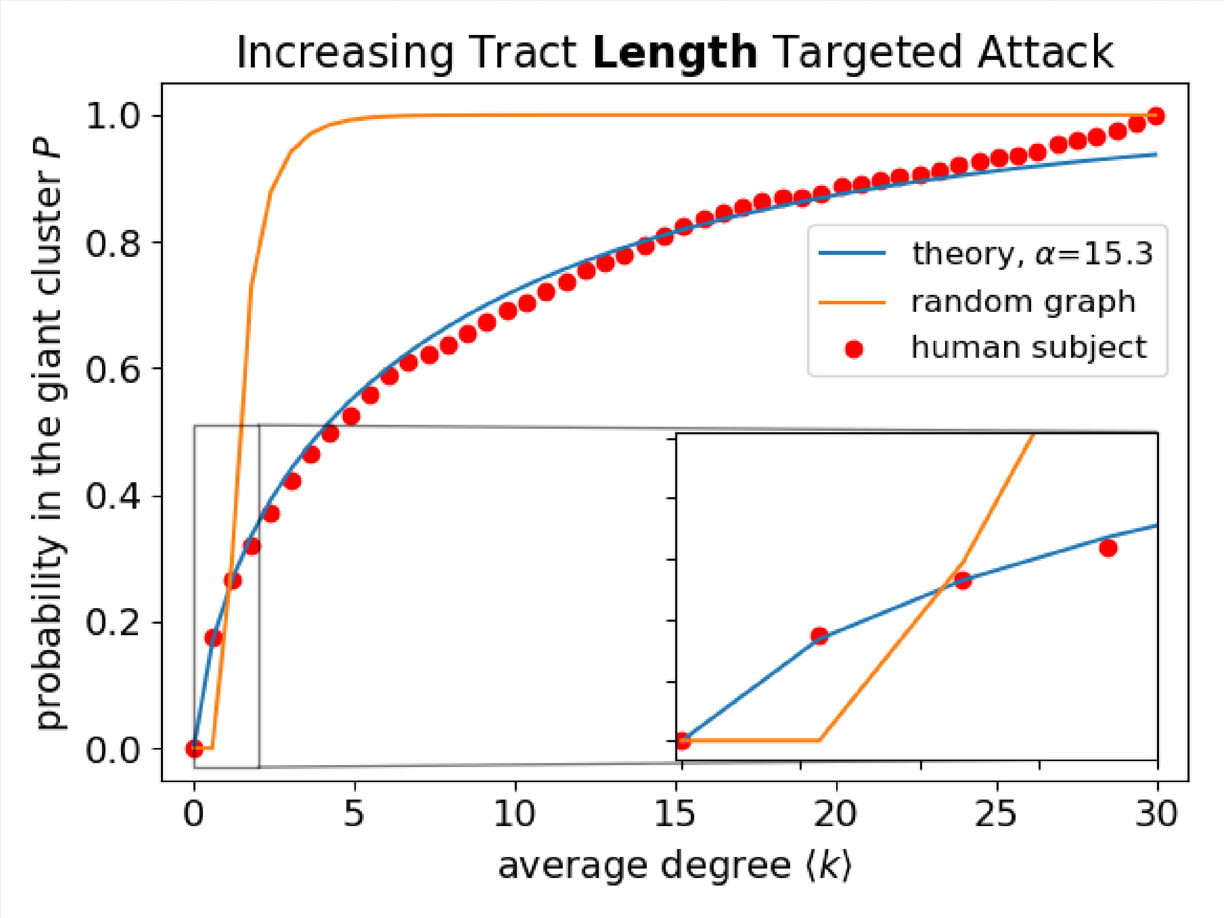
Analytical equation for P curve

$$\boxed{P(\langle k\rangle) = 1 + \left(\frac{1}{1-2/\alpha}\right) W\left[\left(\frac{2}{\alpha}-1\right) e^{-(1-2/\alpha)} e^{-\langle k\rangle/\alpha}\right]}$$

W := Lambert W function

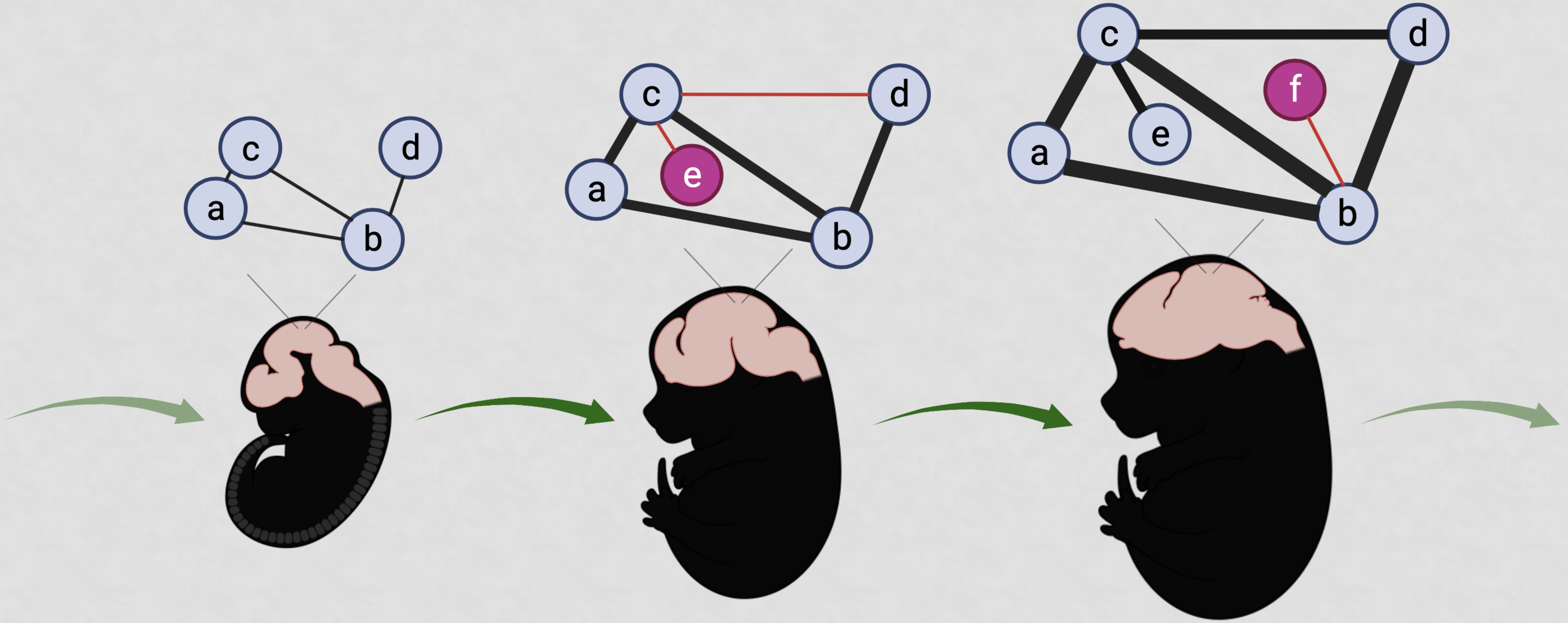
α is the only parameter!

Theory captures experiment with fitted α



Summary of Part 1: Inferred neurodevelopmental rules

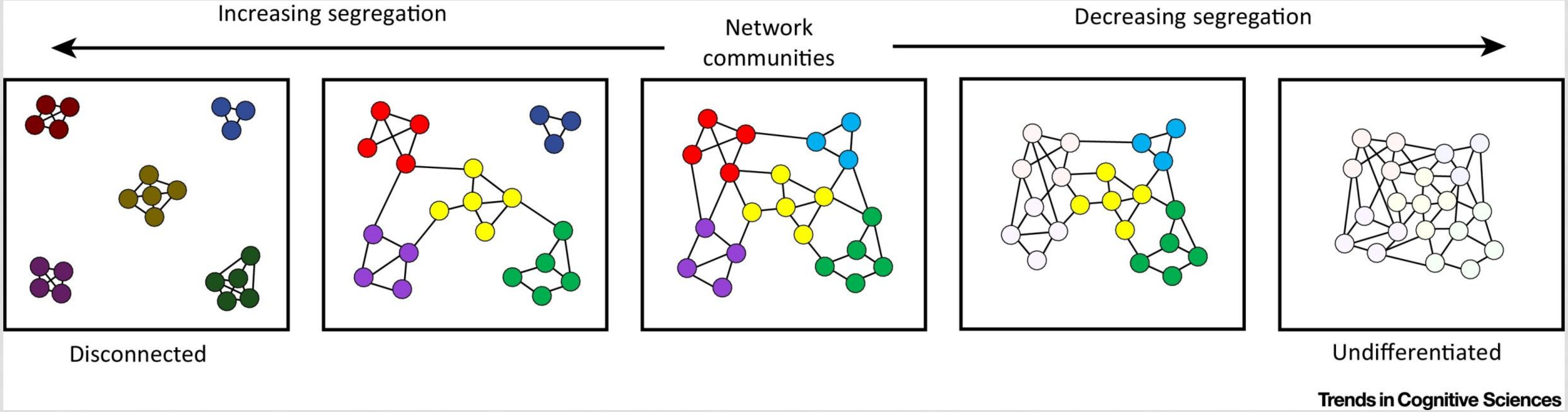
1. Tracts emanate from regions in the giant cluster
2. Earliest tracts become the longest and densest



Existence of a path does not guarantee swift travel

Image from Weather Underground

Integration-segregation framework captures global dynamics



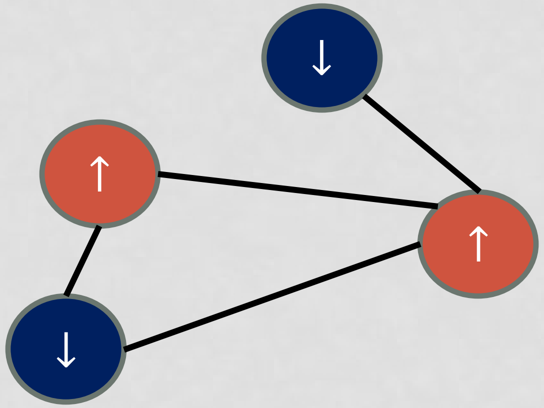
Wig (2017)

- Segregated network has limited local signaling
- Integrated network has extensive global signaling

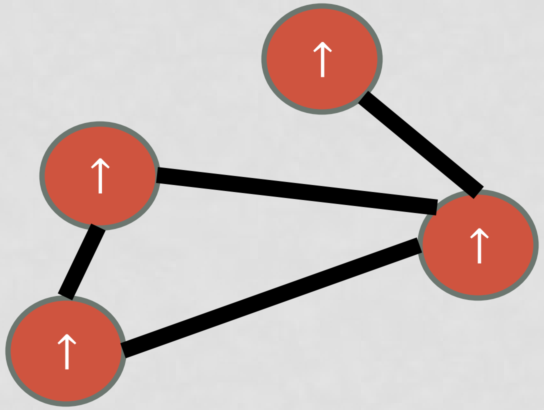
Part 2) How does functional dynamics change with age?

A. More integrated?
B. More segregated?
C. Or something else??

Capturing brain dynamics through neuronal coupling



low coupling λ

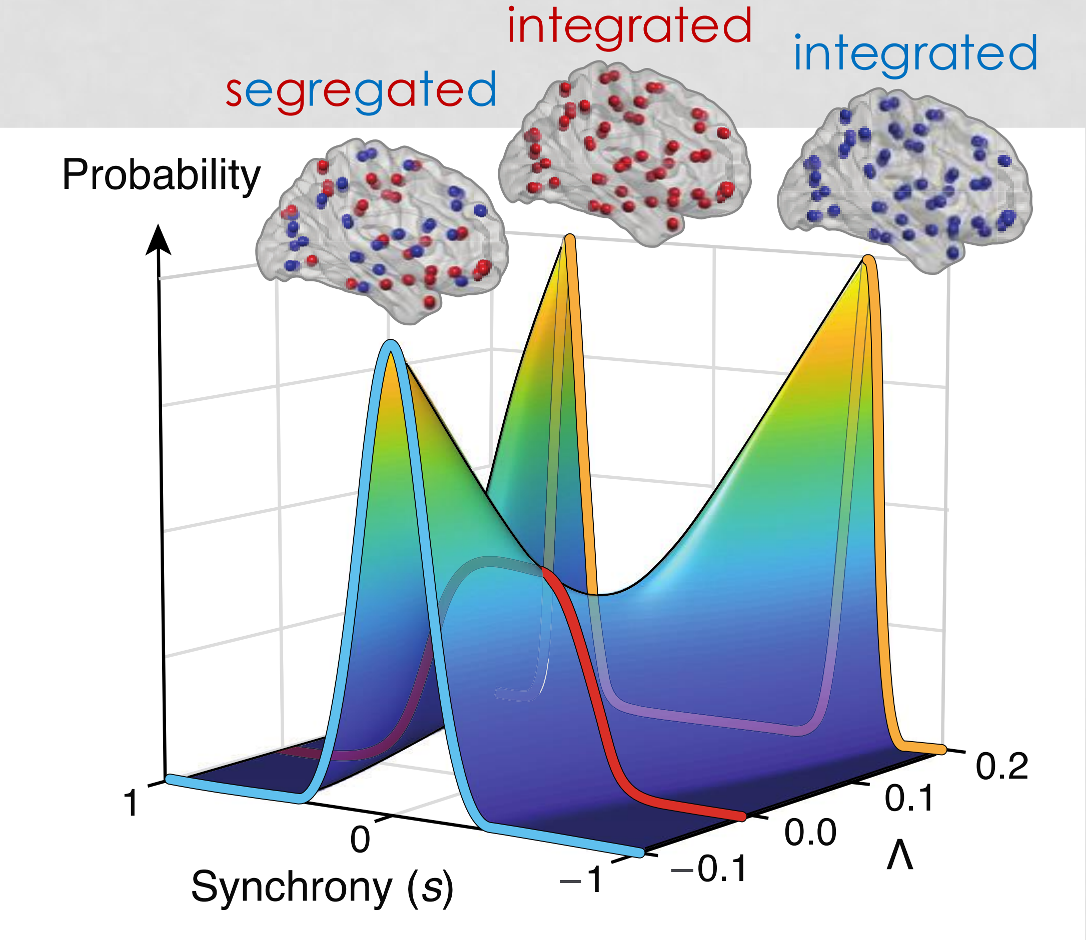


high coupling λ

$$\text{Synchrony} = \frac{1-1+1-1}{4} = 0$$

$$\text{Synchrony} = \frac{1+1+1+1}{4} = 1$$

Ising model predicts two phases: integrated and segregated



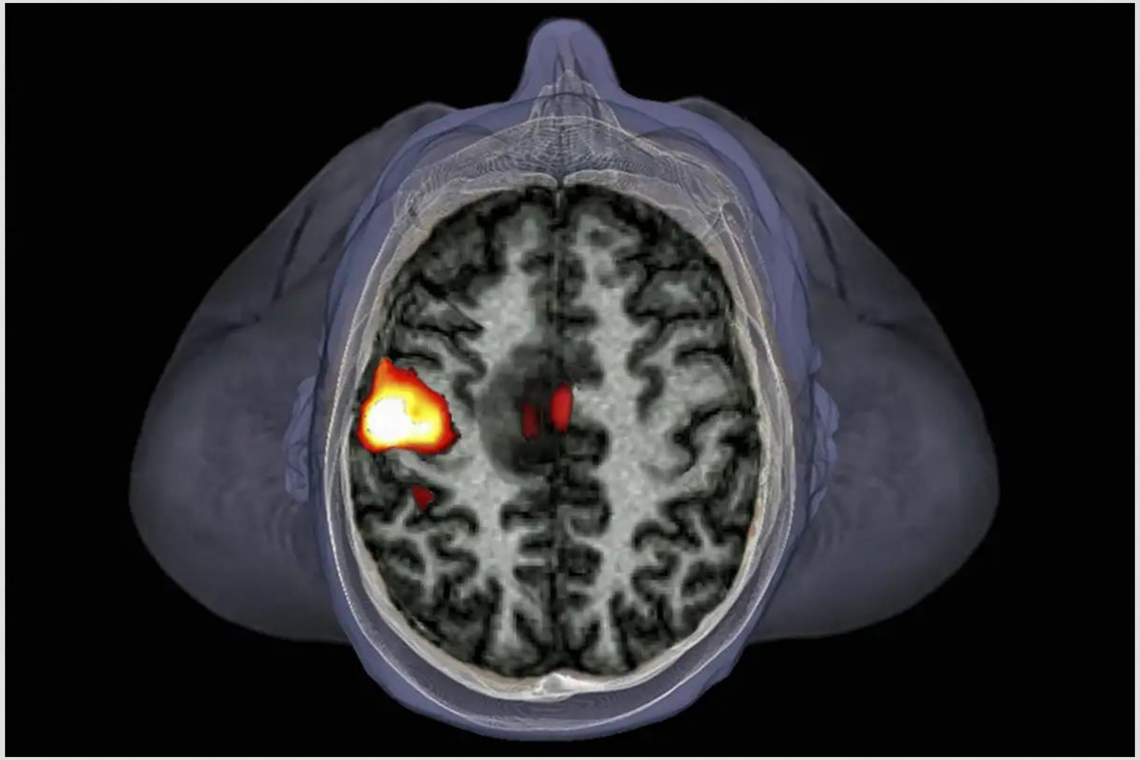
$$P(s) \propto \binom{N}{N(1+s)/2} e^{\lambda N^2 s^2}$$

- Λ is the rescaled coupling strength λ
  - $\Lambda = (\lambda - \lambda_{critical})/\lambda_{critical}$

Weistuch, Mujica-Parodi, **RR**, … (2021)

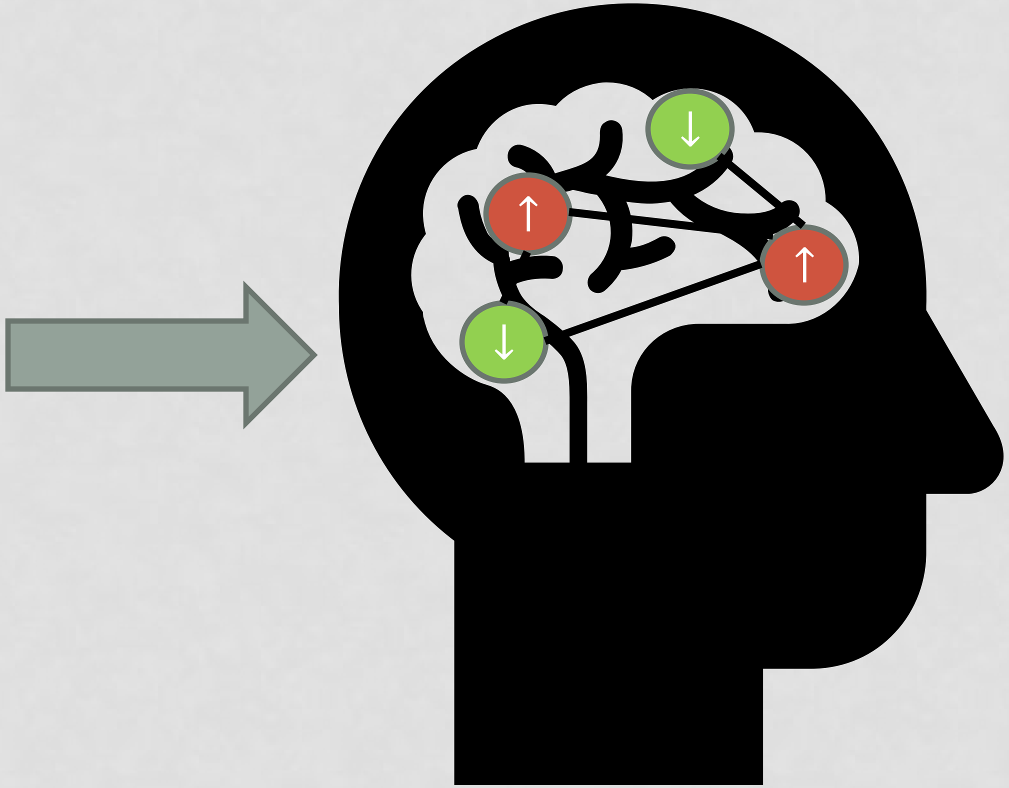
Functional MRI measures brain region activity by blood-oxygen-level-dependent signaling

Brain image

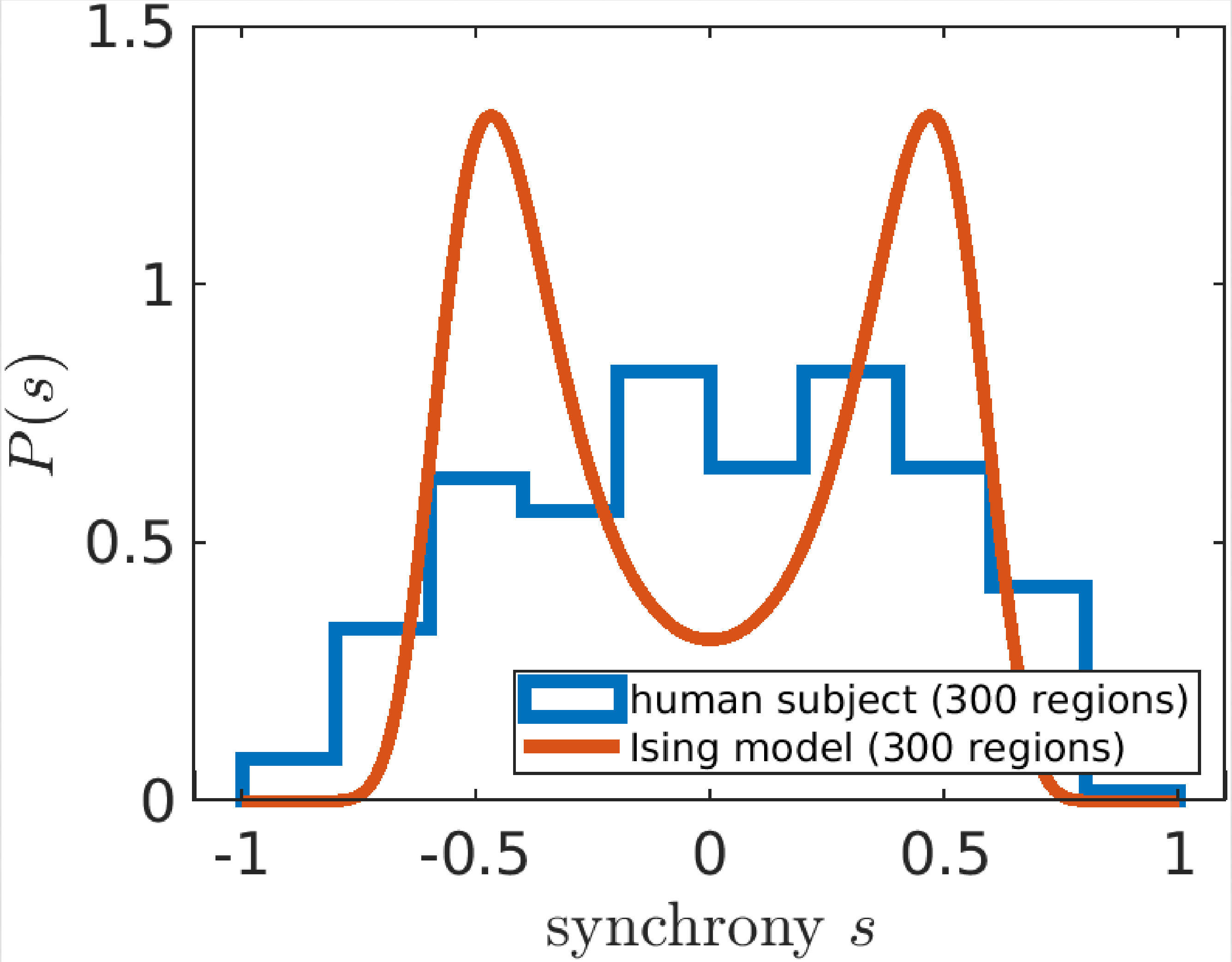


Zephyr/Science

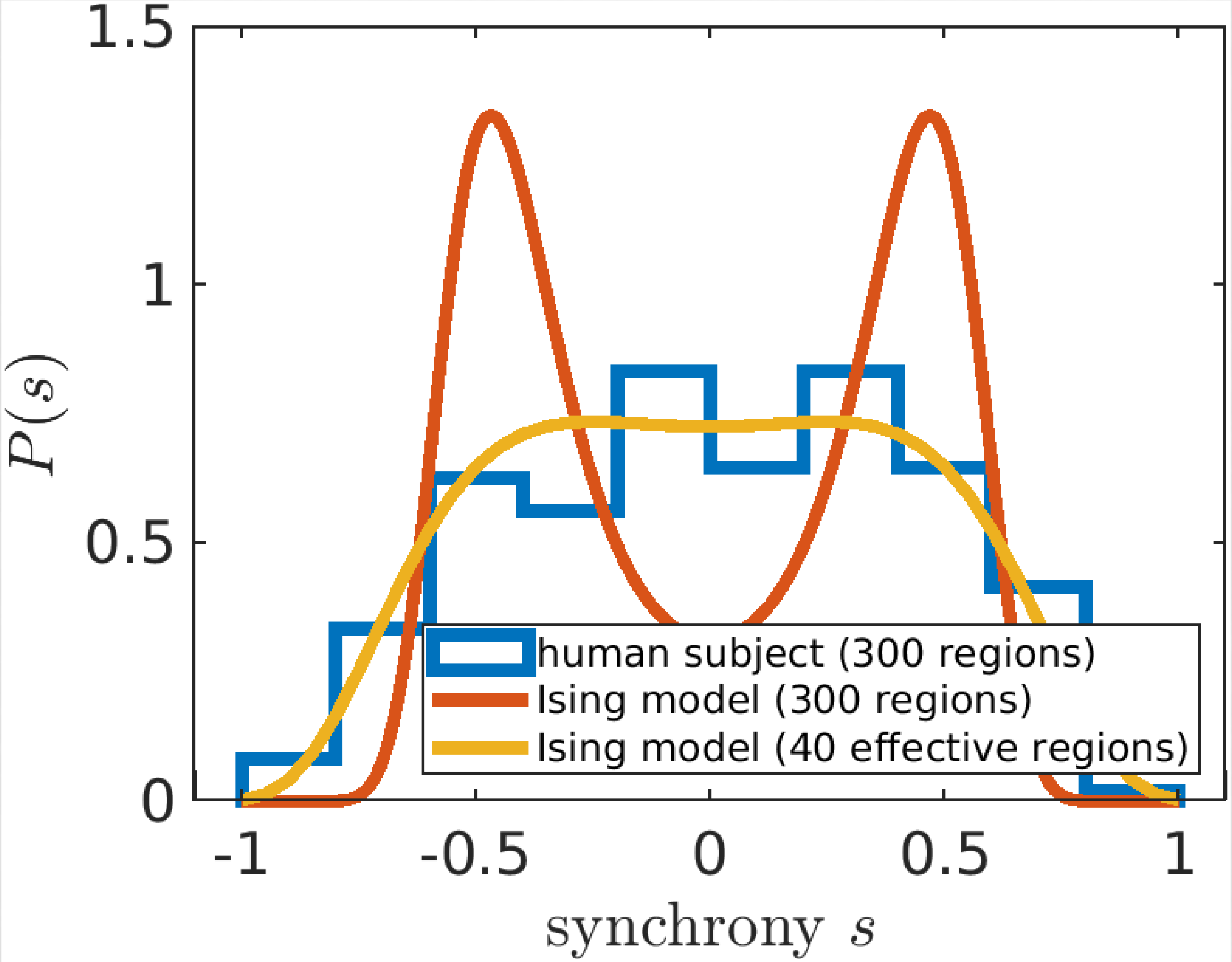
Ising spins



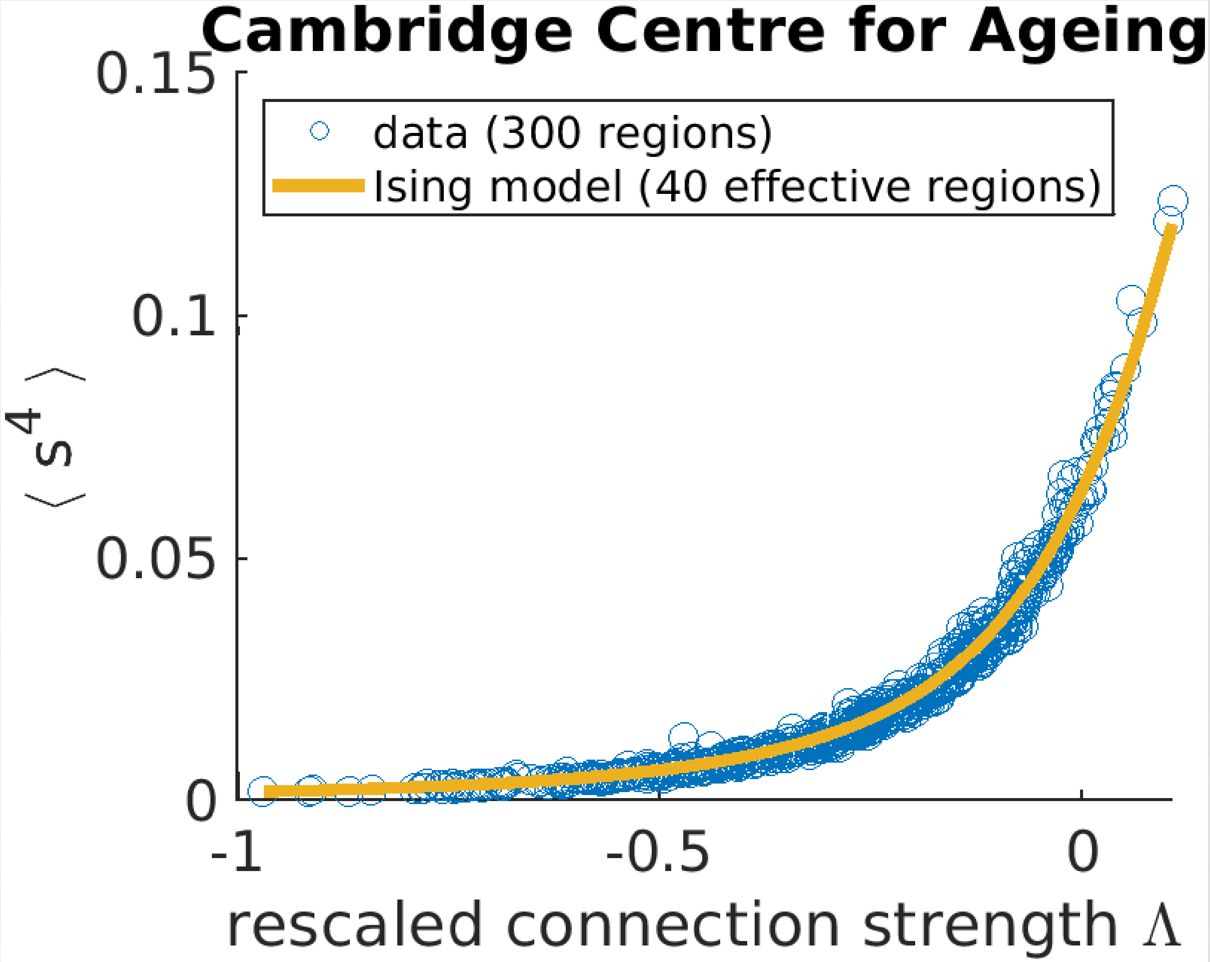
Ising model is inaccurate for arbitrary subject



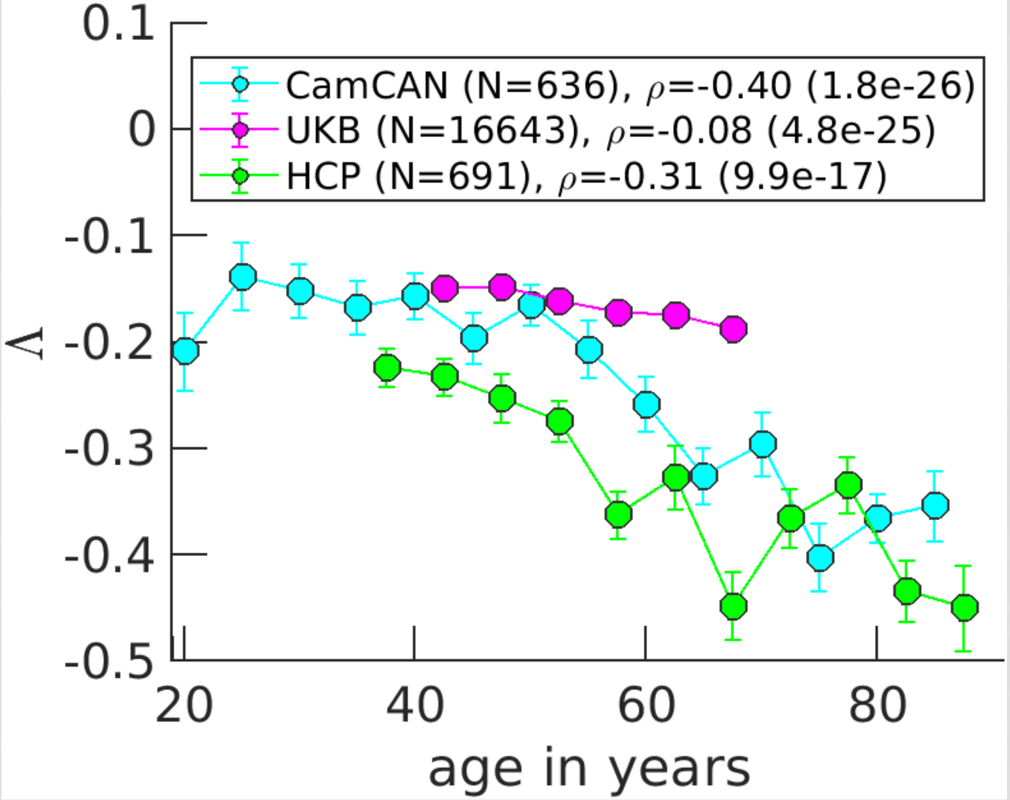
Ising model with N_{eff} is accurate for arbitrary subject

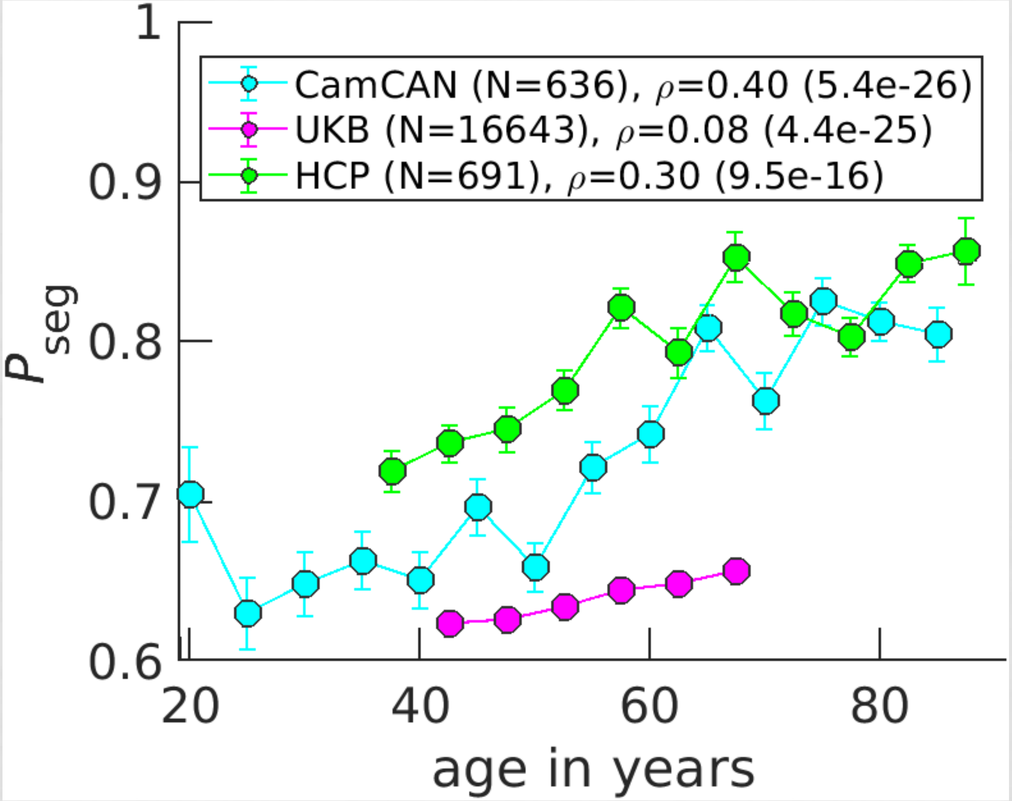


Ising model with N_{eff} is consistently accurate across subjects



Brains become more segregated with age





RR et al. (2024)

P_{seg} = probability to be in the segregated network

Why young and old have distinct network organization?

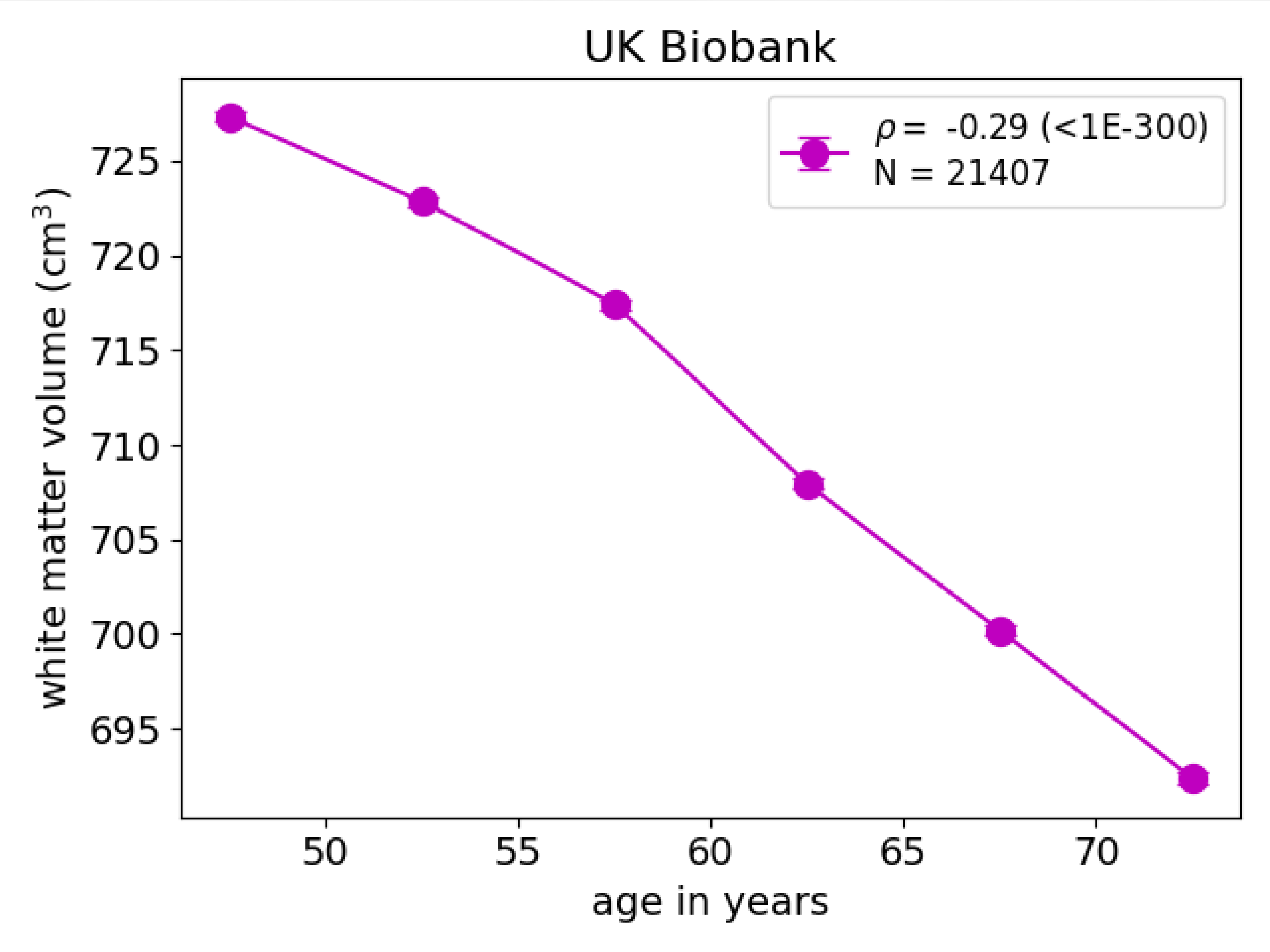
Physics answer:

- Younger individuals near critical point, P_{seg}(critical) = 0.5
  - Experimental data: $P_{seg} \sim 0.7$
- Older individuals essentially random, P_{seg}(random) = 1
  - Experimental data: $P_{seg} \sim 0.85$

Physiological answer?

A. Does connection degradation underly network reorganization?

White matter volume degrades with age

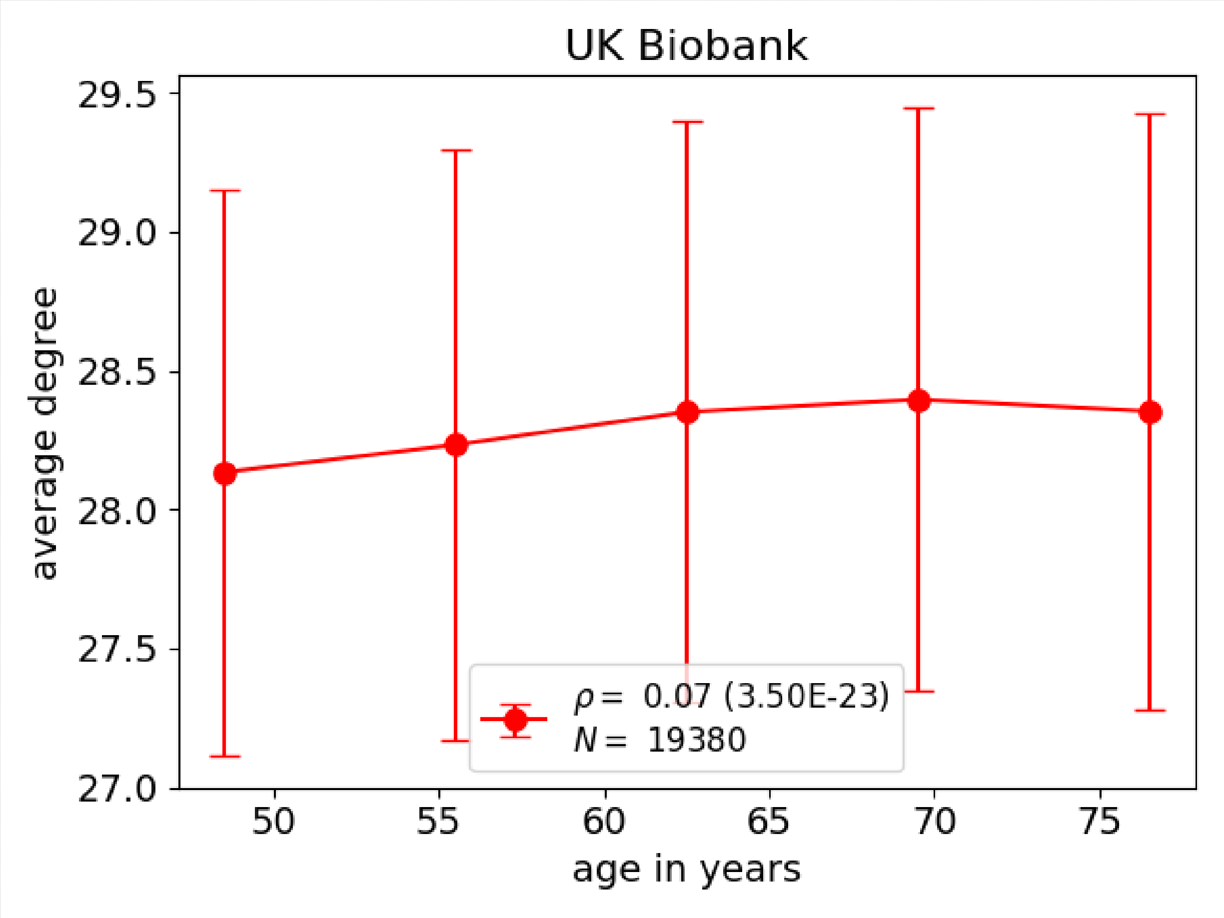


Why does white matter volume decay with age?

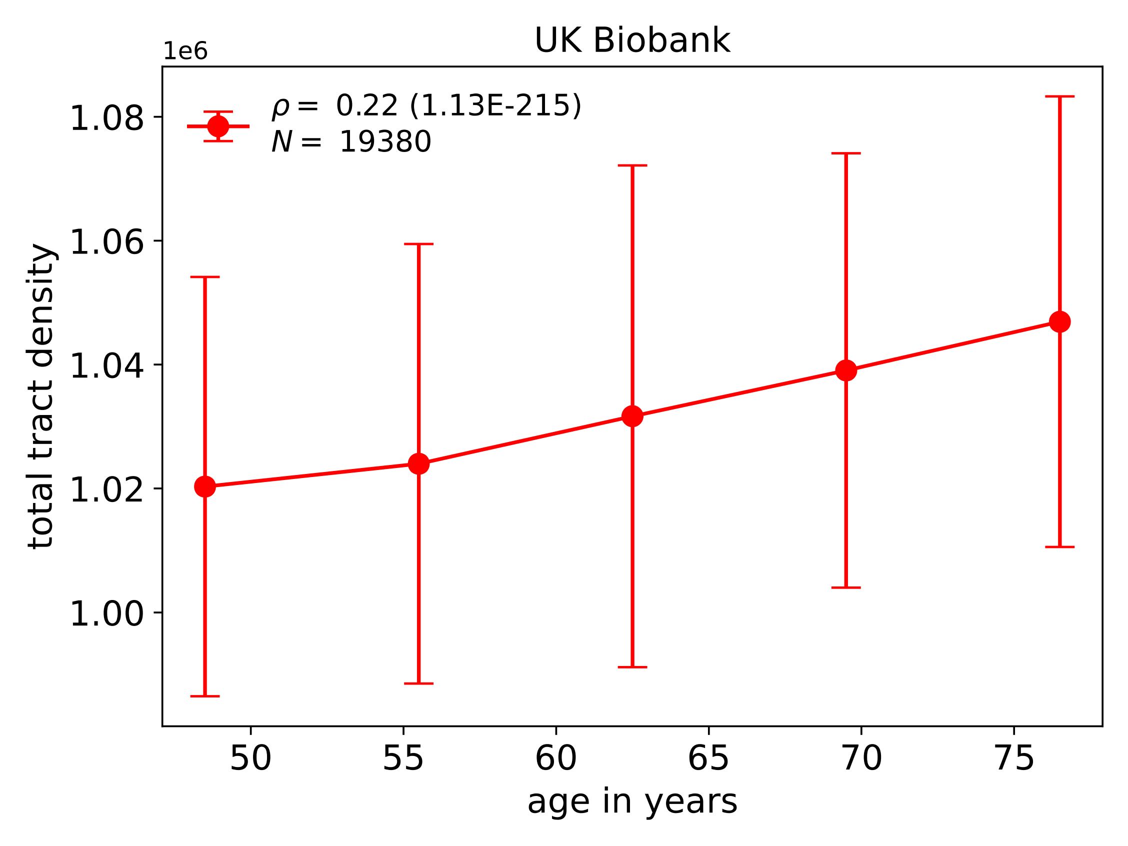
How are white matter tracts connecting neuronal regions damaged?

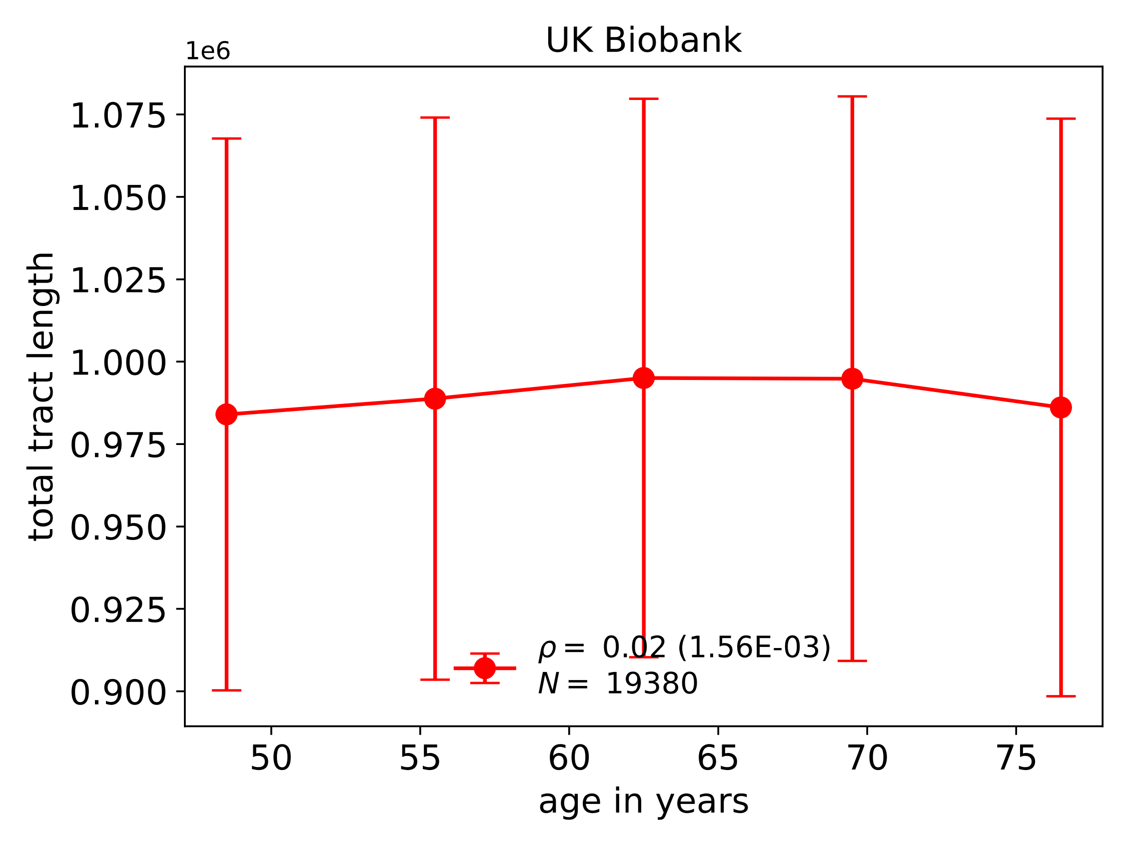
A. Fewer tracts??
B. Thinner tracts??
C. Shorter tracts??

Number of white matter tracts does not degrade with age



White matter tract density nor length degrades with age





Summary of Part 2)

- Brain dynamics reorganize to become more segregated with age

Is there a physiological reason?

- White matter deteriorates with age
  - Unable to identify a specific connection property

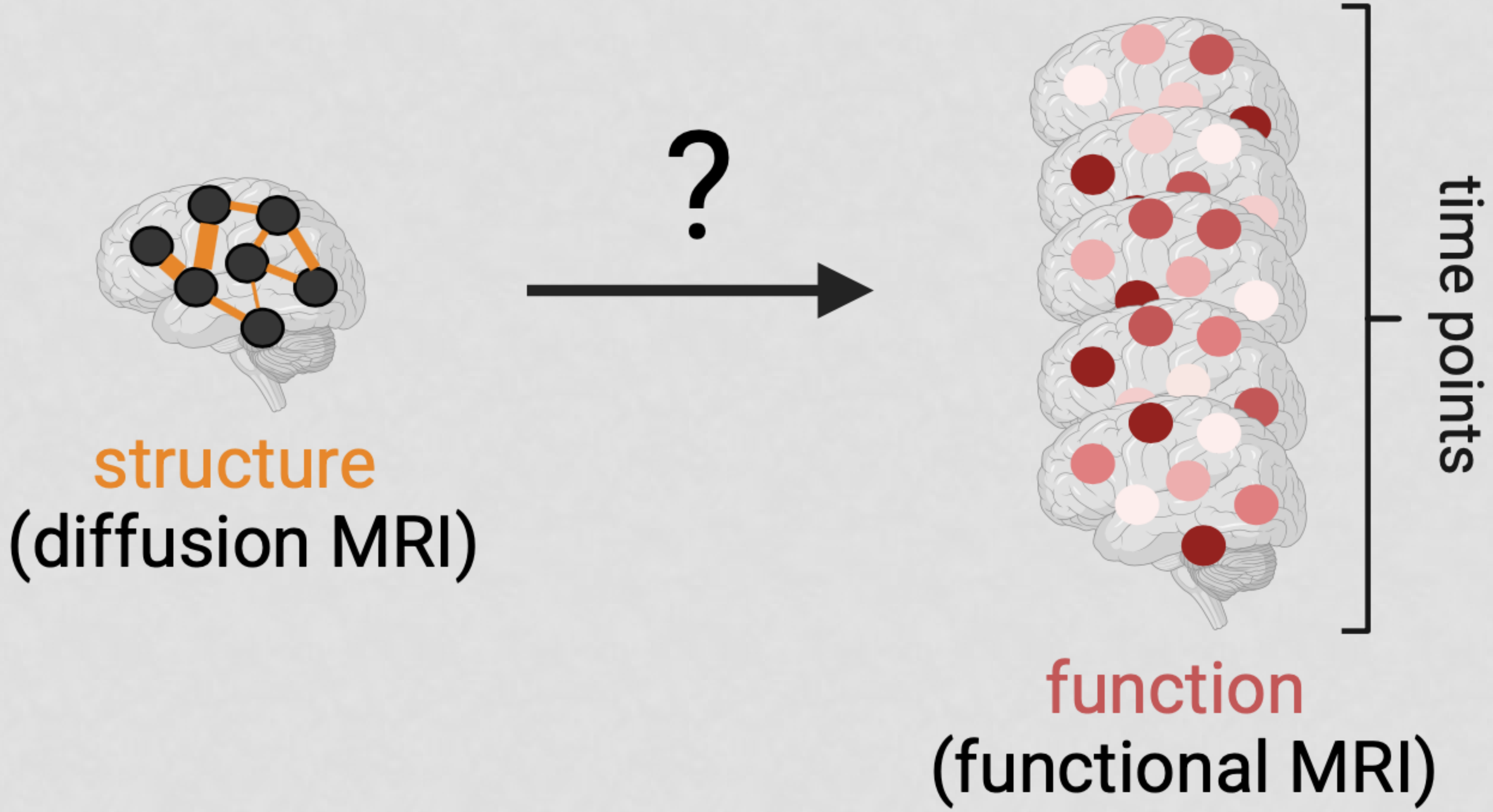
~~A. Fewer tracts~~

~~B. Thinner tracts~~

~~C. Shorter tracts~~

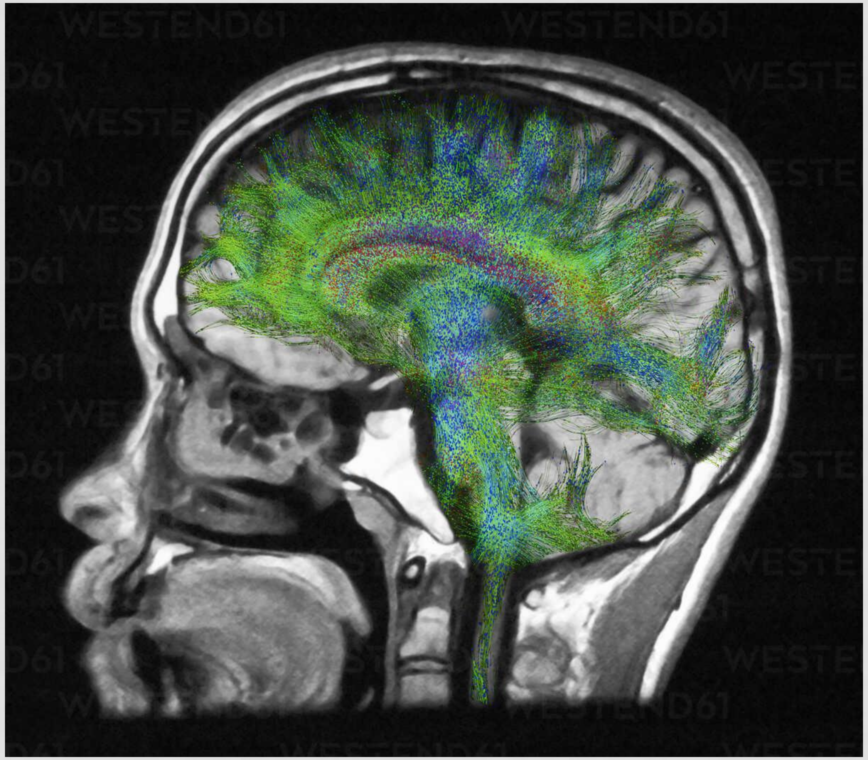
D. Maybe related to myelin reduction?

How does brain structure constrain its function?



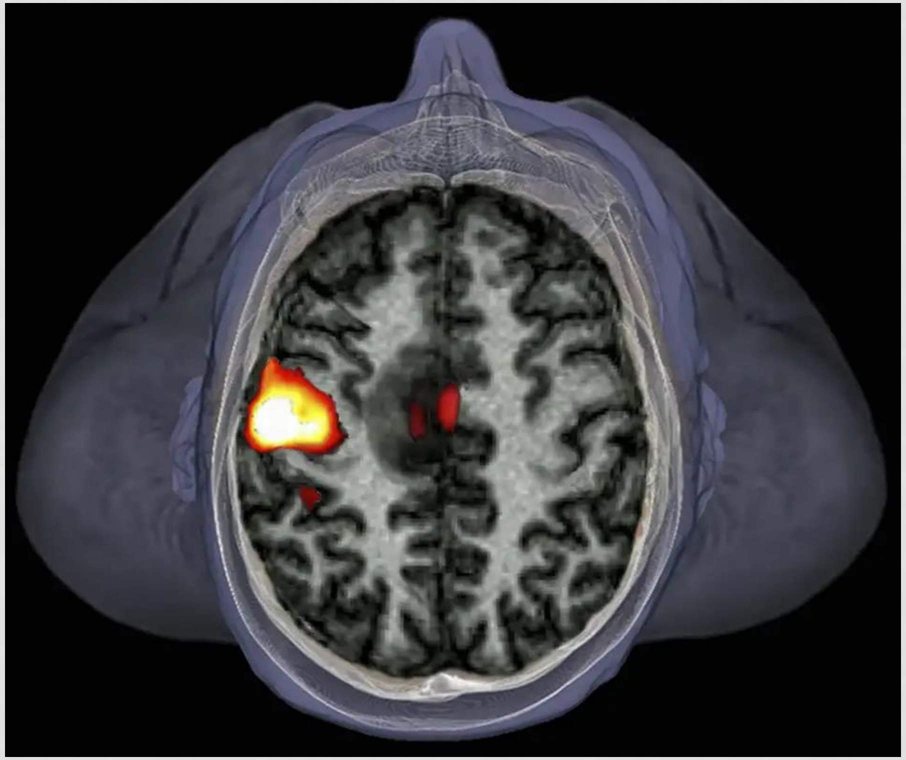
MRI non-invasively measures structure and function

diffusion MRI (dMRI)



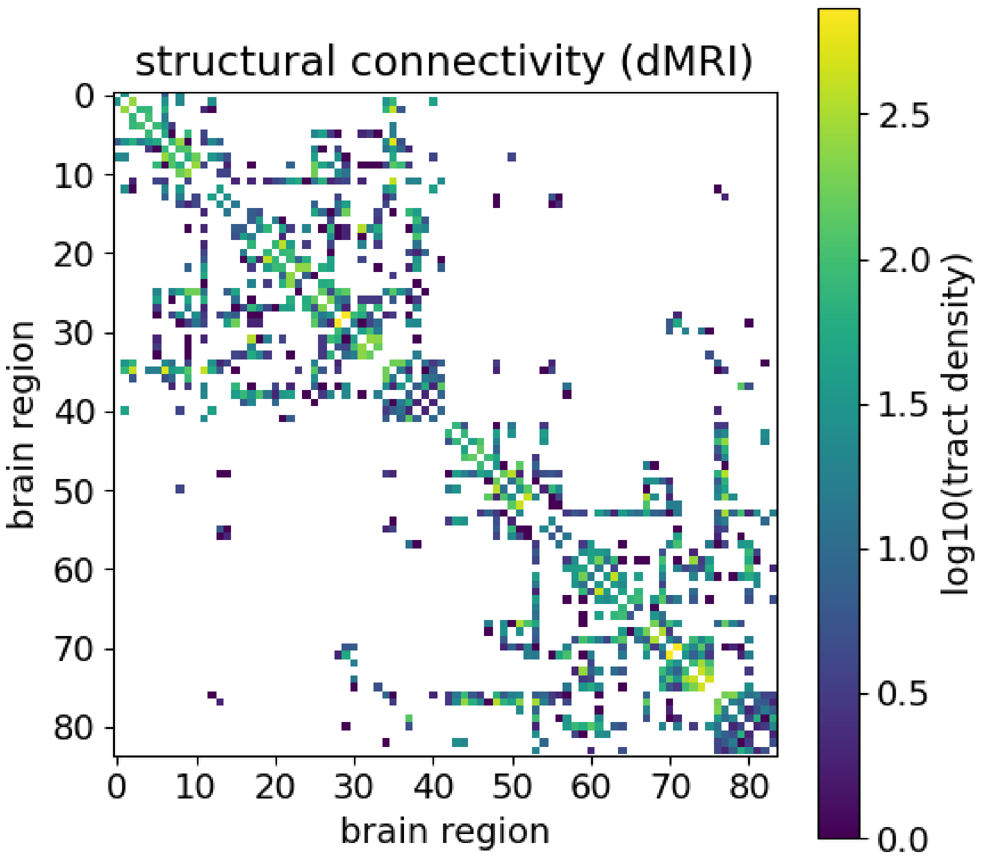
Westend61.de

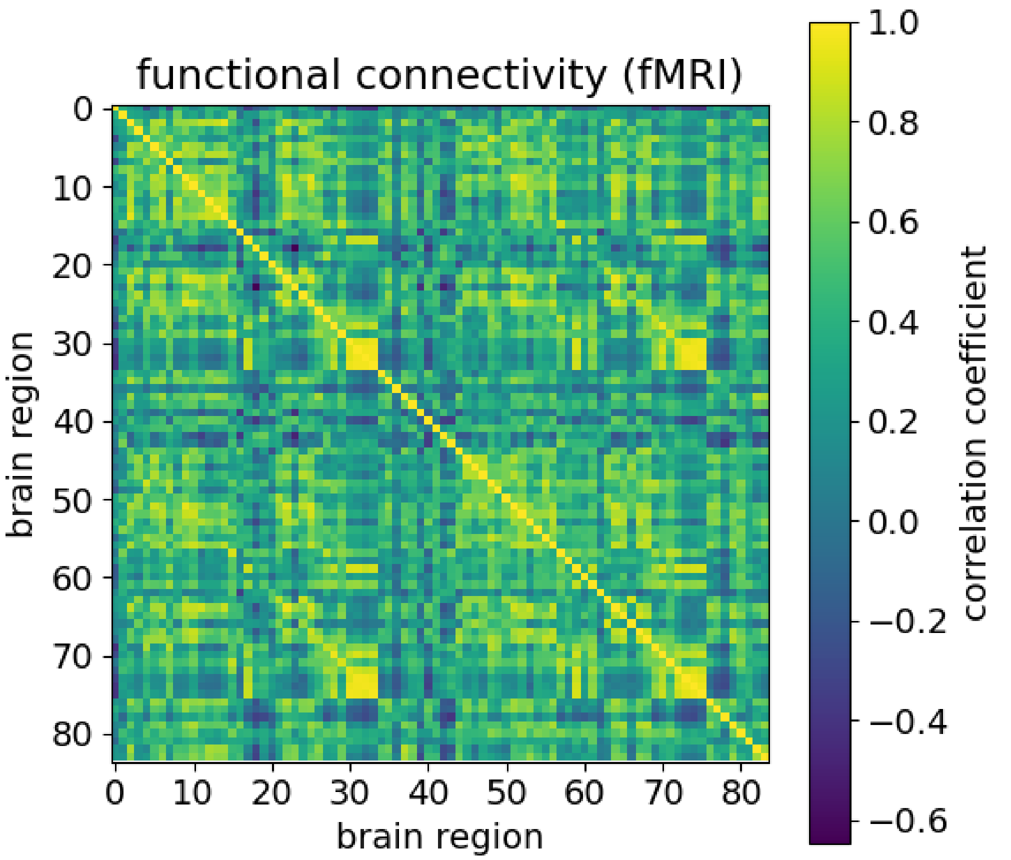
functional MRI (fMRI)



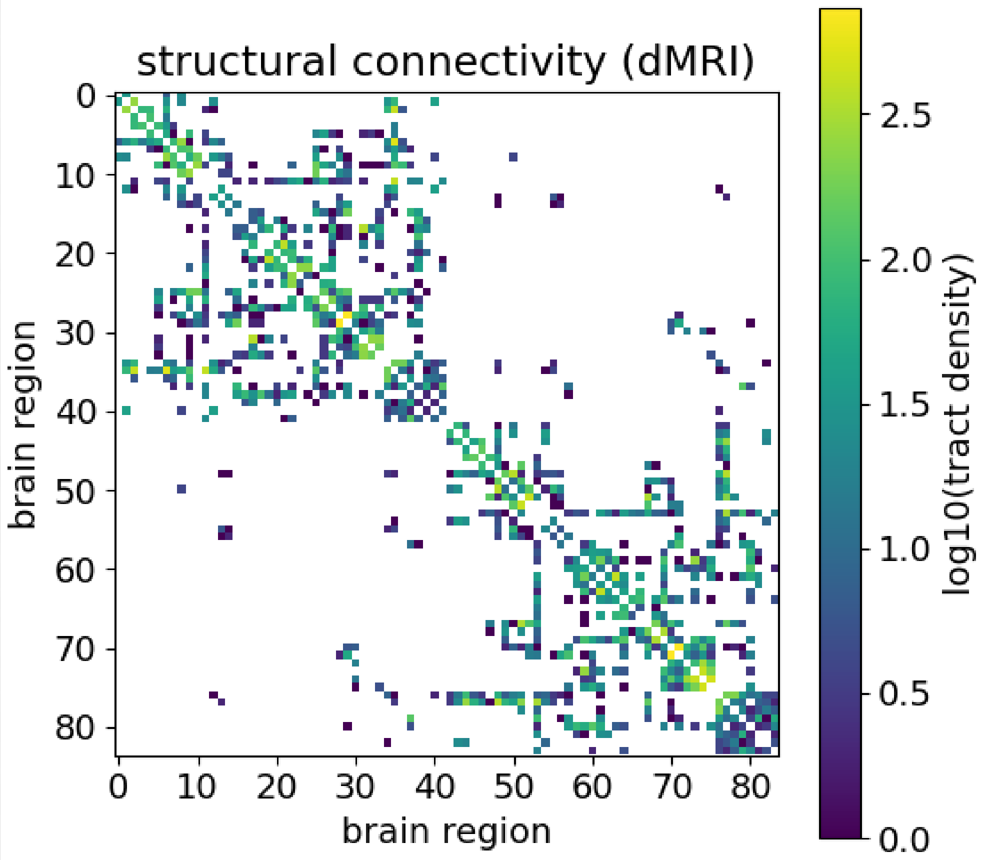
Zephyr/Science

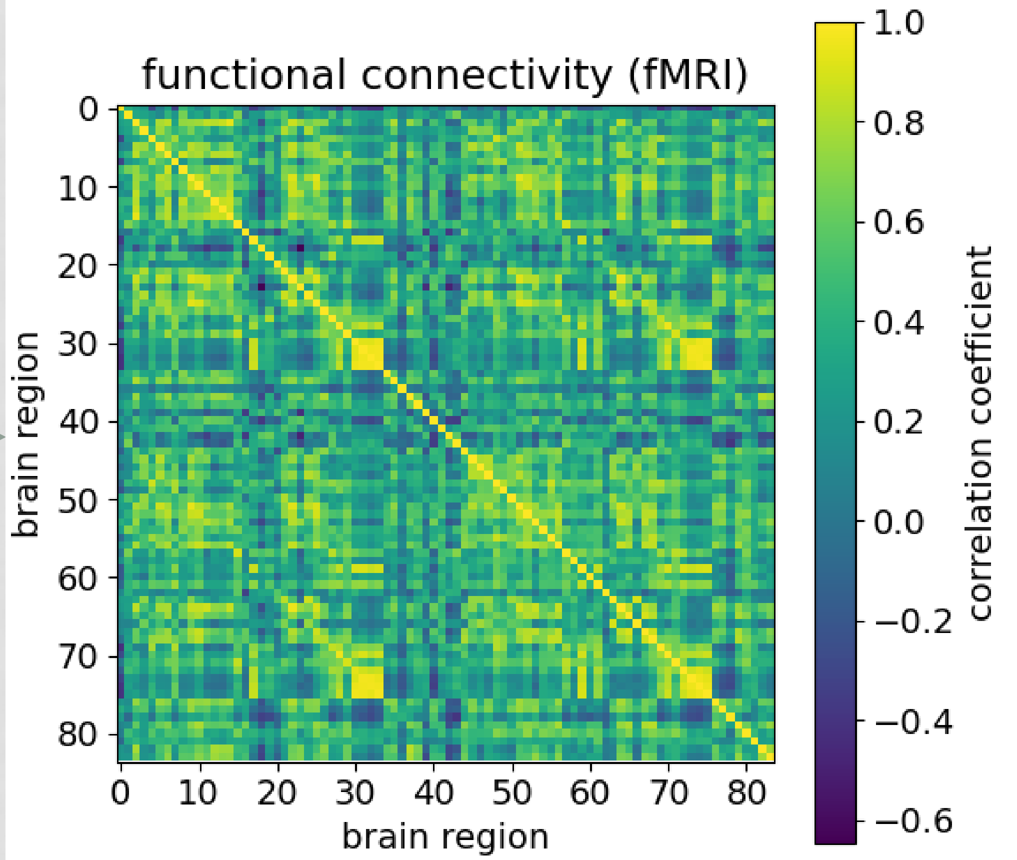
Structure and functional connectivity for an individual





How can we relate the two matrices?





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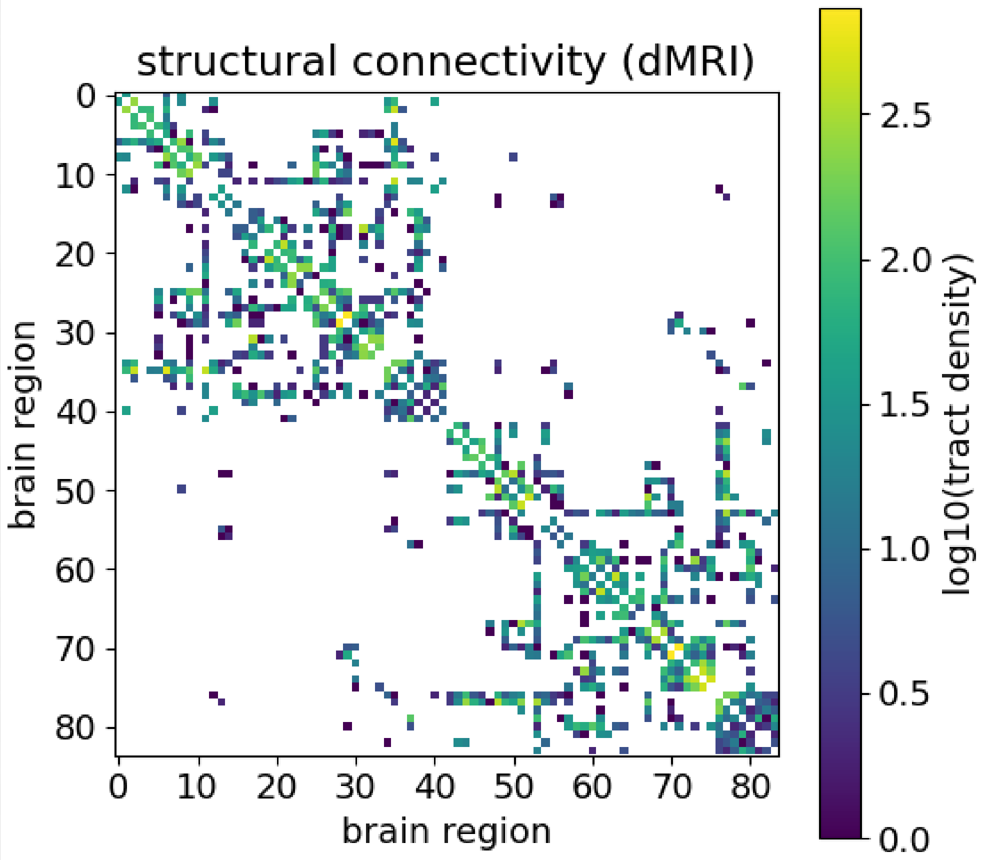
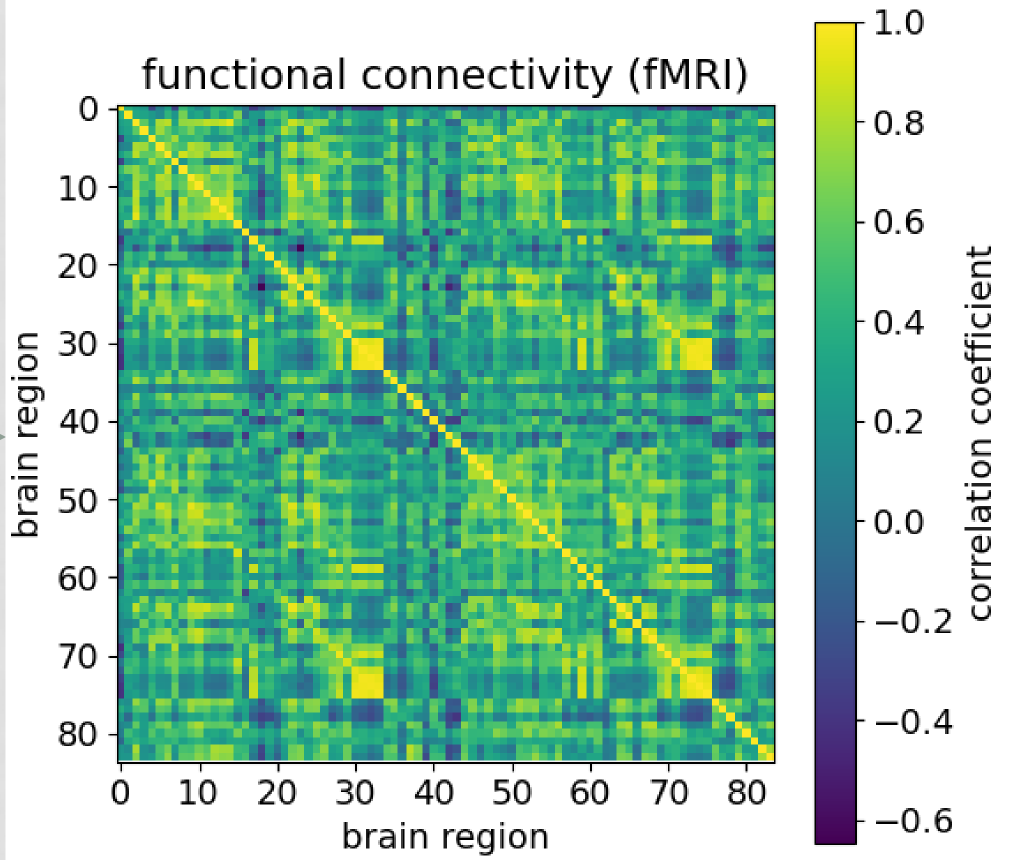
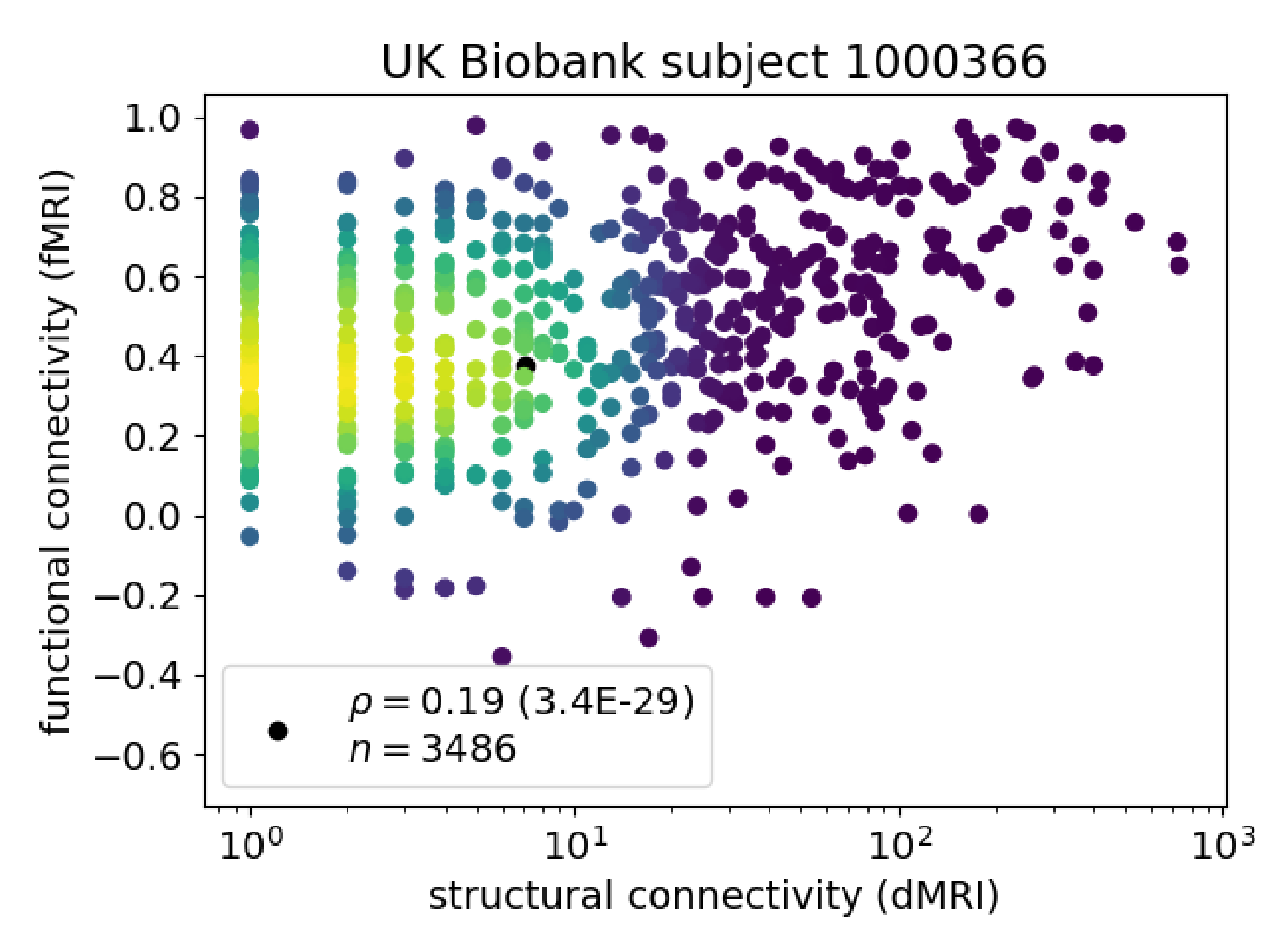


Simply correlate?

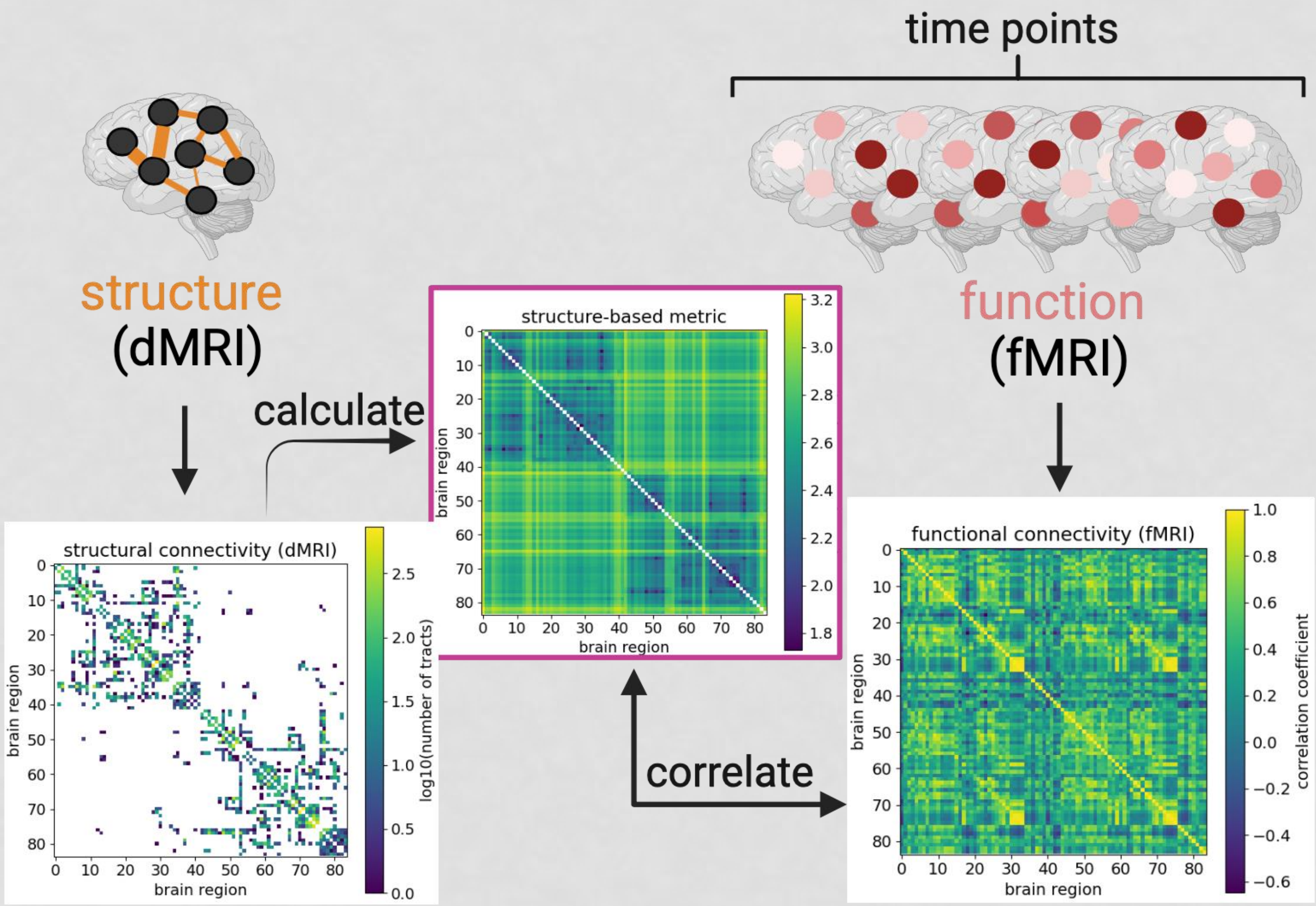


Structural and functional connectivity are poorly correlated



Honey et al. 2009

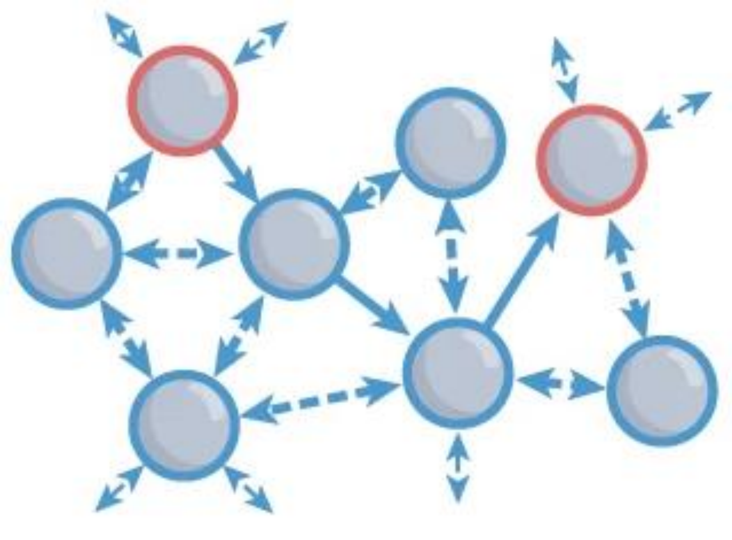
Alternative approach: correlate an intermediate metric with functional connectivity



Possible structure-based metrics

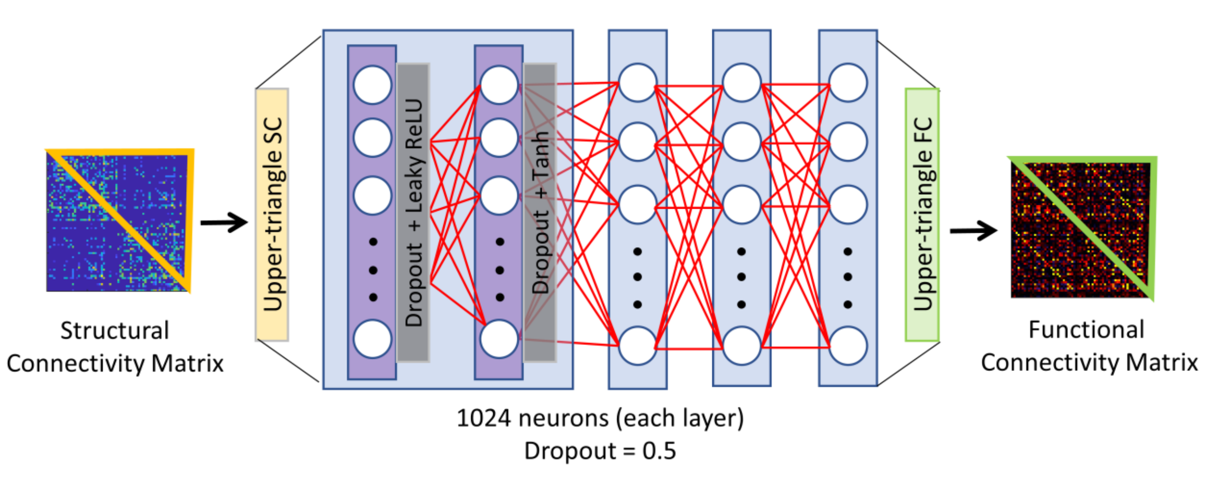
Communication models

- Ex) **Communicability**



Machine learning

- Ex) **Deep neural network**

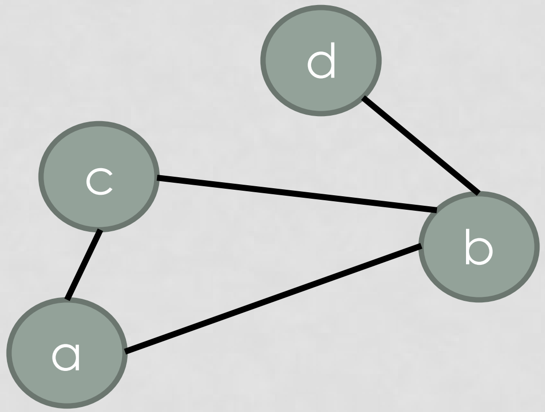


Seguin et al. 2023

Sarwar et al. 2021

Another structure-based metric: commute time

- **Commute time =** average number of steps to randomly walk to and from a to d



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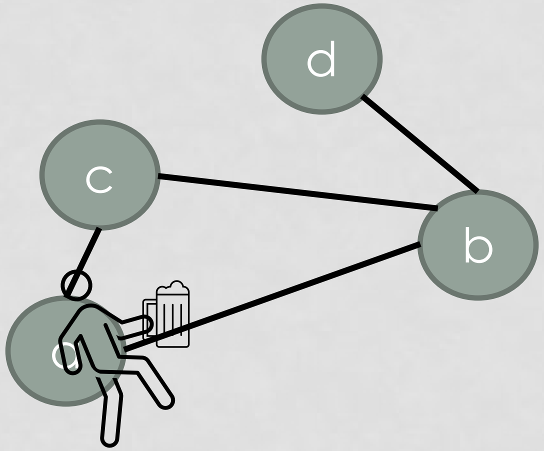

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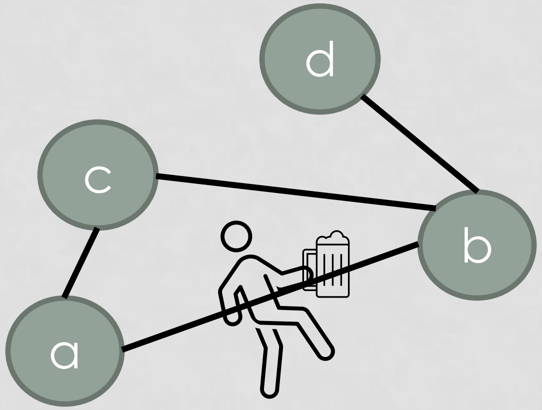

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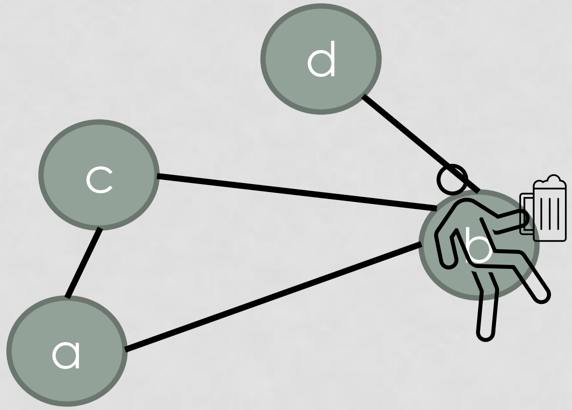

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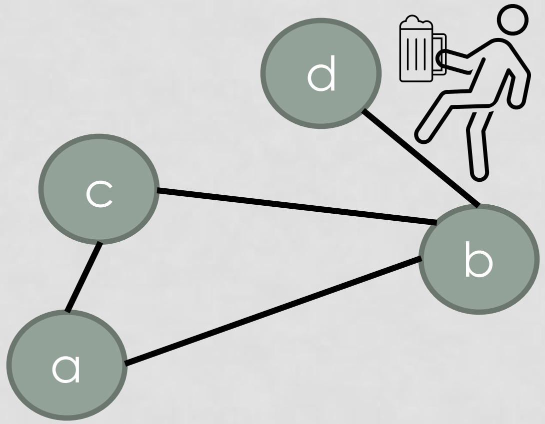


Commute time is derived from Markovian dynamics

$$\text{commute time} = \left([\Gamma^{-1}]_{ii} + [\Gamma^{-1}]_{jj} - 2[\Gamma^{-1}]_{ij}\right) \sum_{k}^{N} W_{kk}$$

- Definition of the Laplacian matrix Γ_{ij} in terms of weighted structural connectivity matrix W_{ij}

$$\Gamma_{\mathrm{ij}} = \begin{cases} \sum_k W_{ik} \ \ if \ i = j \\ -W_{ij} \end{cases}$$

Chennubhotla and Bahar 2007

PART 3 RESULTS

- RESEARCH QUESTION

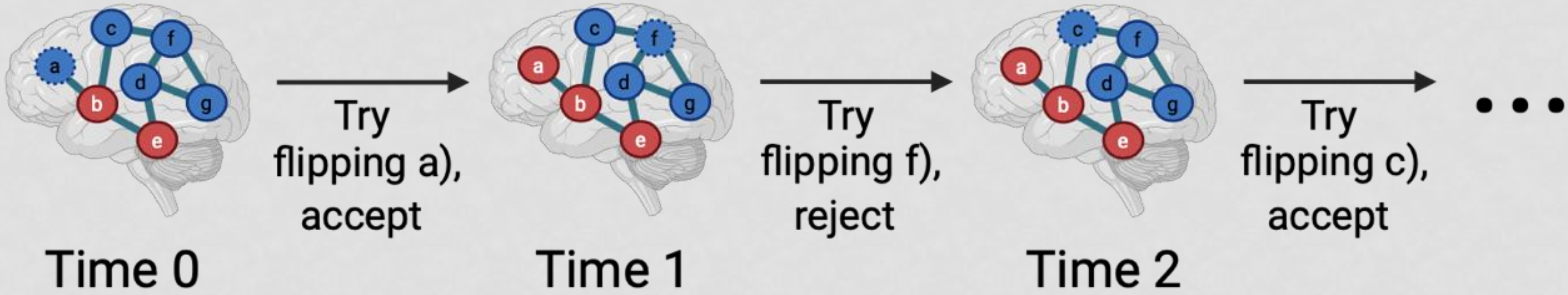
How does brain structure dictate function?

- APPROACH

Calculate commute time from structure to determine whether it correlates with functional connectivity (FC)

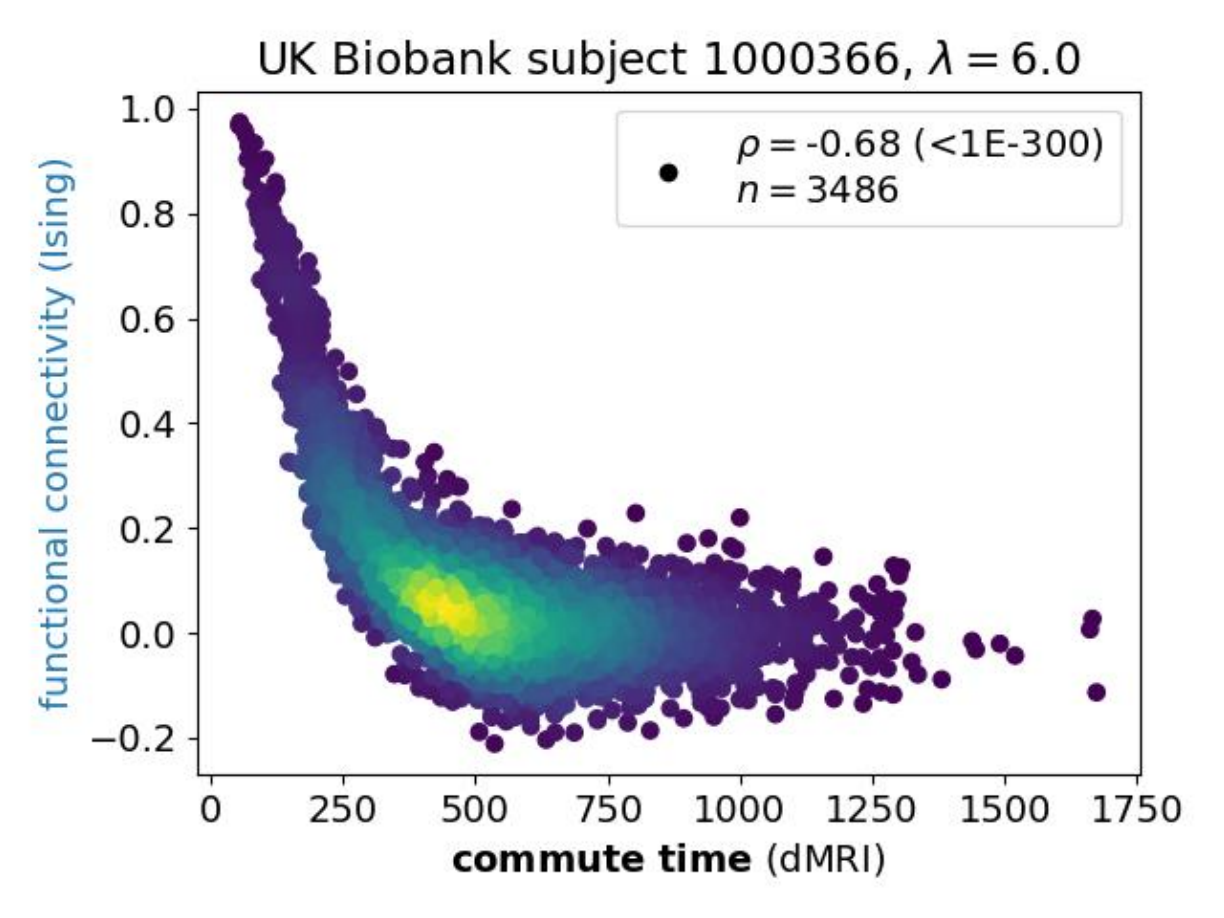
1. Simulated brain function
2. Real fMRI brain data

Simulation protocol

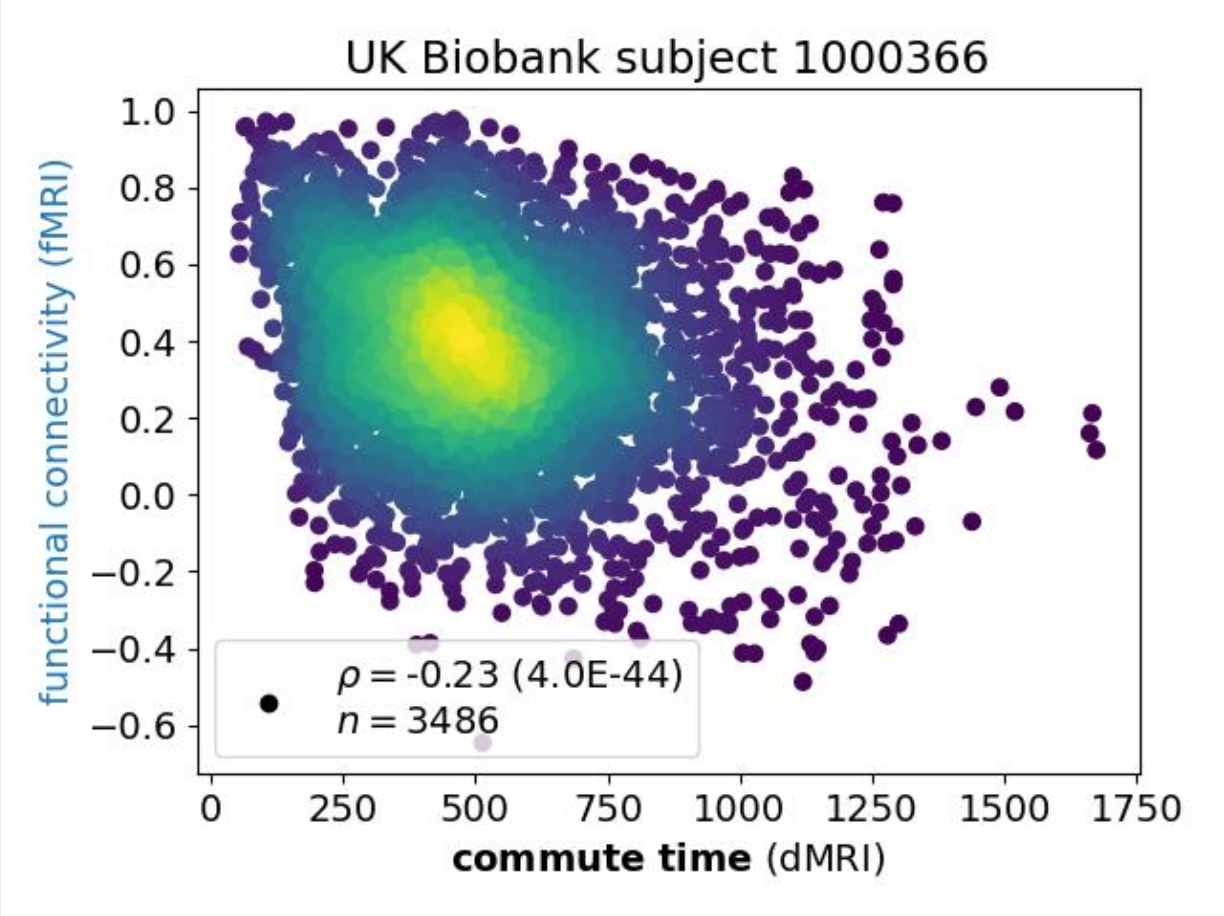


- Accept/reject random spin flips based on Metropolis-Hastings algorithm (equilibrium regime)
- Only two possible states (Ising model)
- One coupling constant parameter λ

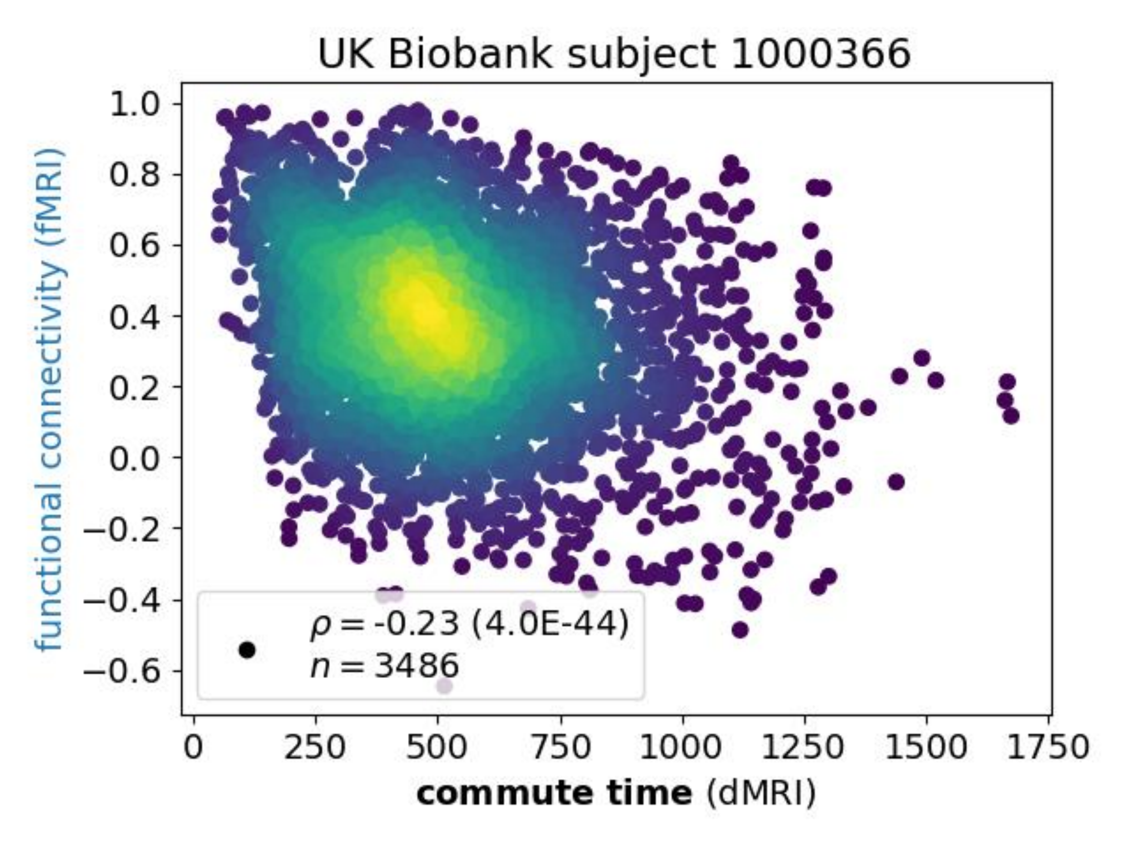
Proof of principle: commute time captures FC

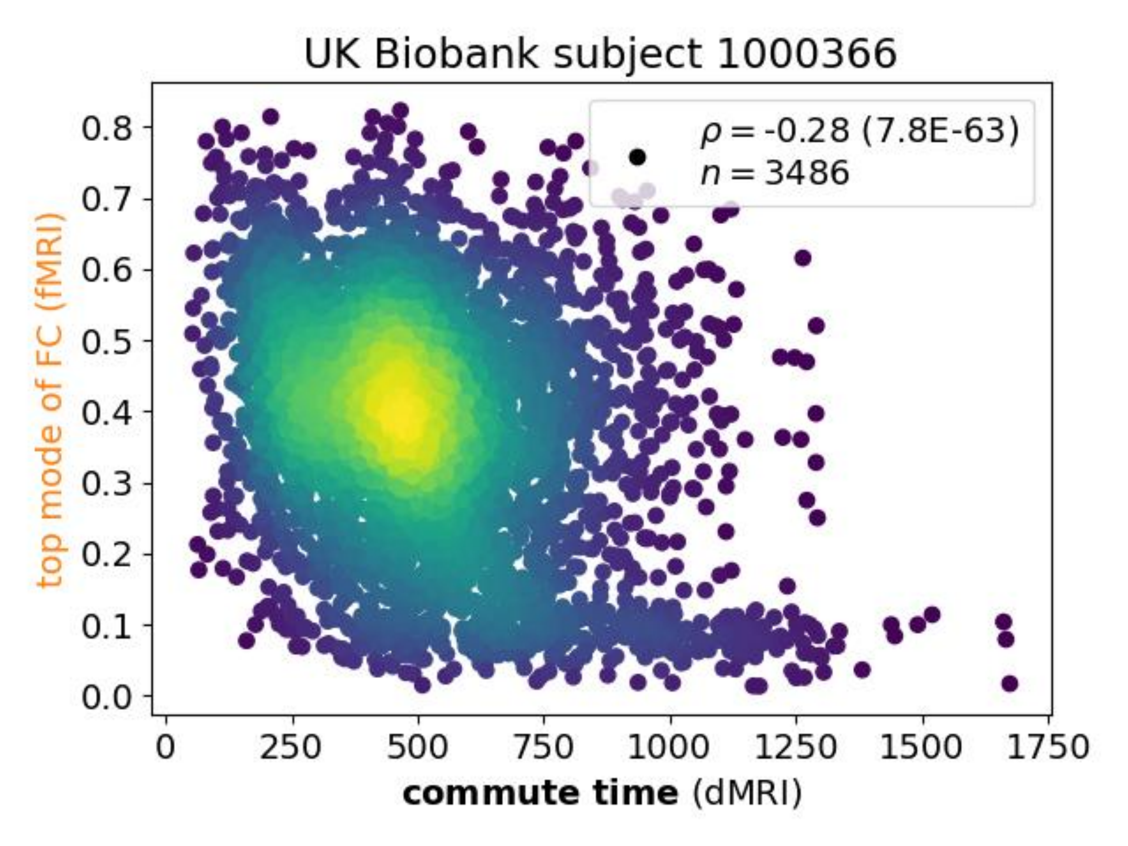


Commute time kind of captures function in a human brain

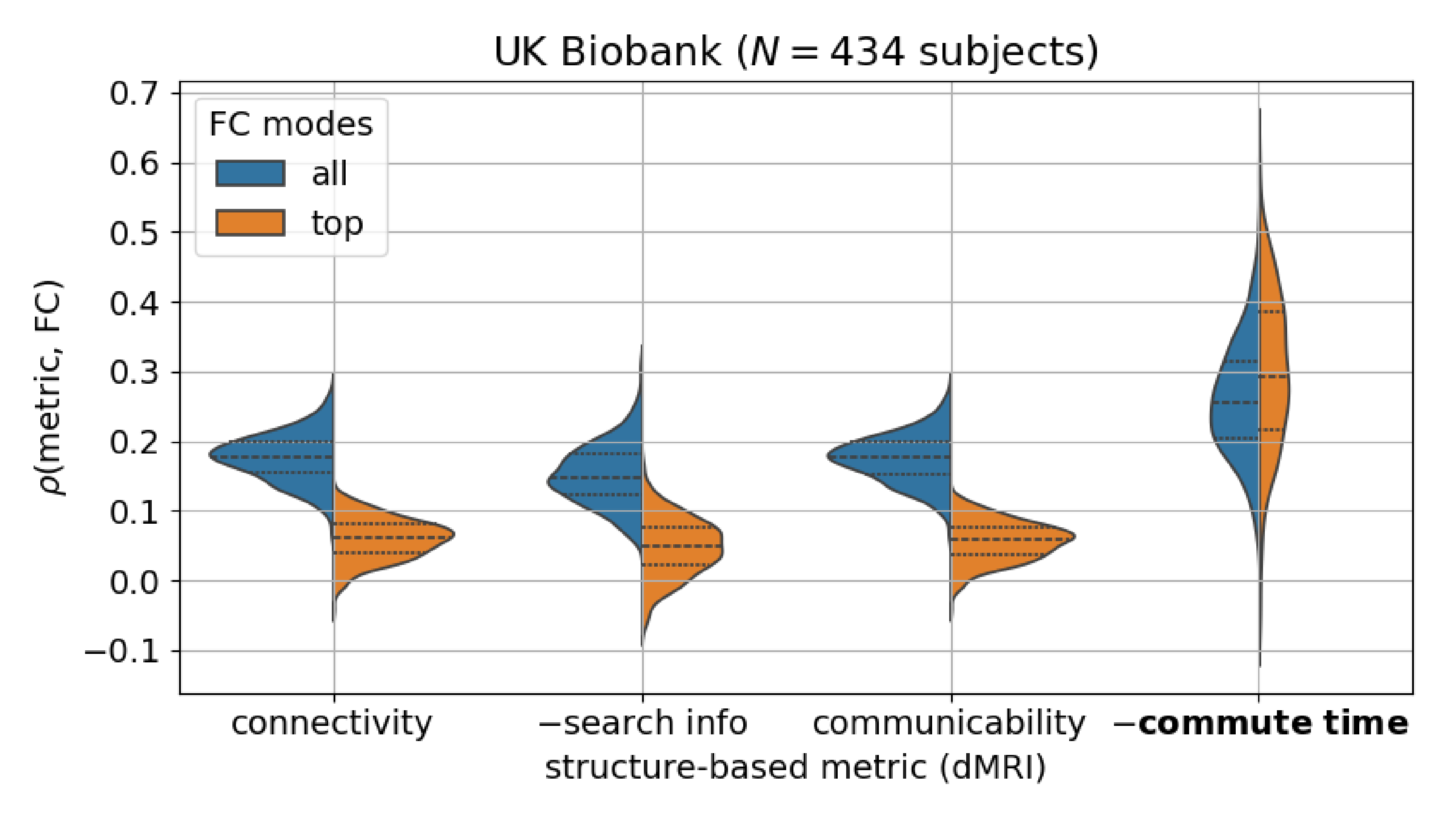


Stronger structure-function correlation for FC’s top mode

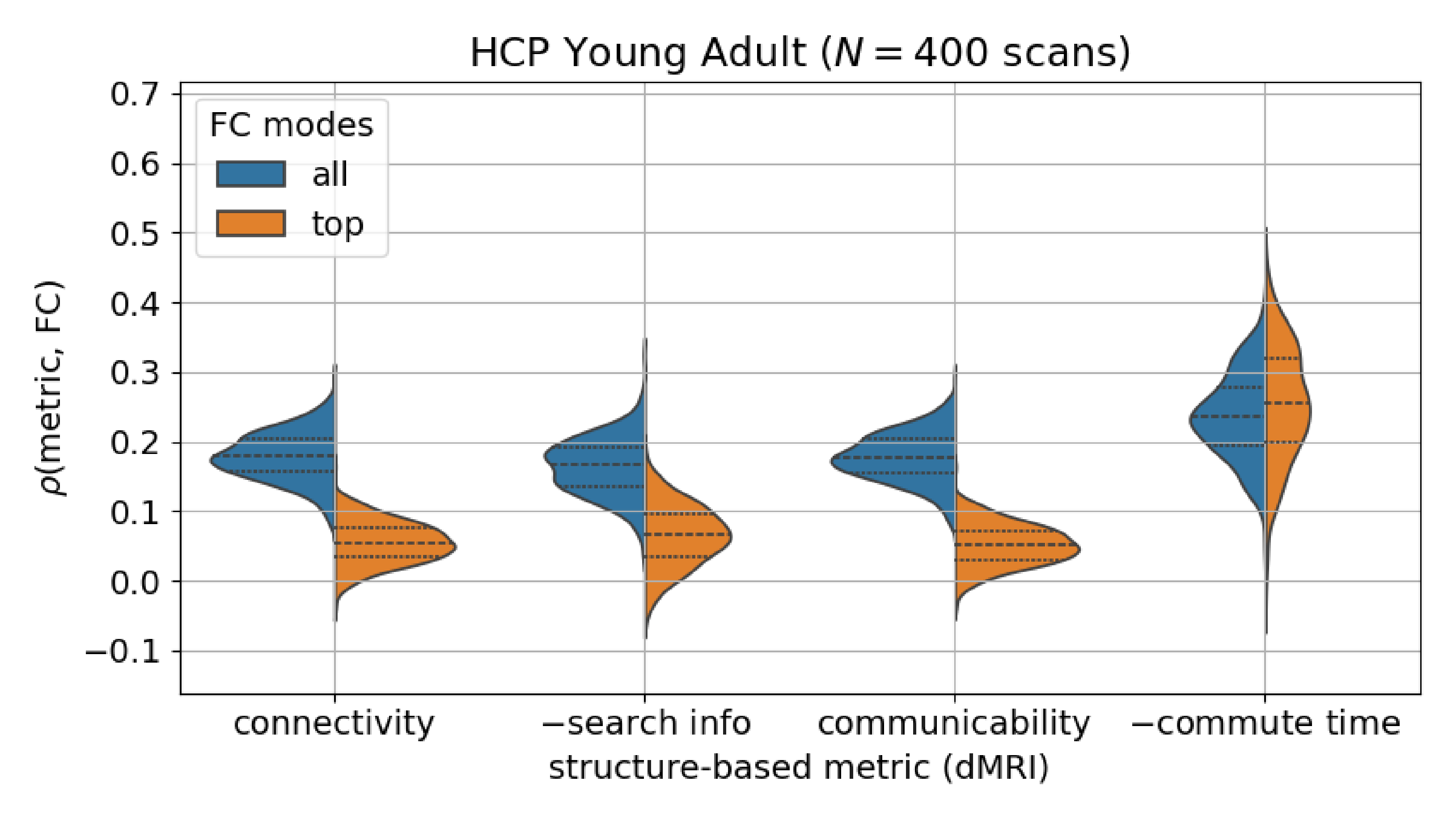




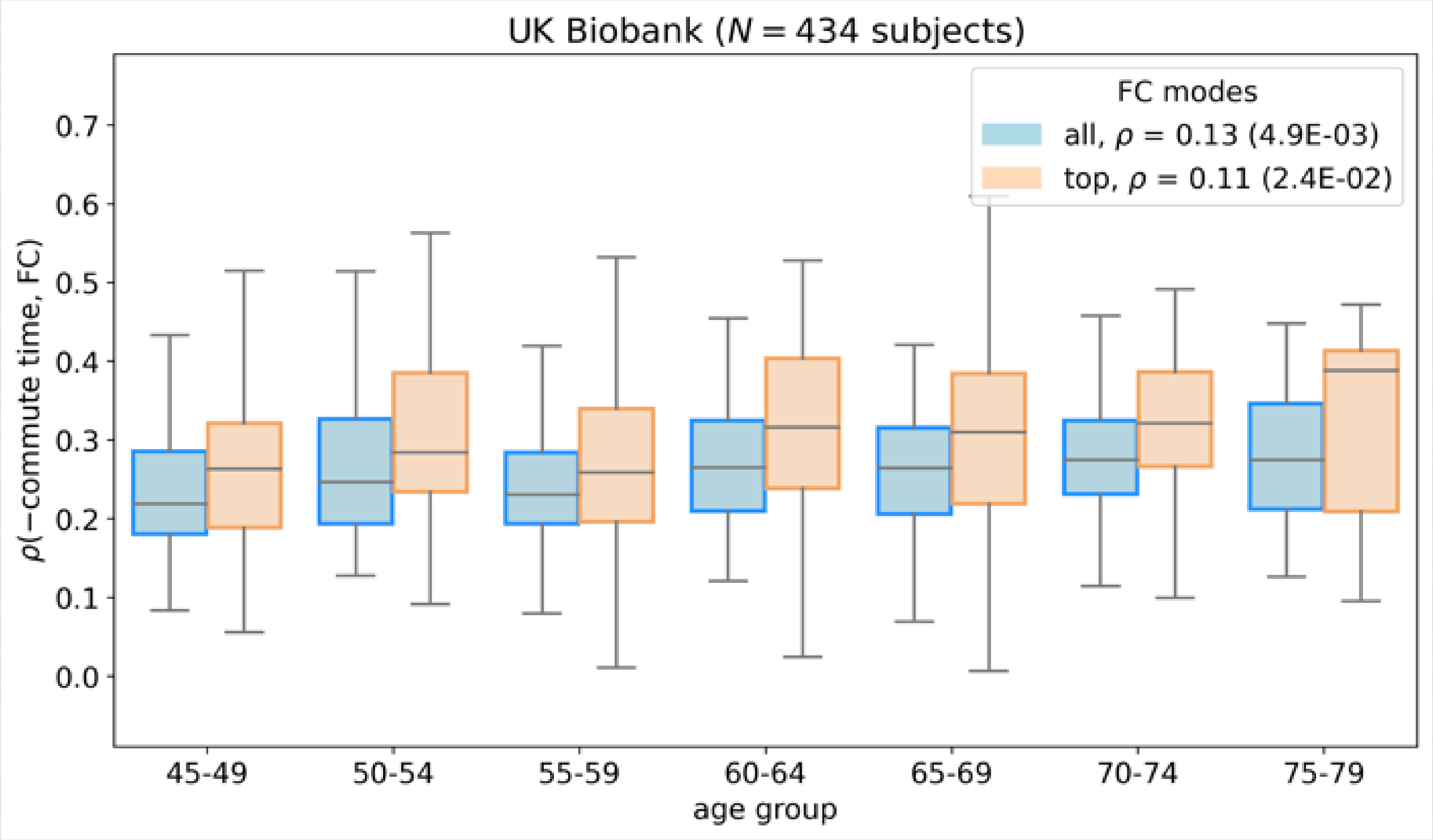
Commute time outperforms other communication metrics



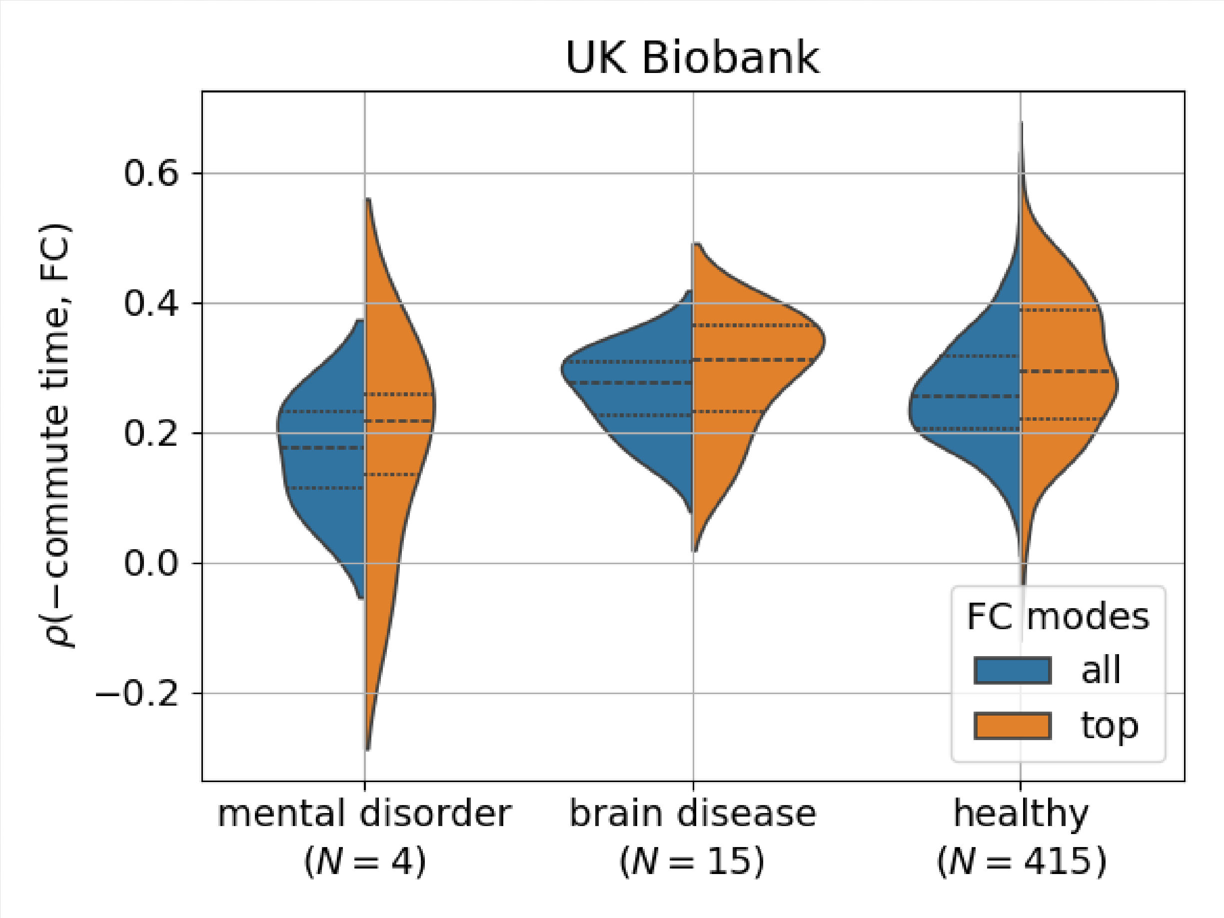
Commute time leading performer in another dataset



Age does not underlie large variation in commute time-FC correlation



Mental health does not underlie large variation in commute time-FC correlation

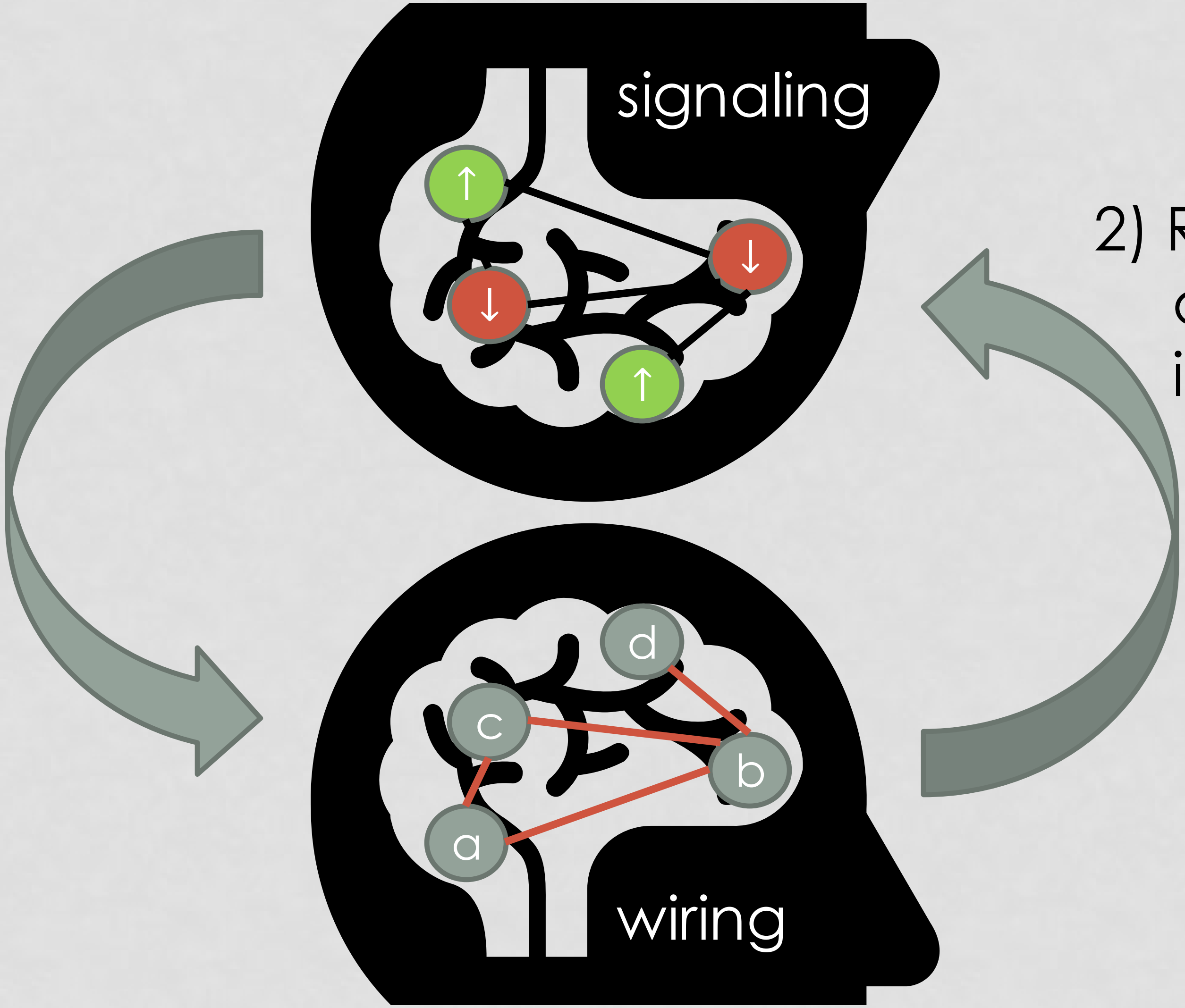


Part 3 summary: Commute time links structure to function

- Physically grounded in Markov chains
  - Random walker traversing a network structure
    - Differentiates between nodes with no physical edge between them
- Can calculate via mathematical expression with no parameters!
  - No need for numerics or parameter fitting

- Commute time – FC correlation still weak, $\langle\rho\rangle = -0.26$
  - Increases to $\langle\rho\rangle = -0.36$ when only considering the top mode
  - Machine learning predicted FC – empirical FC correlation, $\langle\rho\rangle = 0.55$

We investigated the two-way relationship between brain structure and function

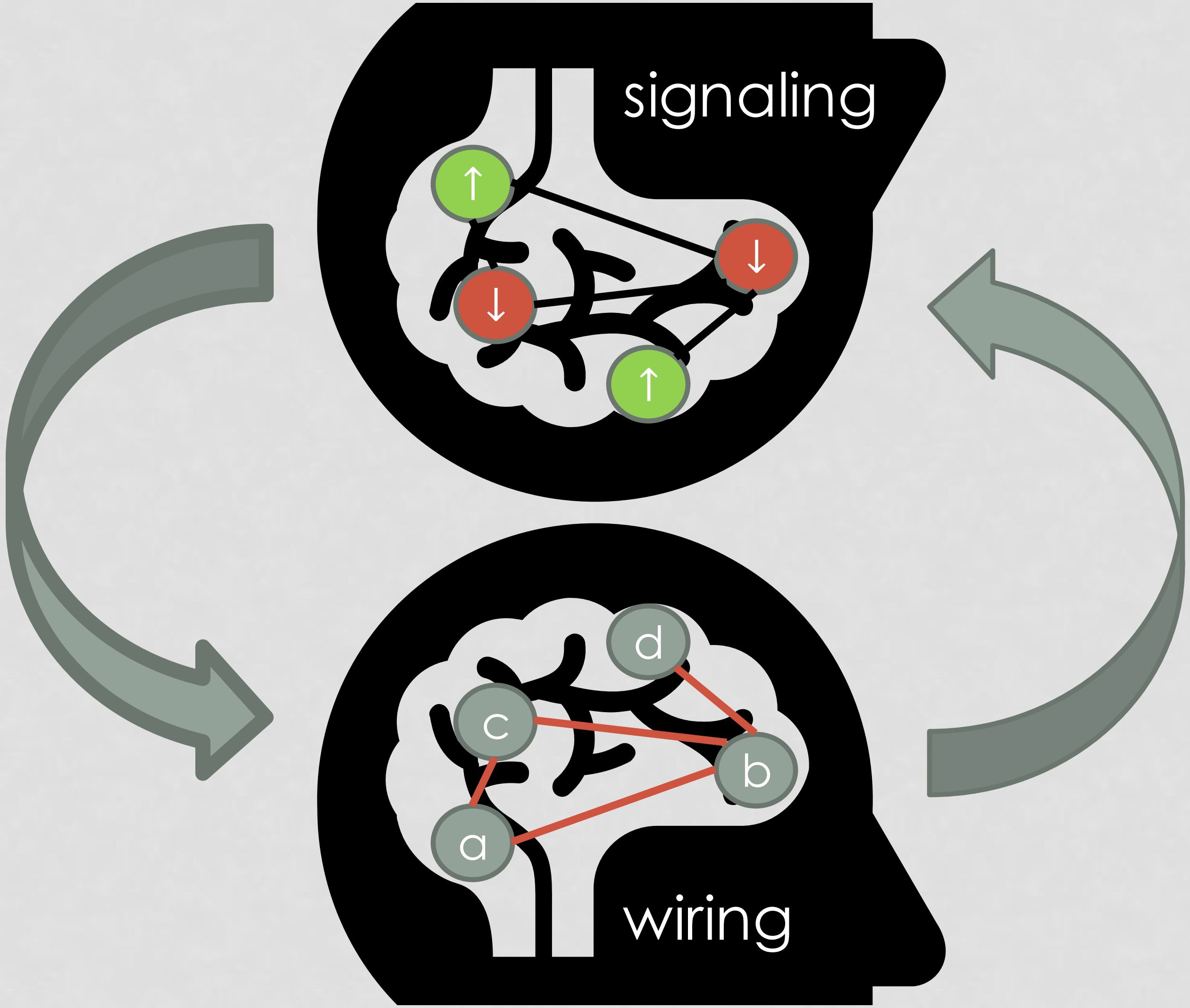


1) Tracts develop from regions in the giant cluster

2) Regional coupling decreases as age increases

3) Signals traverse the network like a random walk

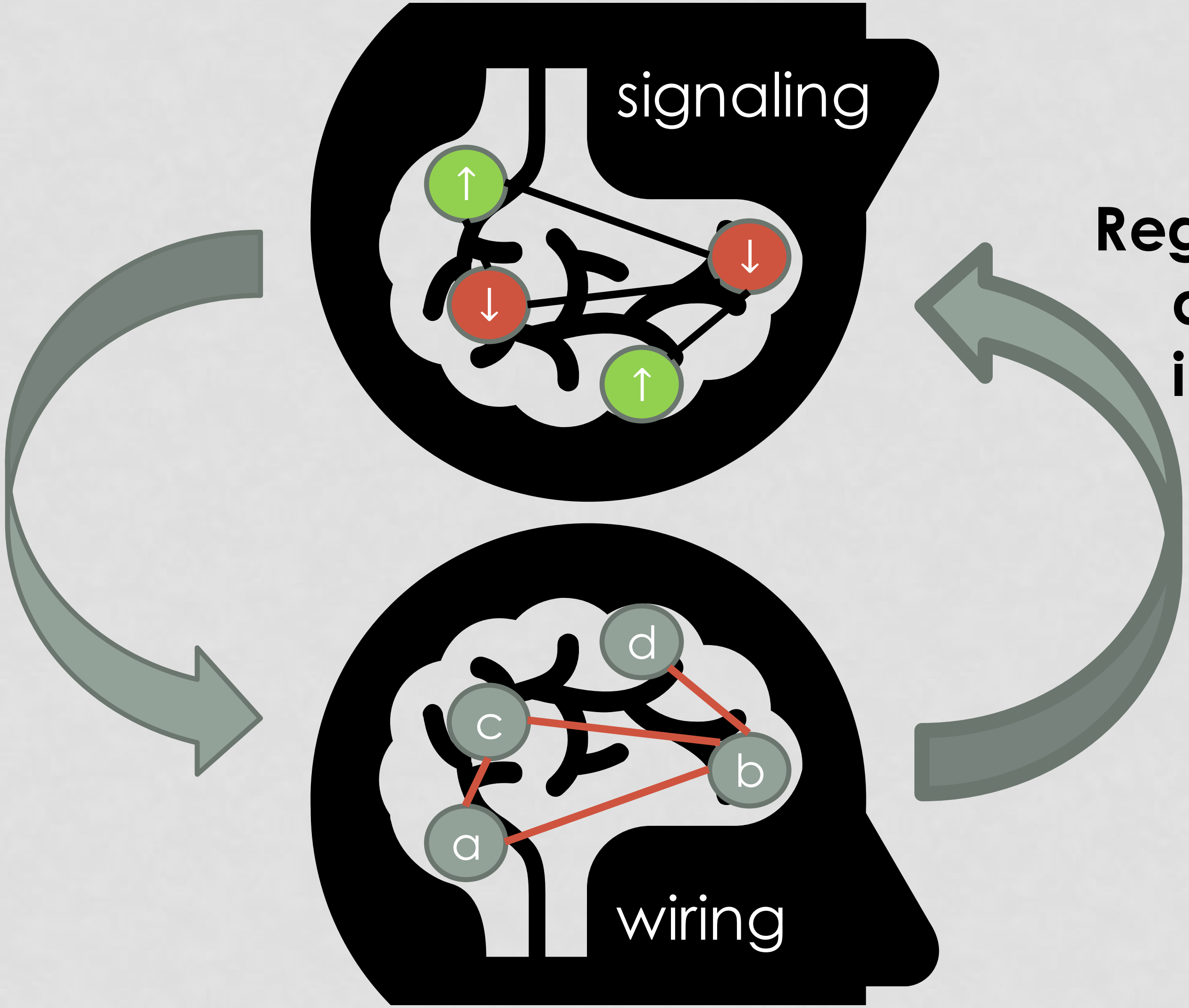
Part 1: **signaling dictates wiring**



Tracts develop from regions in the giant cluster

RR et al. (2023)

Part 2: wiring dictates signaling

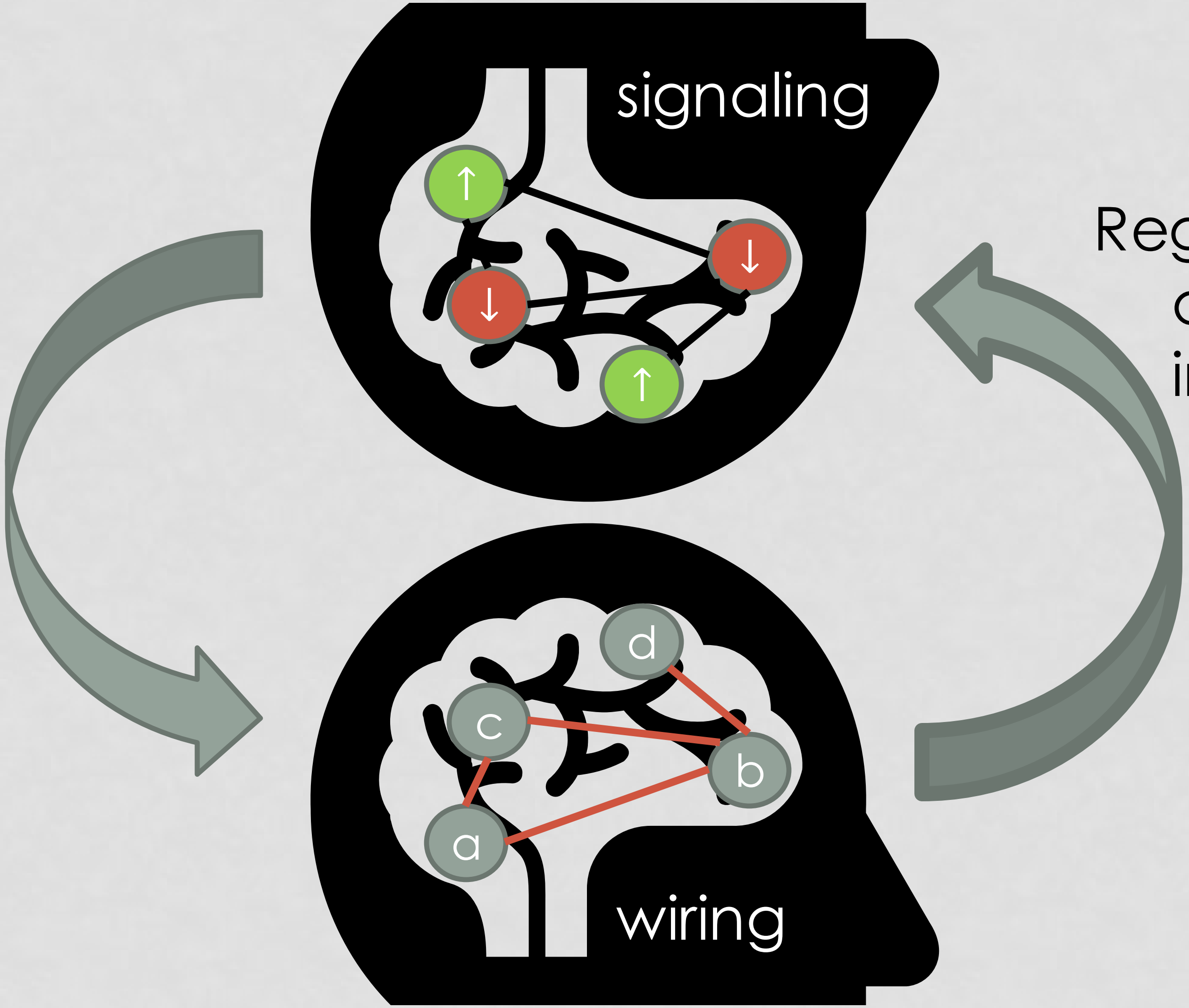


Tracts develop from regions in the giant cluster

Regional coupling decreases as age increases

Weistuch et al. (2021)
RR et al. (2024)

Part 3: **wiring dictates signaling**



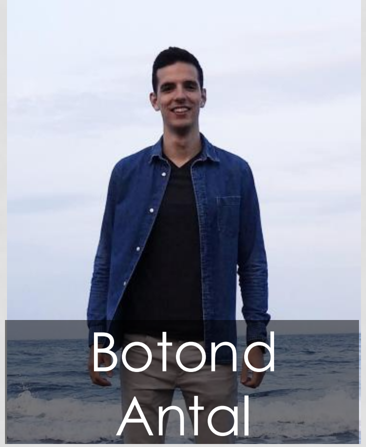
Tracts develop from regions in the giant cluster

Regional coupling decreases as age increases

Signals traverse the network like a random walk

RR et al. (under review)

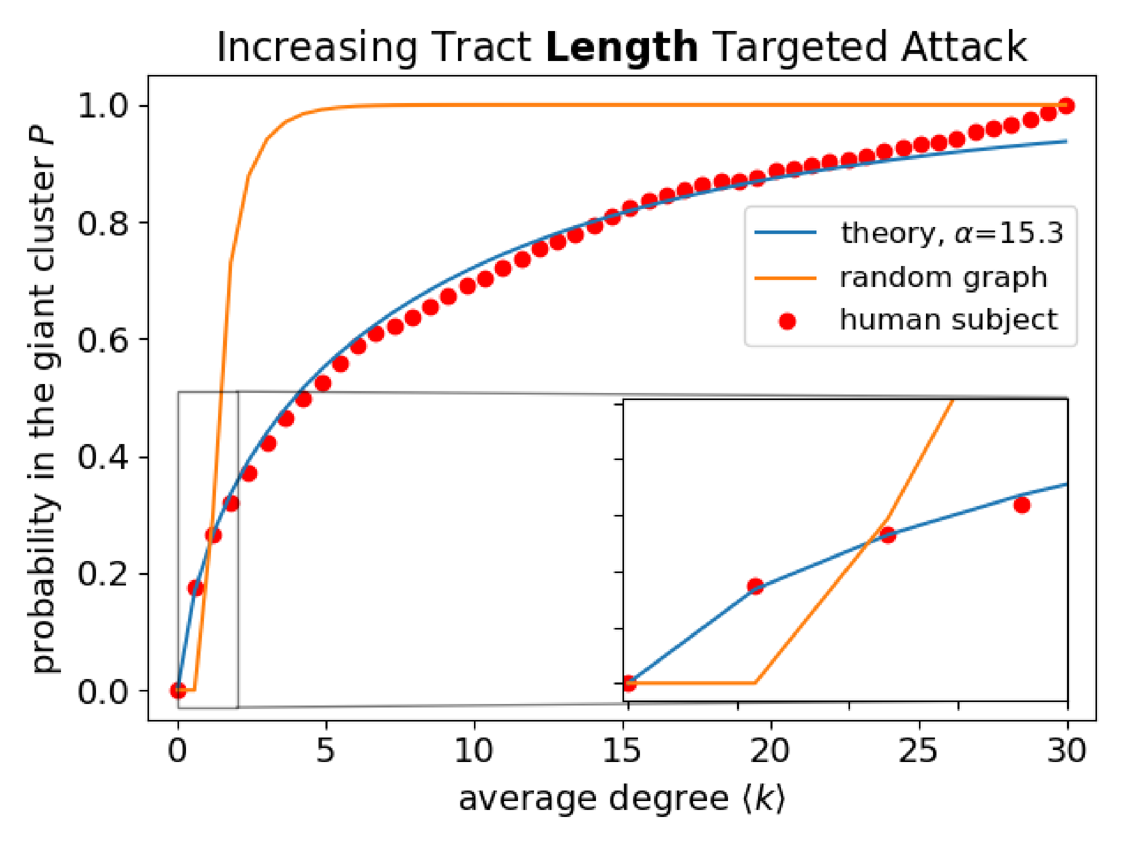
Acknowledgements

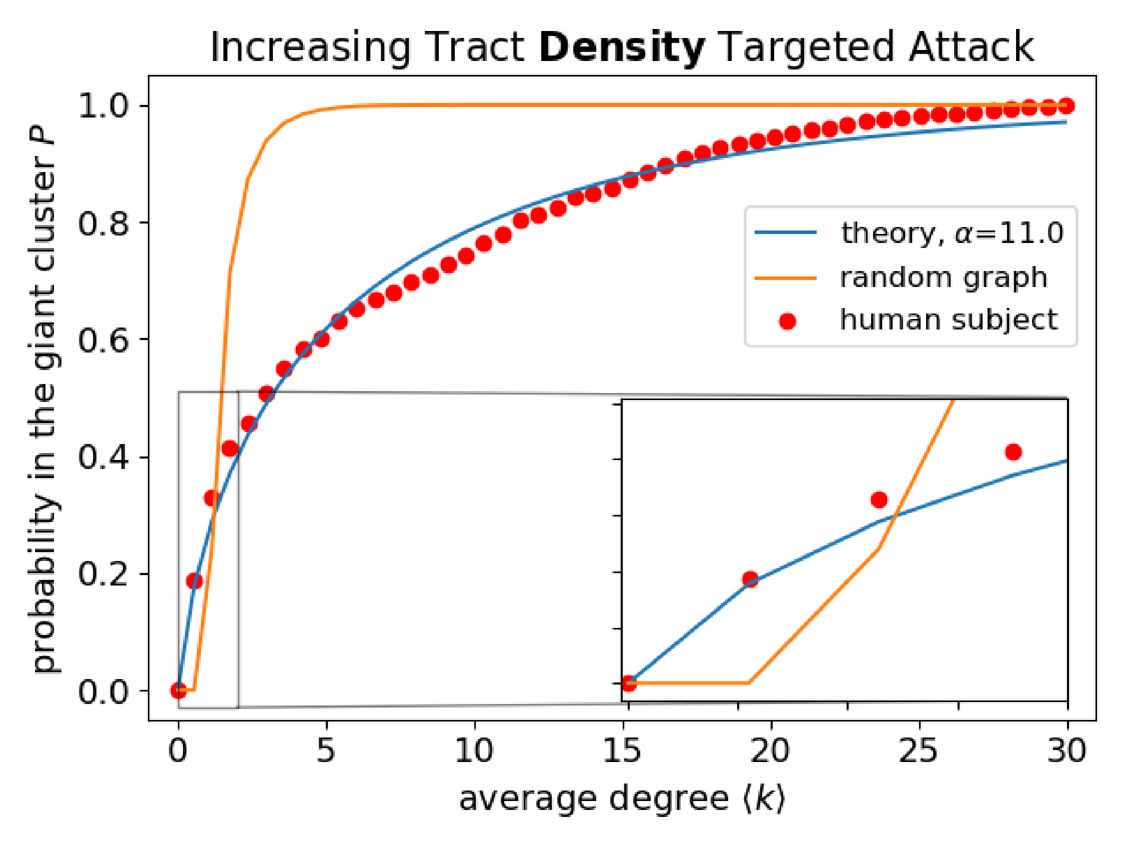


Questions??

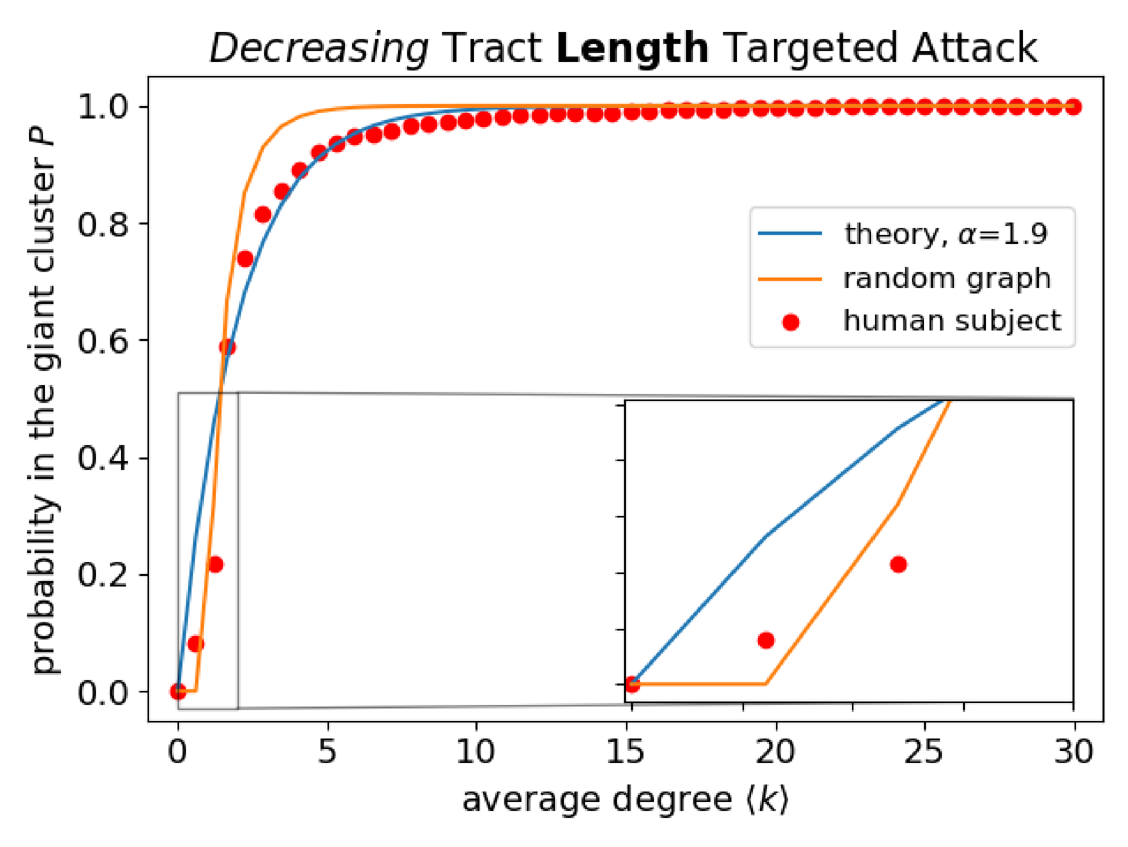
Supplementary slides

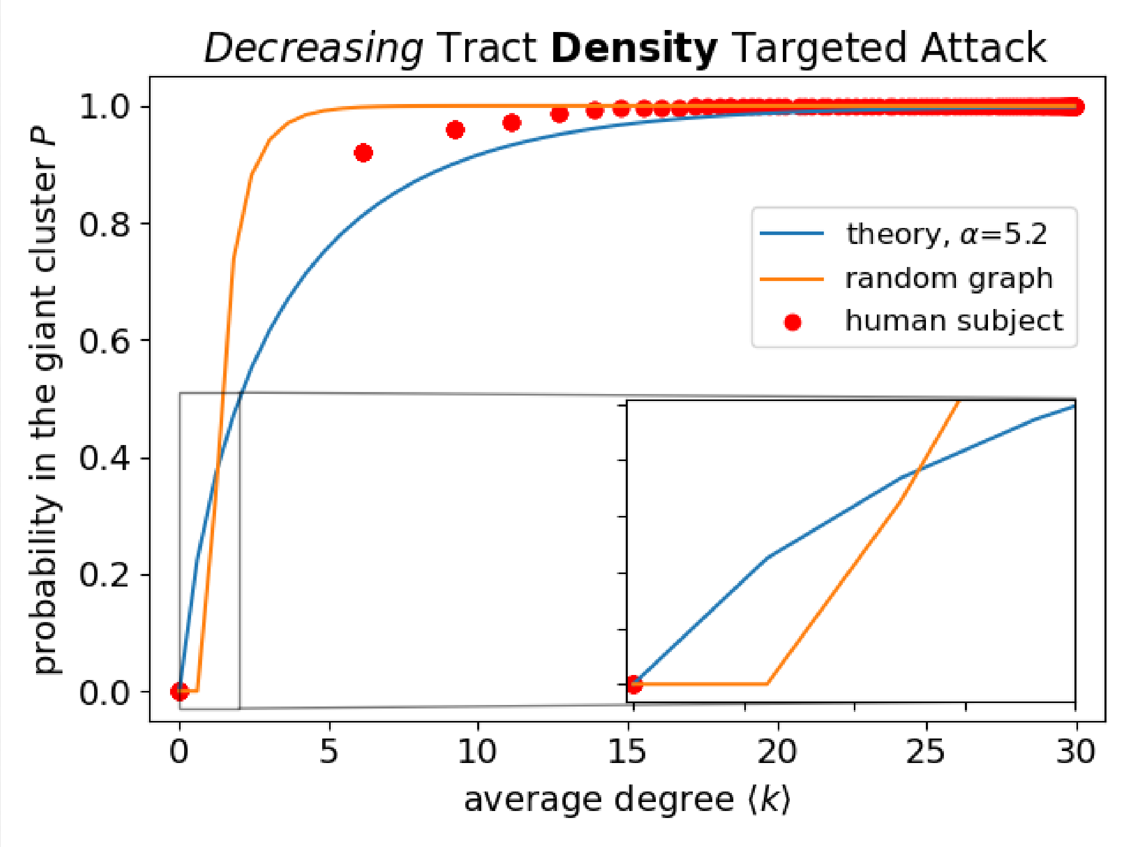
Theory captures experimental P curves with fitted α



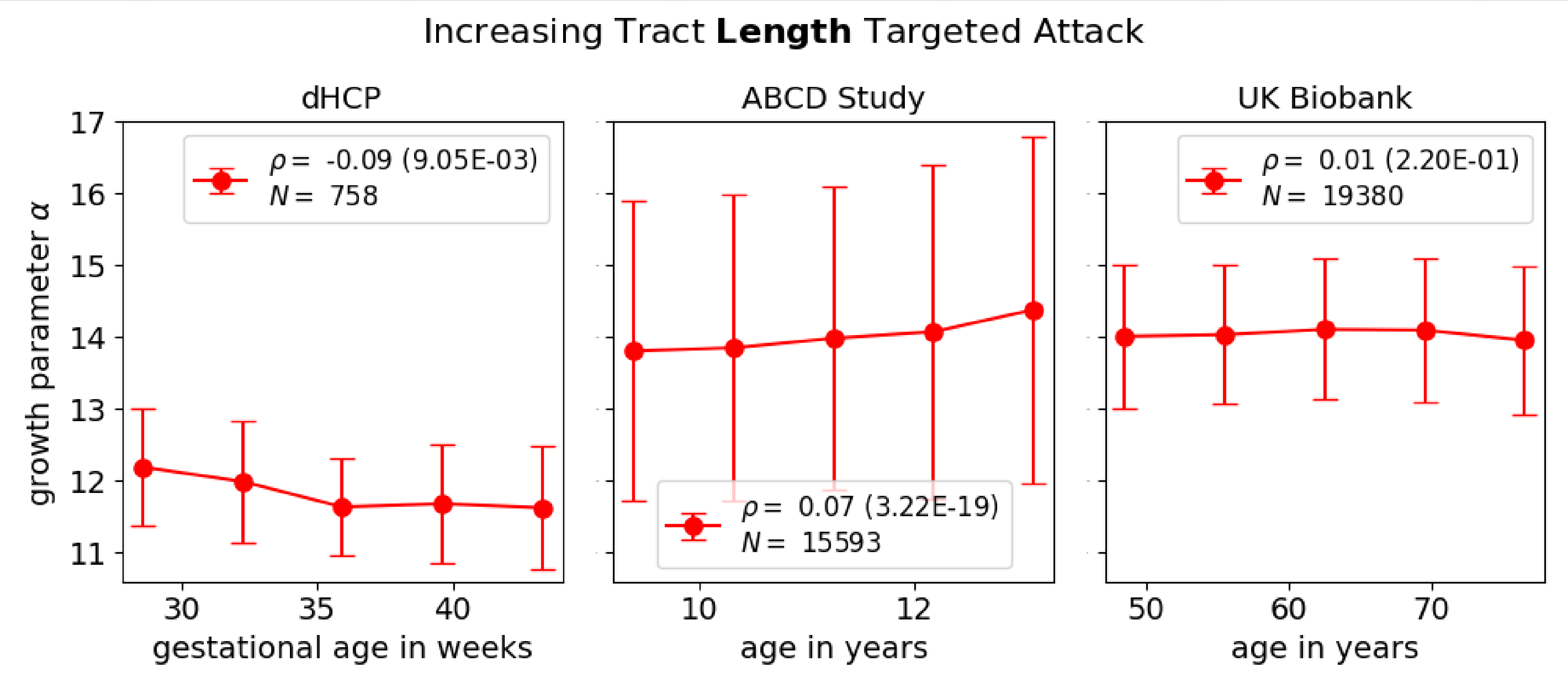


Decreasing tract length targeted attack essentially random; incomplete for tract density

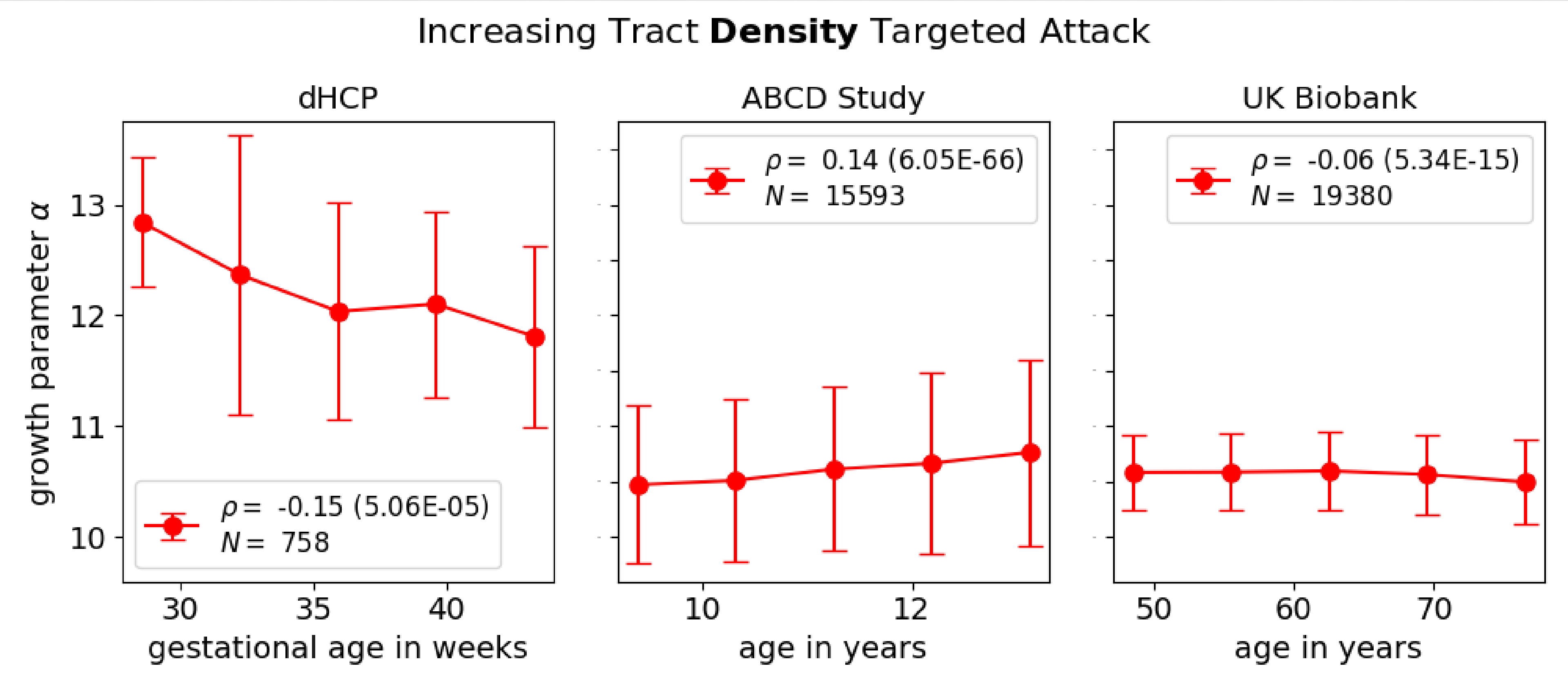




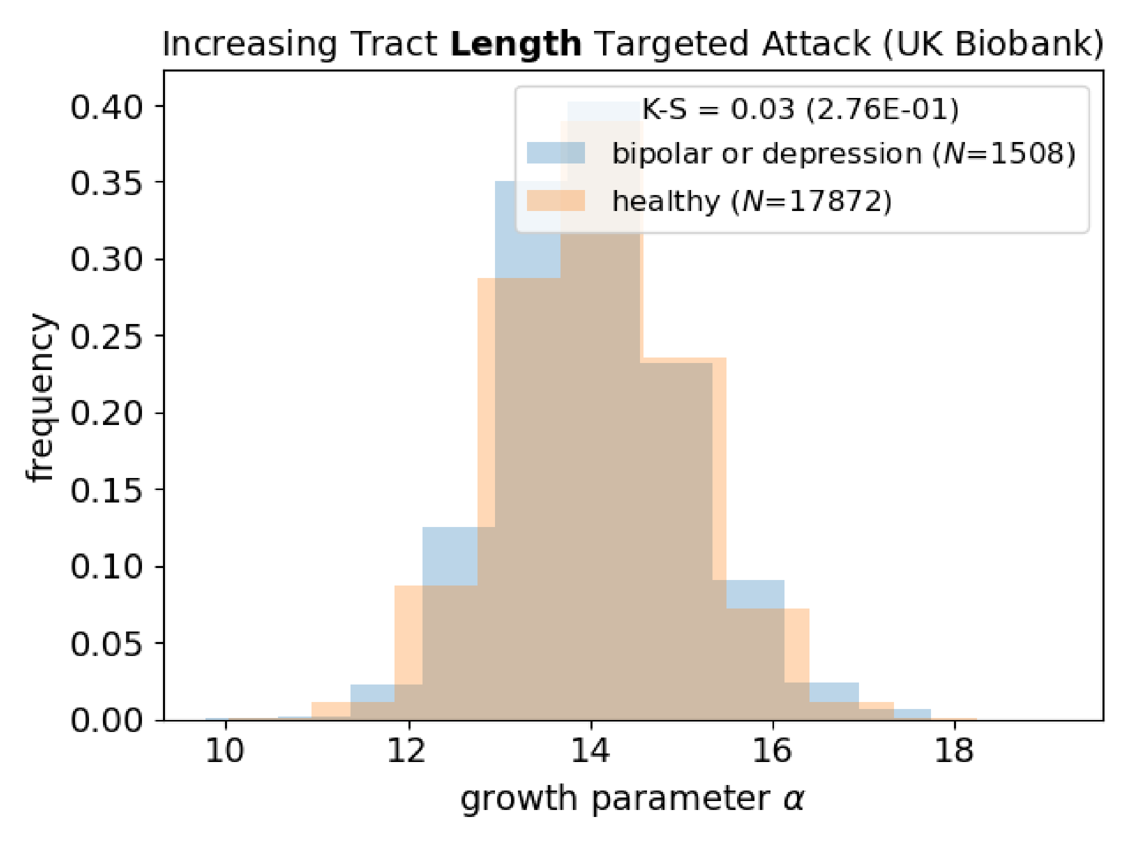
α values across individuals across datasets

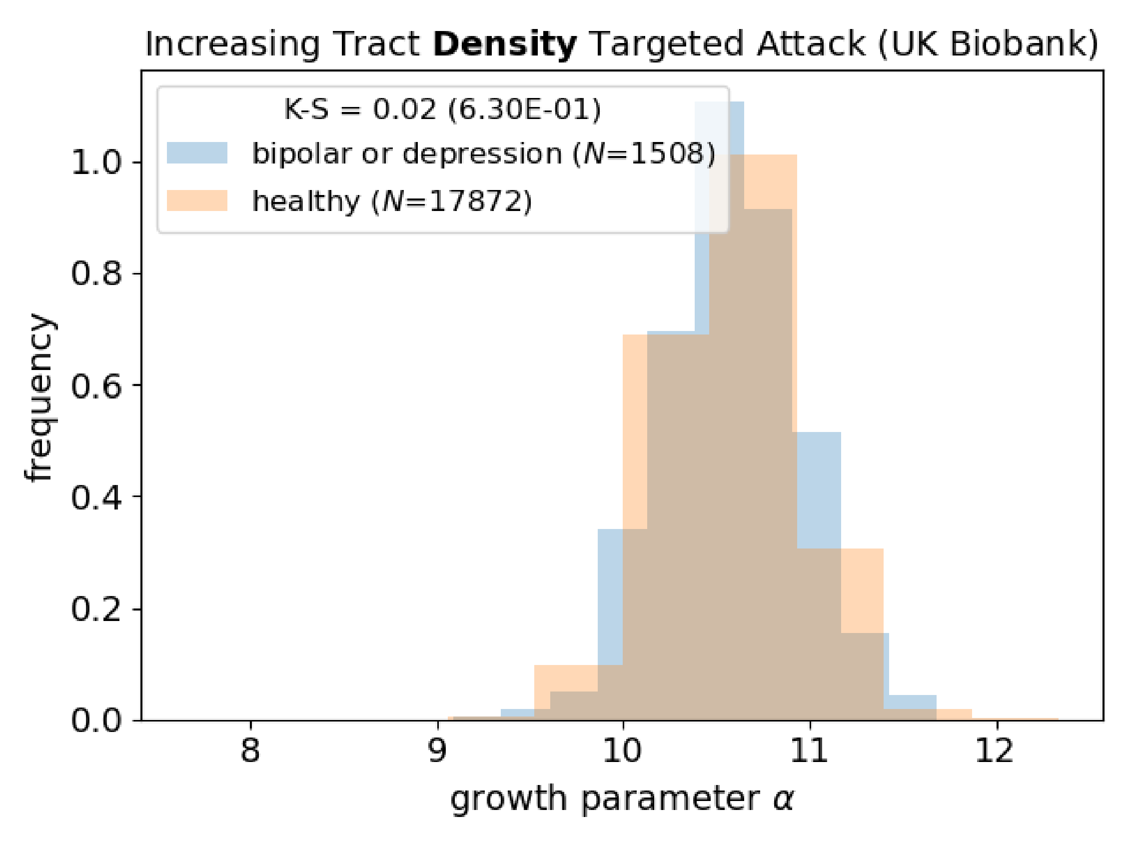


α values across individuals across datasets

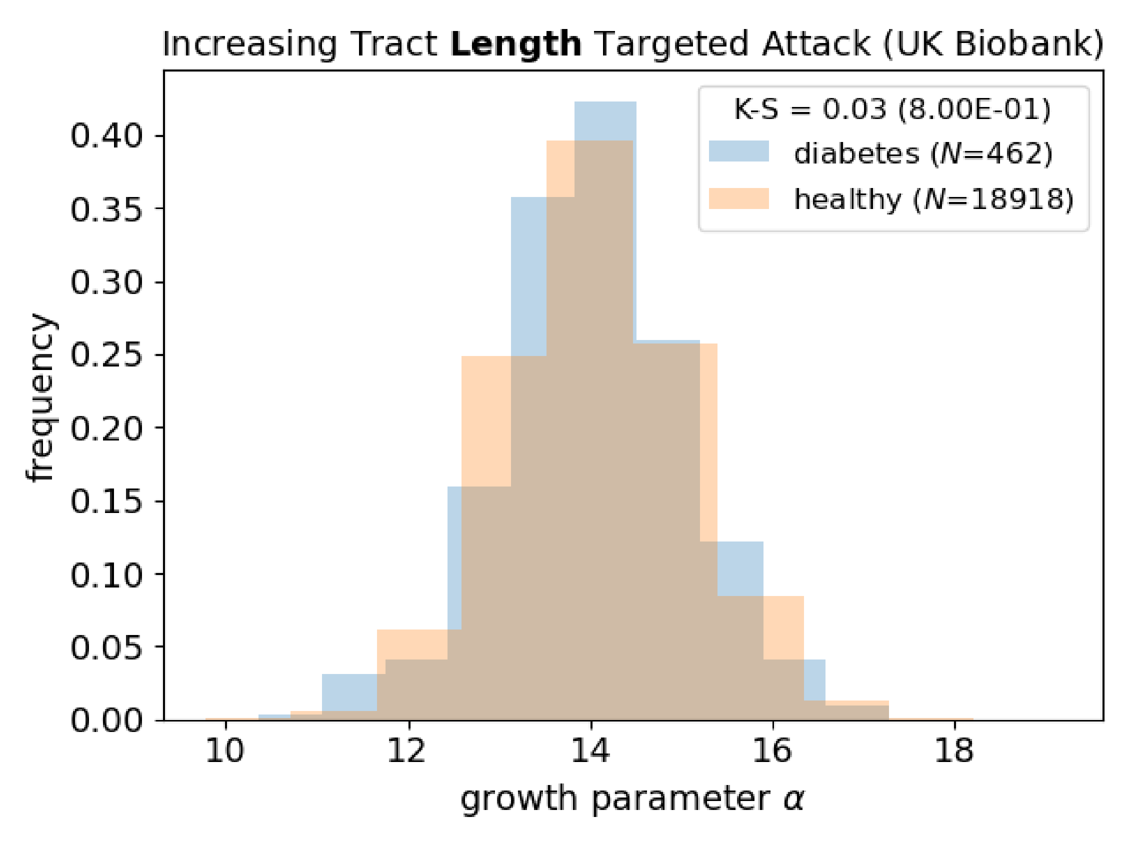


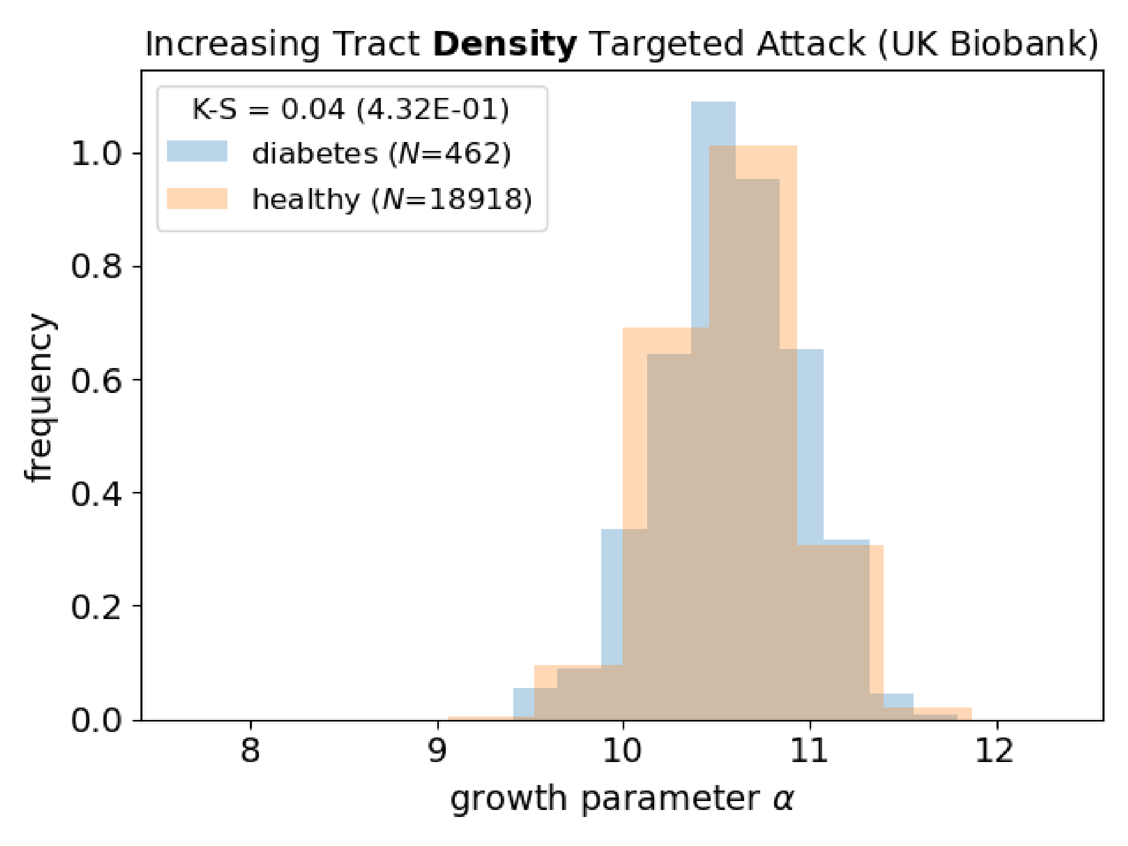
α values across individuals with bipolar or depression





α values across individuals with diabetes





Deriving an analytical equation encoding mechanism

- The probability p that n nodes have $E + 1$ edges during growth:

$$\begin{aligned} p(n|E+1) &= p(n|E)p(n \to n|E \to E+1) + p(n-1|E)p(n-1 \to n|E \to E+1) \\ &= p(n|E)[1 - p(n-1 \to n|E \to E+1)] + p(n-1|E)p(n-1 \to n|E \to E+1) \end{aligned}$$

- By counting the number of possible edge additions, we can explicitly calculate the transition probability $p(n \to n+1 \,|\, E \to E+1)$.

$$p(n \to n+1|E \to E+1) = \frac{\frac{1}{\alpha}n(N-n)}{\frac{1}{2}n(n-1) - E + \frac{1}{\alpha}n(N-n)}$$

N := total number of nodes at end of development

$1/\alpha$:= probability of forming a new node (*<u>fit to experimental P curve</u>)

Deriving an analytical equation encoding mechanism

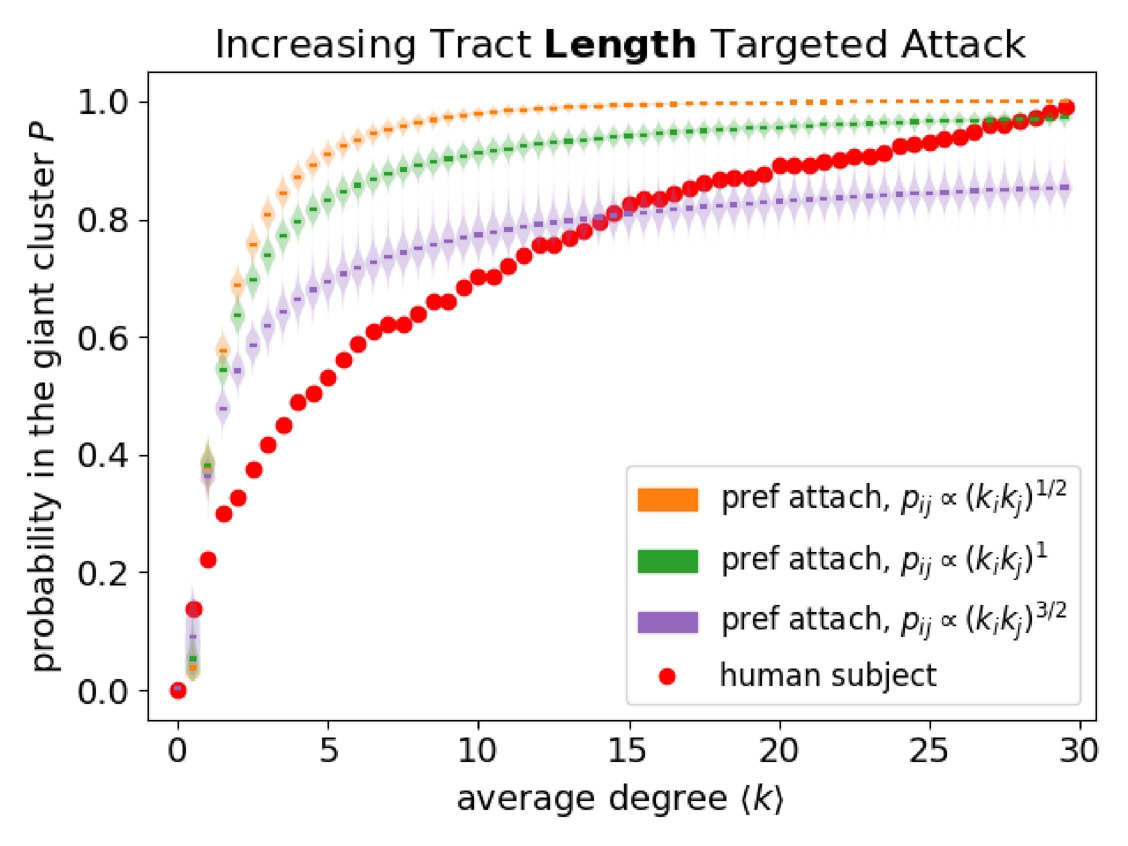
- Plugging in the transition probability into the difference equation, taking the $N \to \infty$ limit, and defining $P = n/N$ and $\langle k \rangle = 2E/N$, we get a partial differential equation,

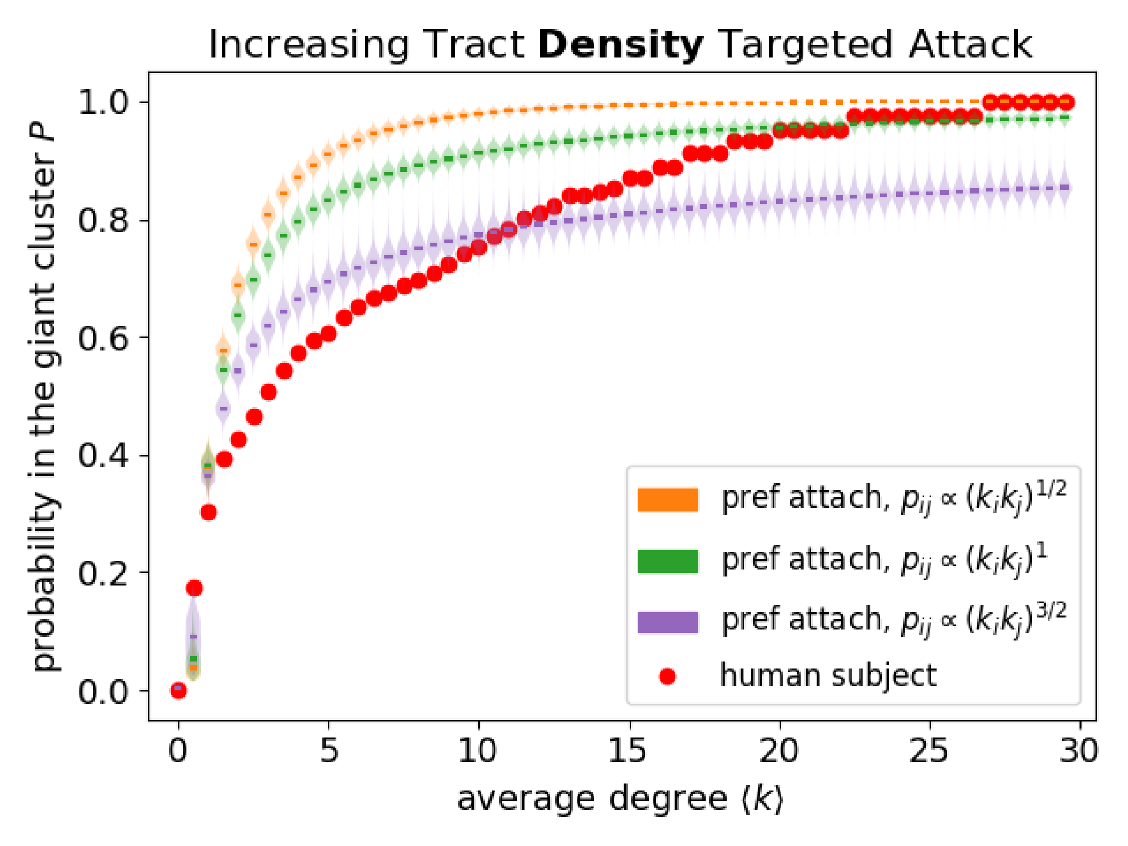
$$\frac{\partial p(P|\langle k\rangle)}{\partial \langle k\rangle} = -\frac{\partial}{\partial P}\left\{\frac{1-P}{2-(2-\alpha)P}p(P|\langle k\rangle)\right\}$$

- Solving the differential equation using the method of characteristics gives an equation for $P(\langle k \rangle)$,

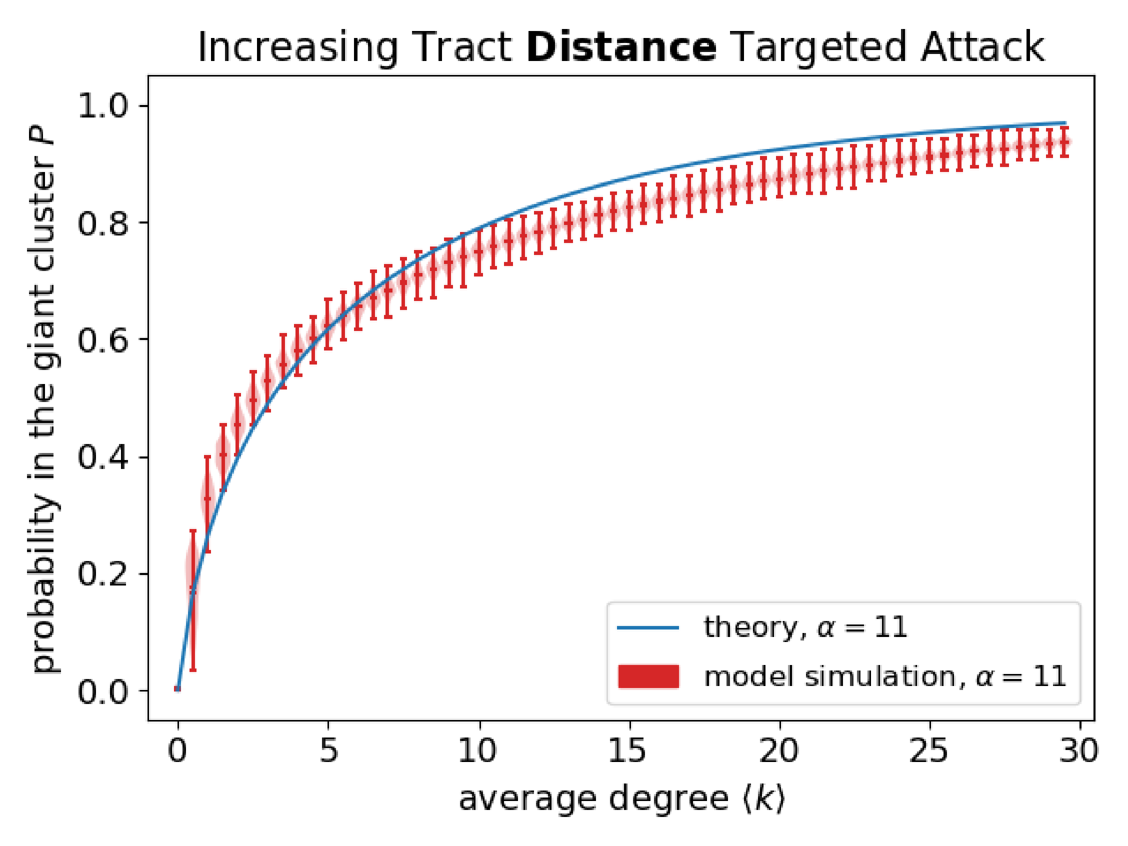
$$P(\langle k\rangle) = 1 + \left(\frac{1}{1-2/\alpha}\right) W\left[\left(\frac{2}{\alpha}-1\right)e^{-(1-2/\alpha)}e^{-\langle k\rangle/\alpha}\right]$$

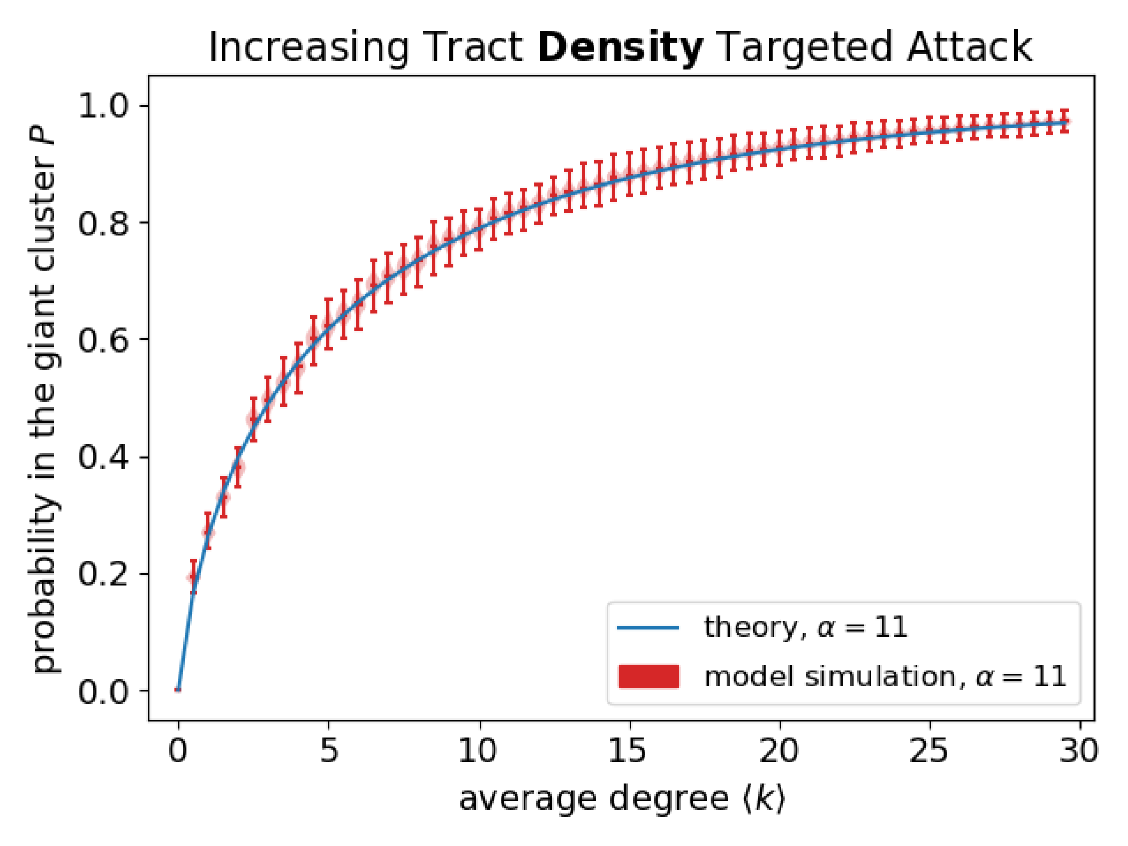
General preferential attachment models do not capture experiment



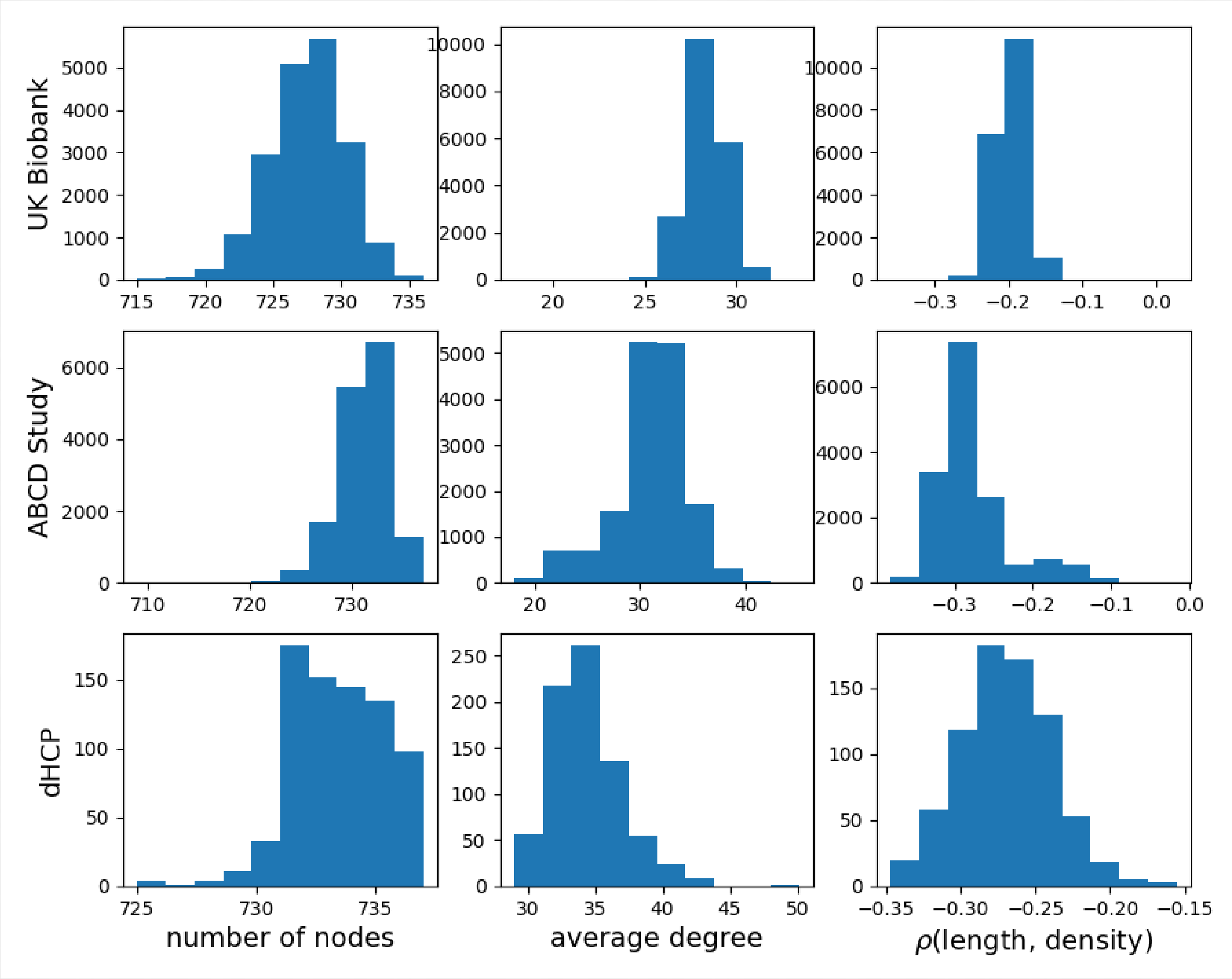


Simulations verify Early Path Dominance model

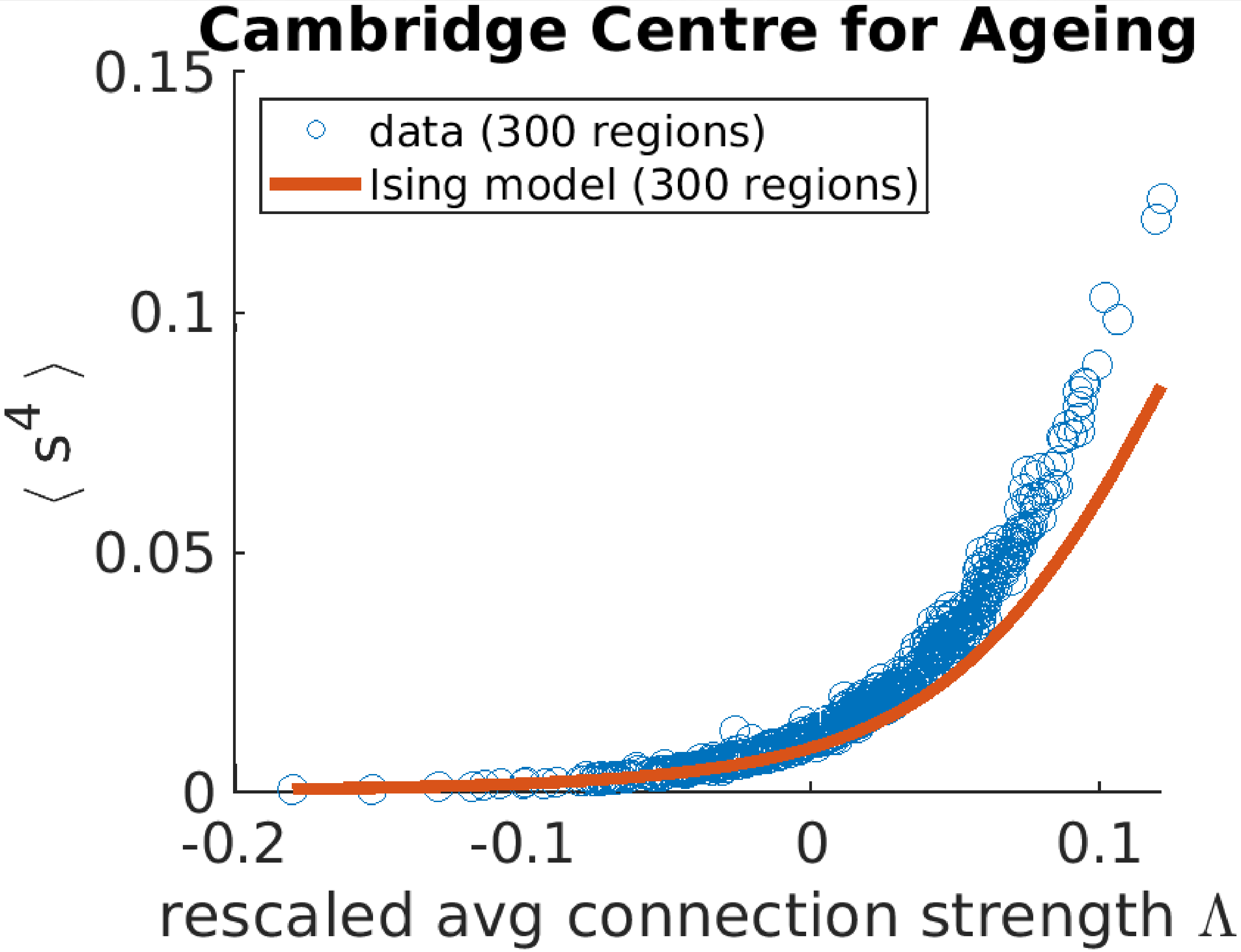




Basic network properties of datasets



Ising model consistently inaccurate for subjects with $\Lambda > 0$



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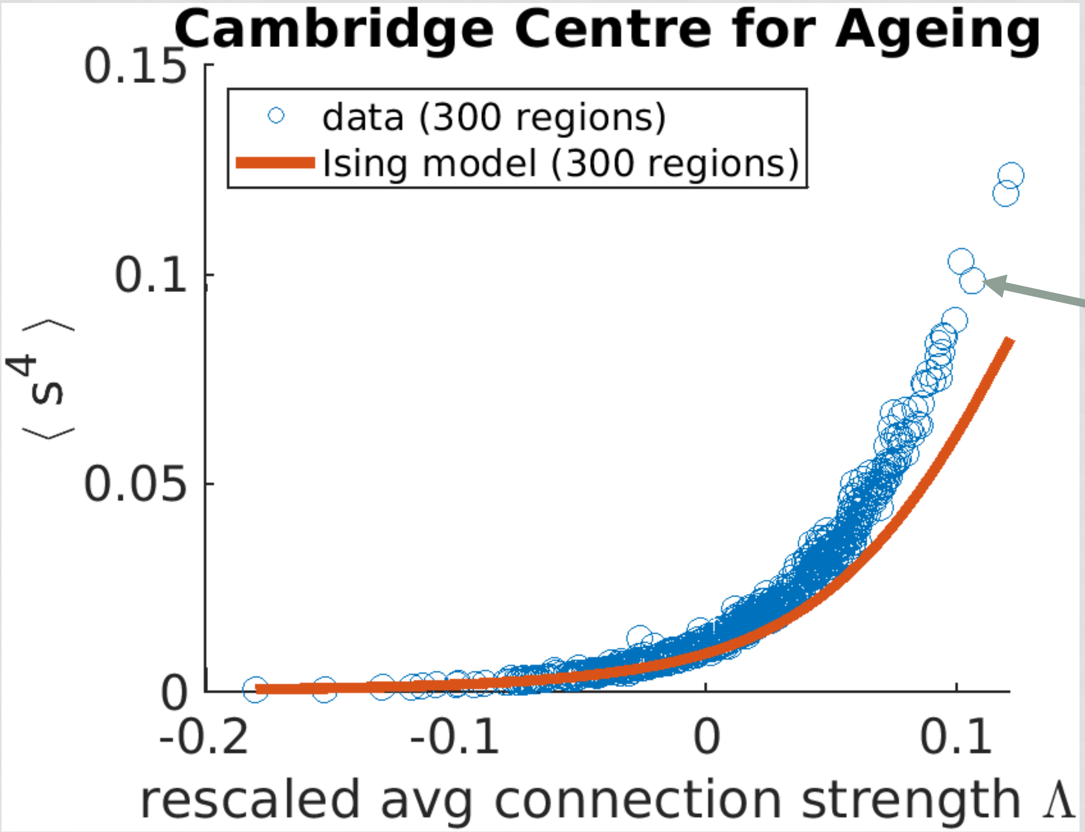
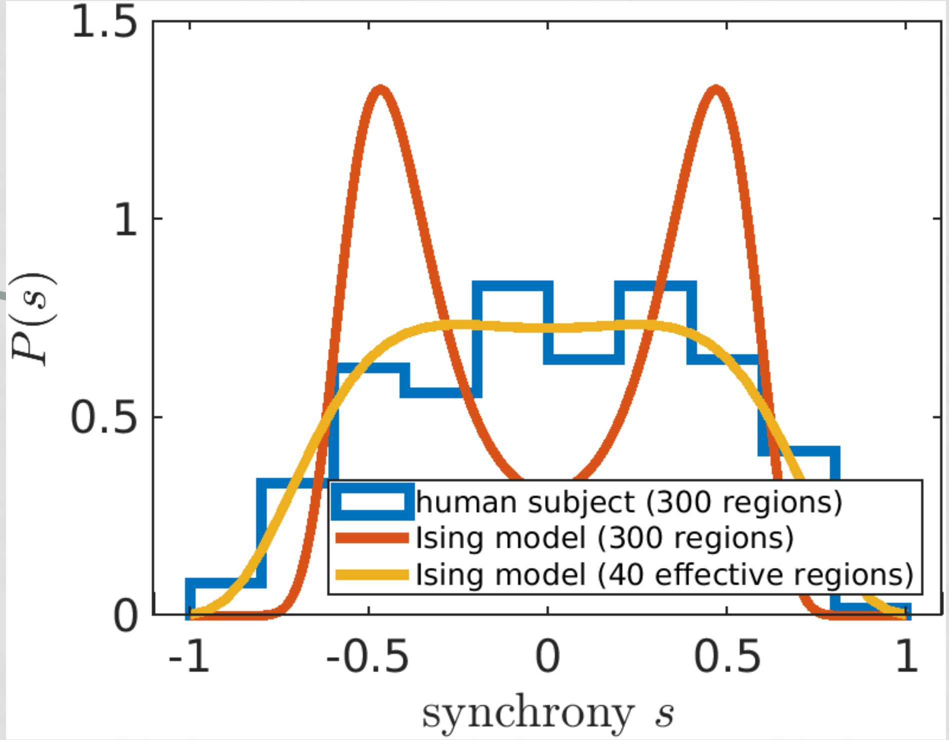
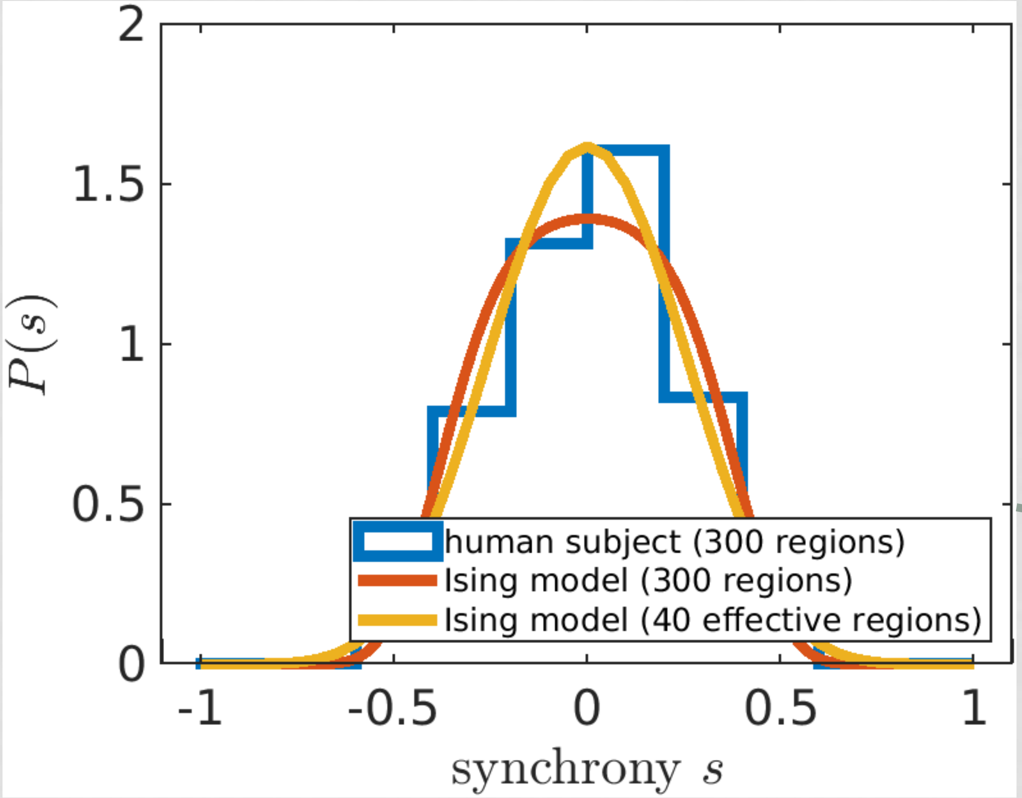
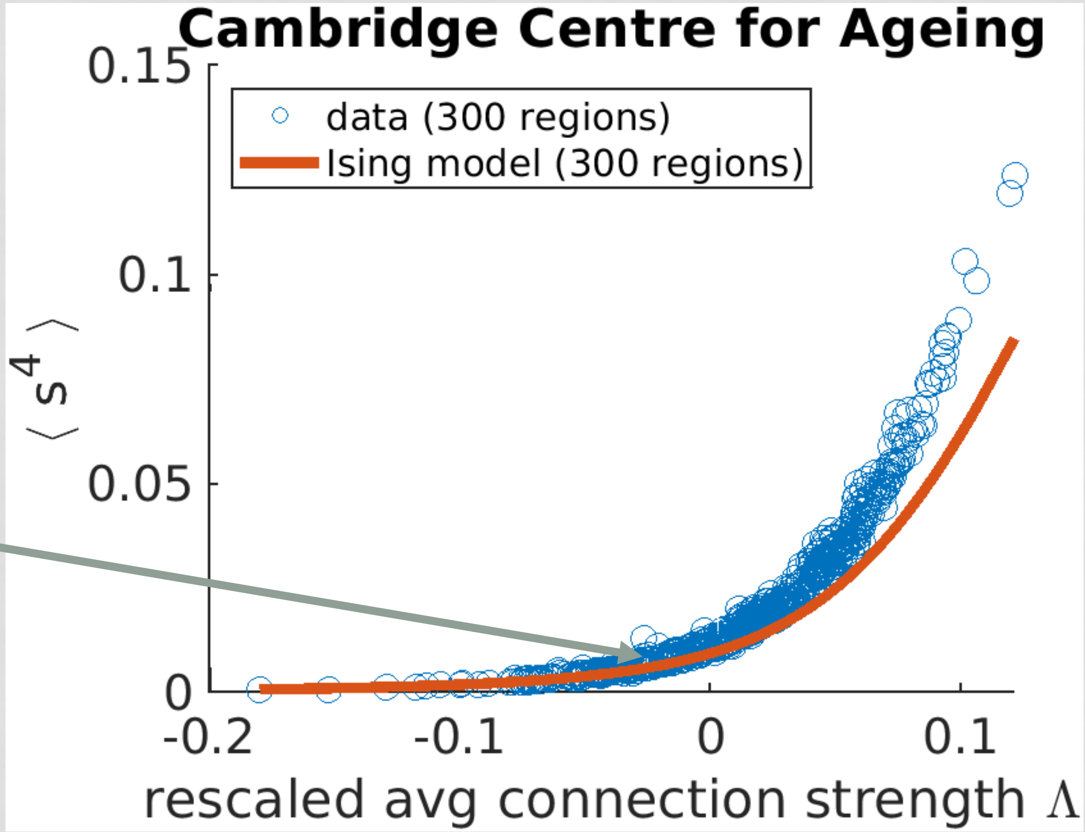


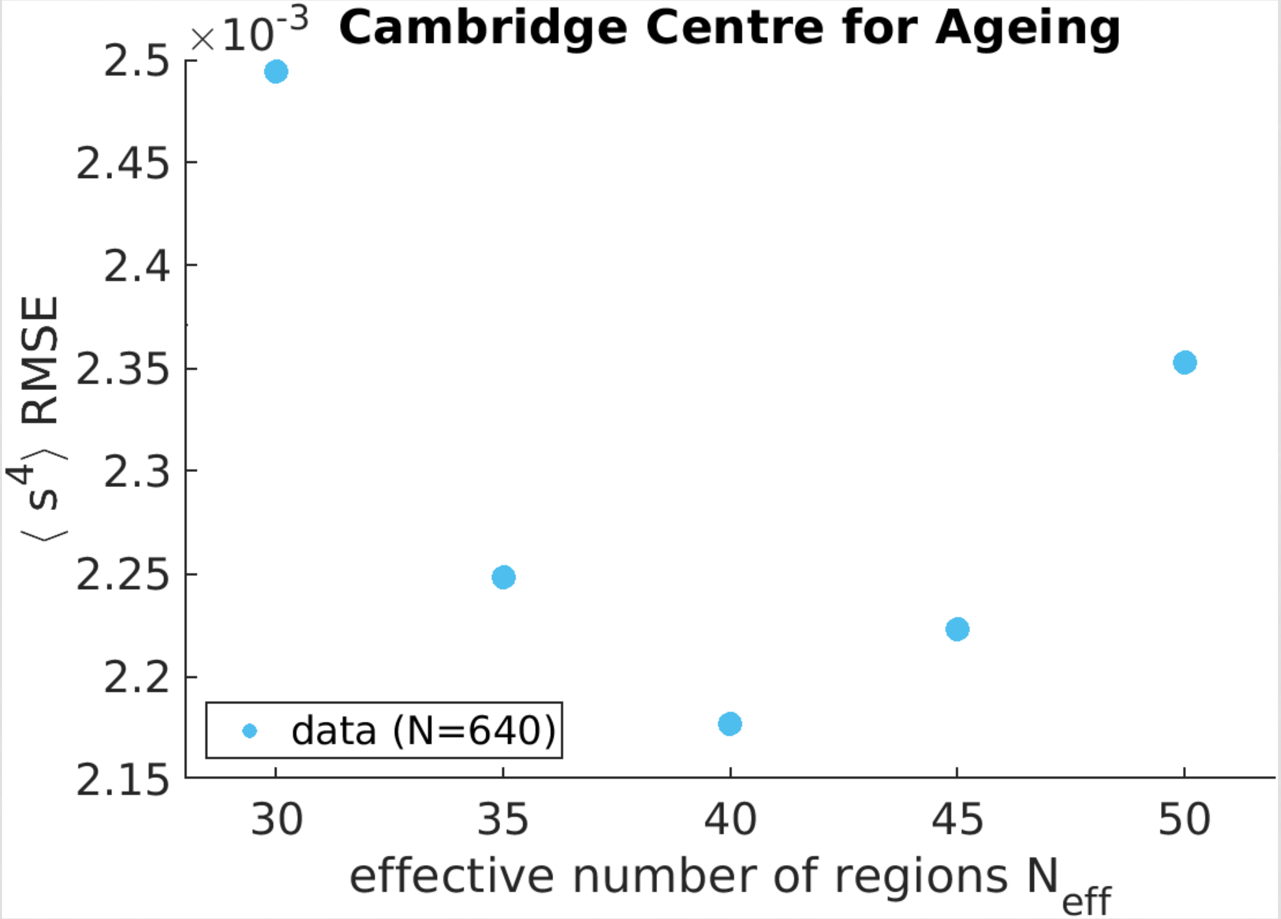


Ising model is accurate for subjects with $\Lambda < 0$





Minimizing <s^4> root mean square error to identify N_{eff}



N_{eff} for different datasets and parcellations

N_{eff}	Seitzman atlas (300 regions)	No atlas (125879 voxels)
Cambridge Centre for Ageing	40	65
Human Connectome Project	40	125

Ising model to Landau theory

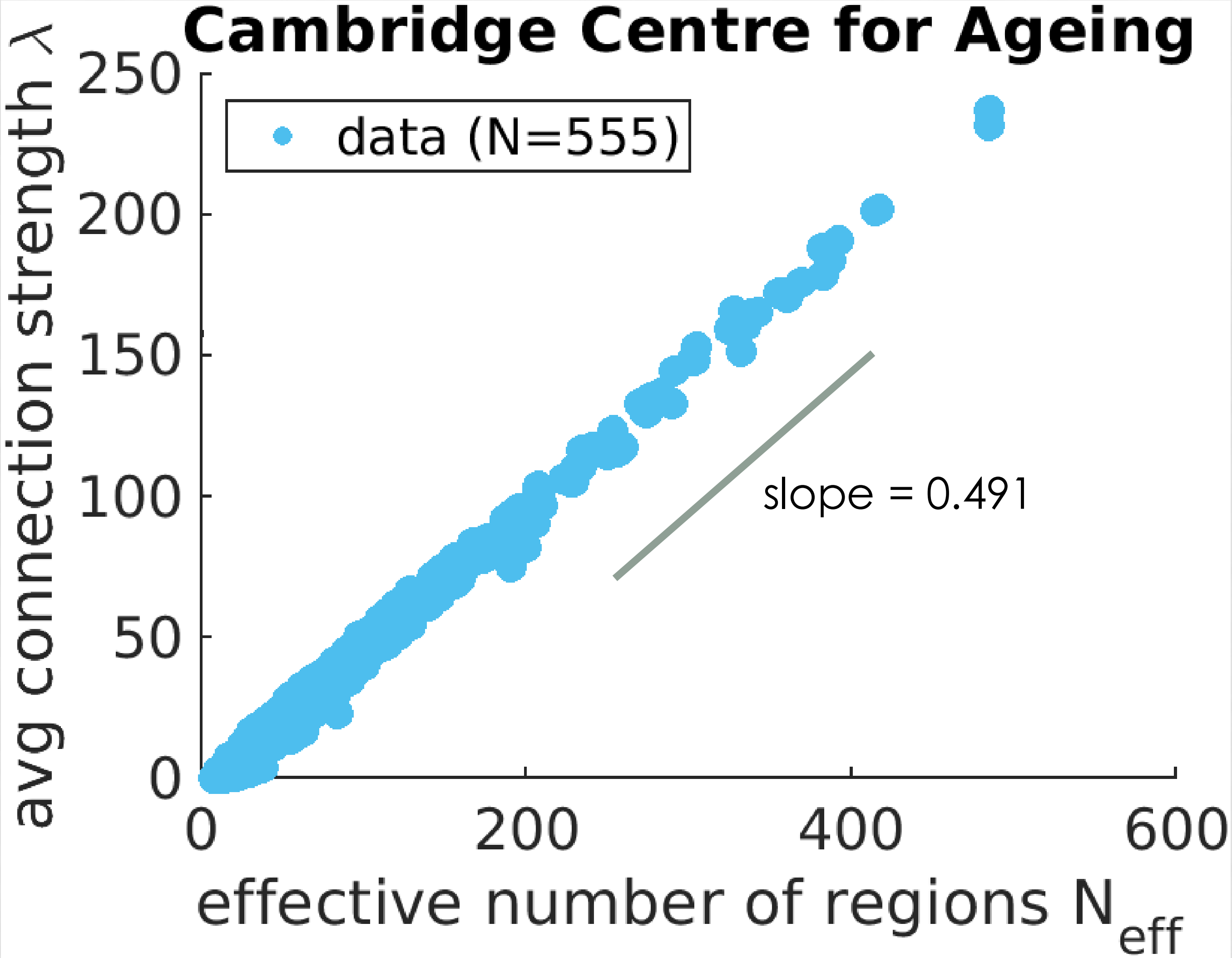
$$P(s) \propto \overbrace{\binom{N}{N(1+s)/2}}^{\text{entropy}} \overbrace{e^{\lambda N^2 s^2}}^{\text{enthalpy}}$$

$$\approx \left[1 - s^2 + s^4/3\right]^{N/2} e^{\lambda N^2 s^2}$$

$$\approx \exp\left[-\frac{N}{2}s^2 - \frac{N}{12}s^4\right] e^{\lambda N^2 s^2}$$

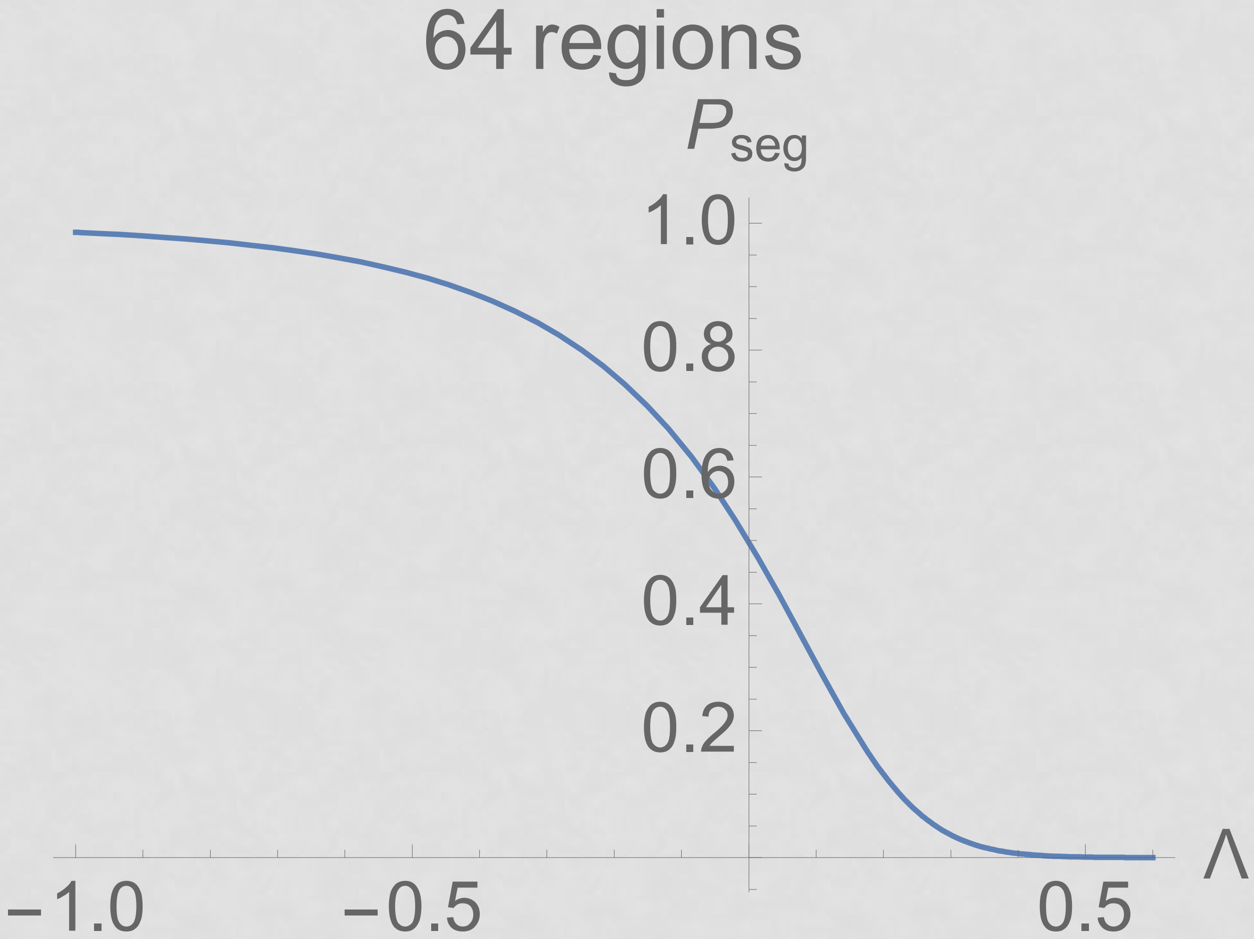
$$= \exp\left[\frac{N}{2}\Lambda s^2 - \frac{N}{12}s^4\right]$$

Fitting N_{eff} per individual is redundant to λ



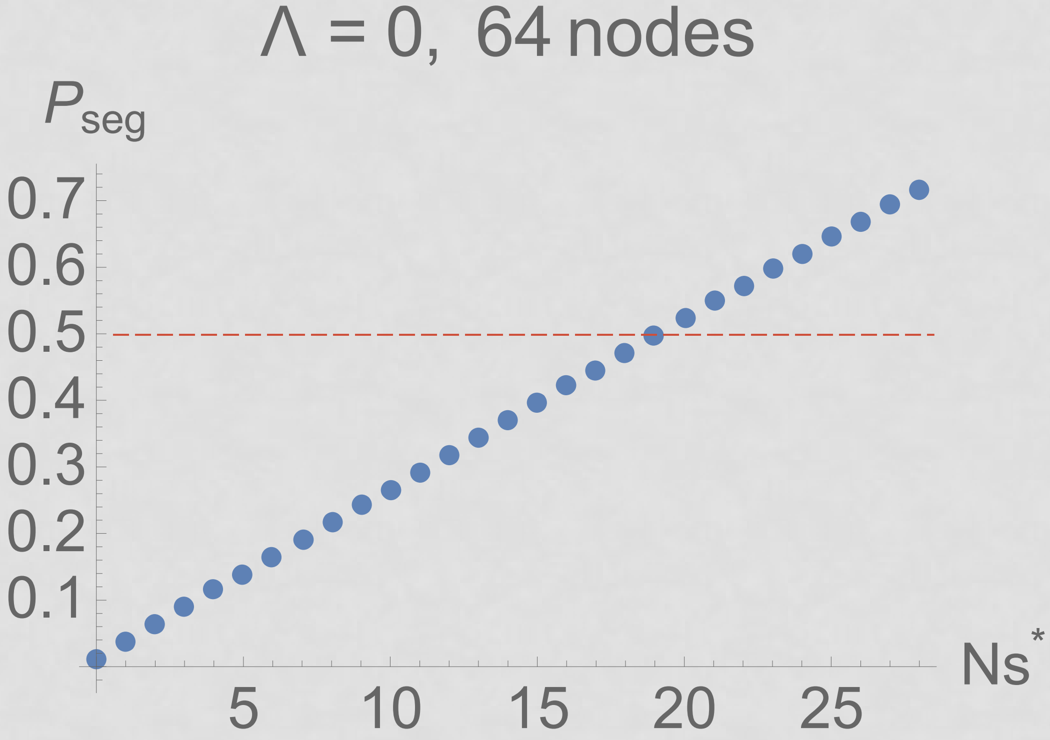
$$\langle s^2 \rangle = -\frac{1}{2\lambda - N_{\mathrm{eff}}}$$

Numerical solution of P_{seg} is sigmoidal across Λ

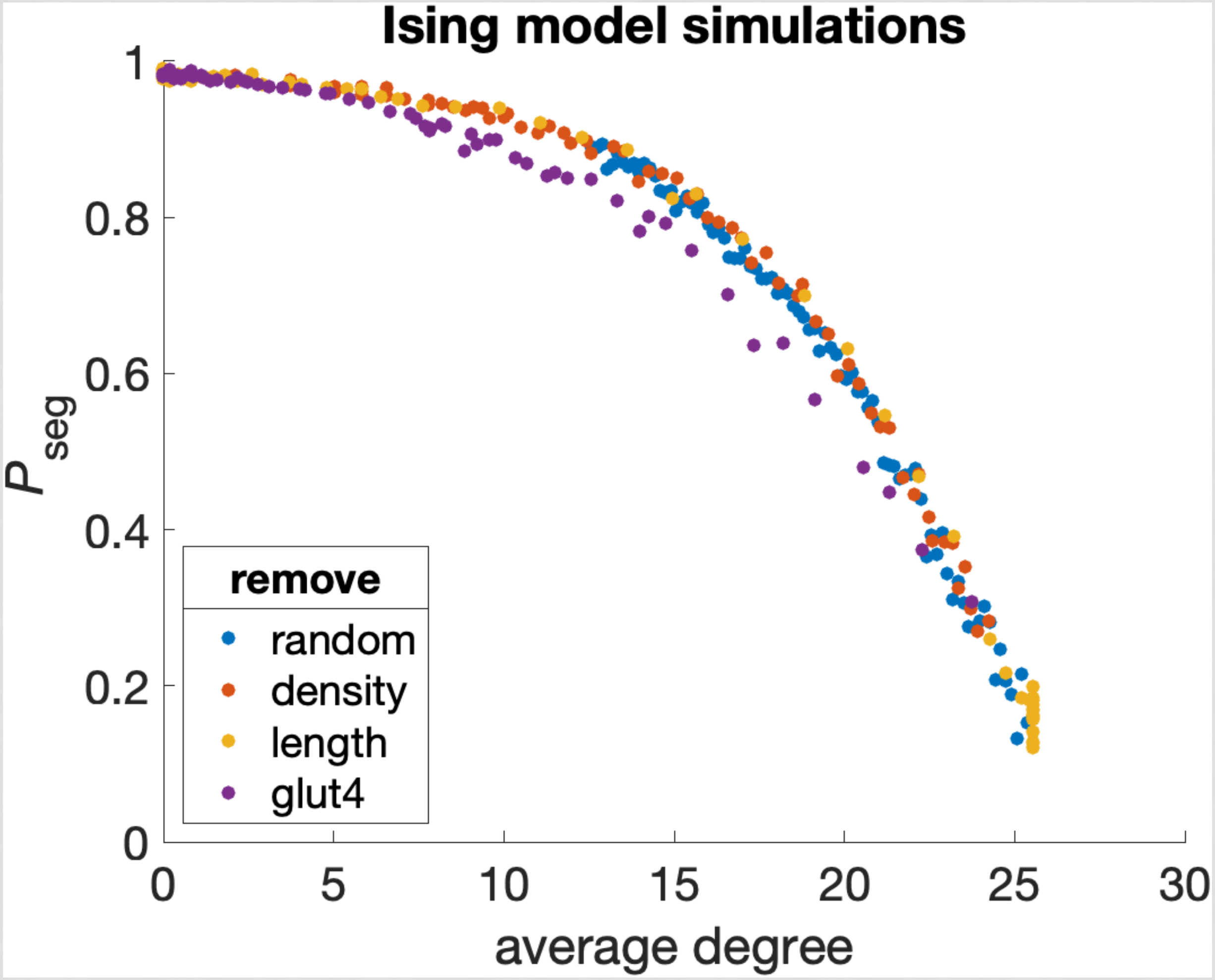


Synchrony threshold s* for defining segregated state

- Set s* such that $P_{seg} = 1/2$ at $\Lambda = 0$



Ising simulations cannot differentiate among specific degeneration mechanisms



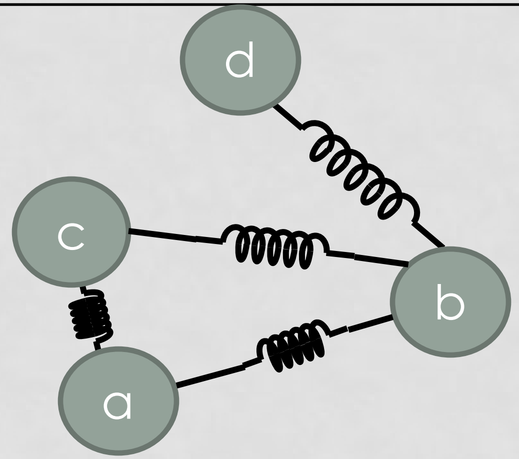
fMRI acquisition parameters

	Field strength	Repetition time (TR)	Echo time (TE)	Flip angle	Voxel size	Number of time points
CamCAN	3T	1970 ms	30 ms	78°	3 x 3 x 4.44 mm^3	241
HCP	3T	800 ms	37 ms	52°	2 x 2 x 2 mm^3	1912
UKB	3T	735 ms	39 ms	52°	2.4 x 2.4 x 2.4 mm^3	490

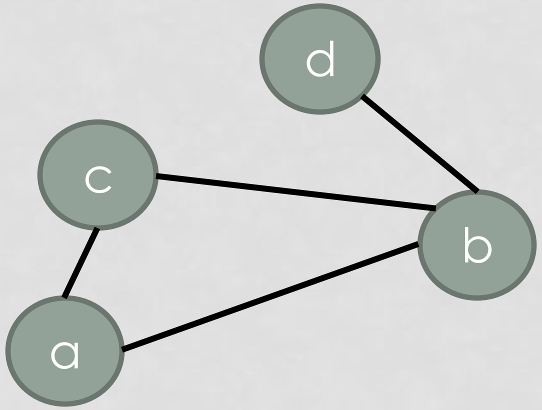
	Age range	<age> ± sd	sex	Health status
CamCAN	18 - 87	54.2 ± 18.6	323 F / 313 M	Healthy only
HCP	36 - 90	59.6 ± 14.9	380 F / 311 M	Healthy only
UKB	45-79	54.8 ± 7.4	8769 F/ 7892 M	All present

Elastic Network Models relates to Markovian random walks

<u>MSF in distances</u>
correlated motions between a and d



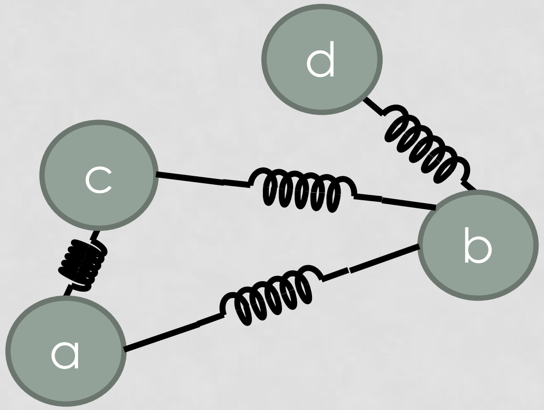
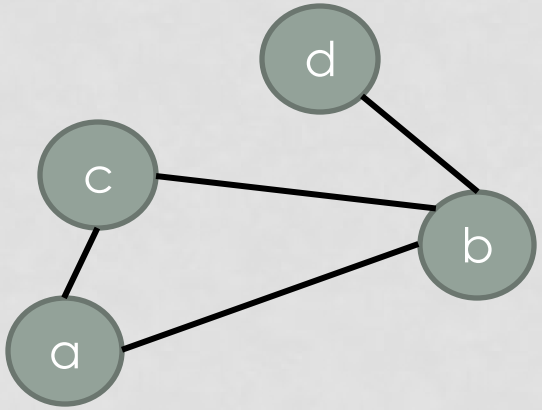
commute time
steps to freely diffuse to and from a to d



MSF = mean-squared fluctuations

**Both mathematical expressions proportional to $[\Gamma^{-1}]_{aa} + [\Gamma^{-1}]_{dd} - 2[\Gamma^{-1}]_{ad}$

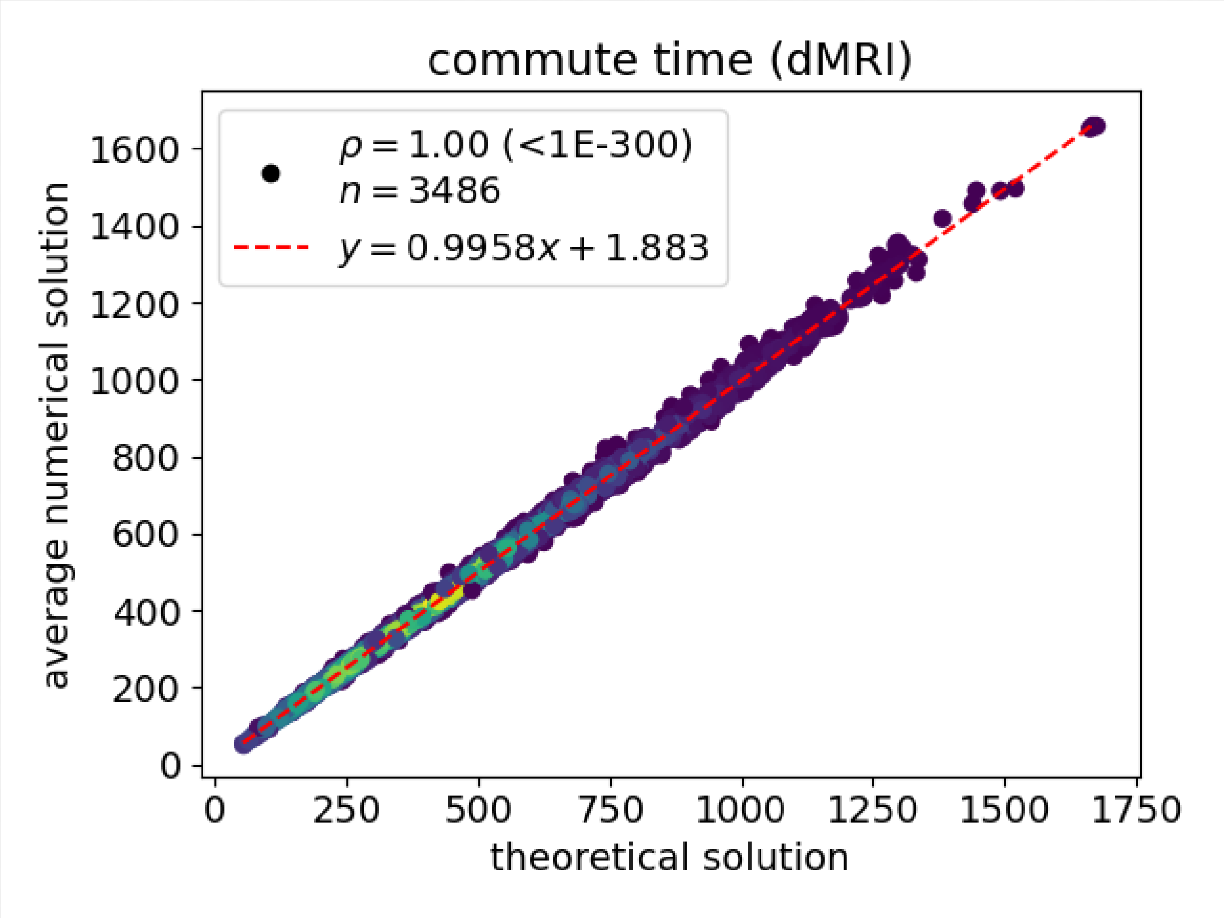
Elastic Network Models relates to Markovian random walks

<u>MSF in distances</u> correlated motions between a and d	commute time steps to freely diffuse to and from a to d
 	

MSF = mean-squared fluctuations

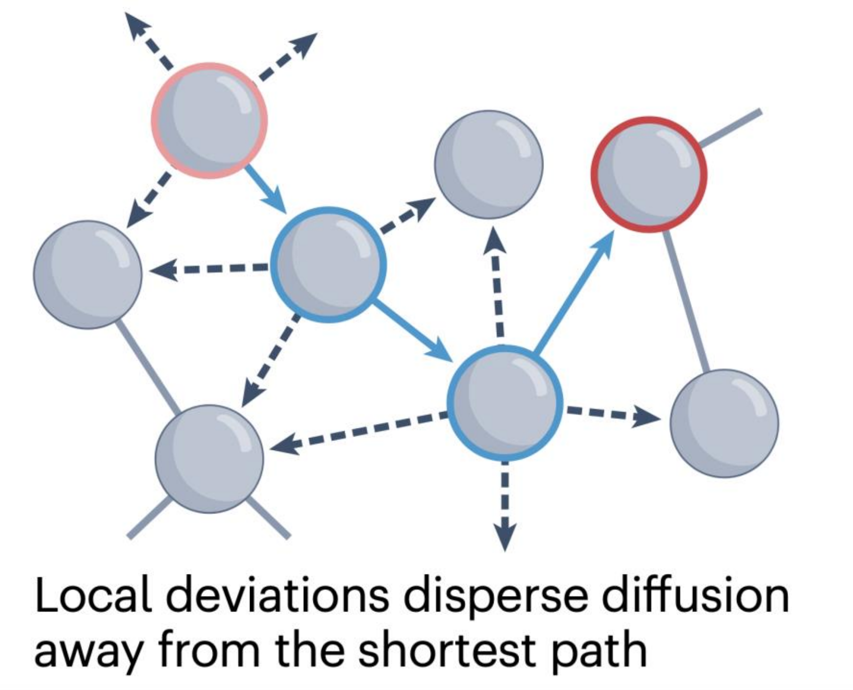
**Both mathematical expressions proportional to $[\Gamma^{-1}]_{aa} + [\Gamma^{-1}]_{dd} - 2[\Gamma^{-1}]_{ad}$

Theoretical expression for commute time matches numerics



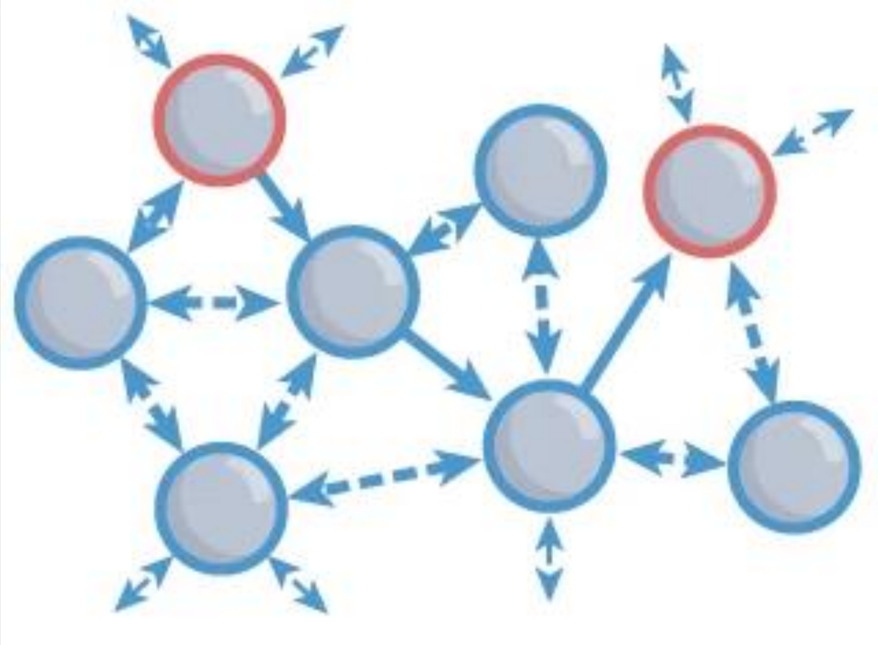
Leading communication metrics in network neuroscience

Search information



- Requires tract lengths

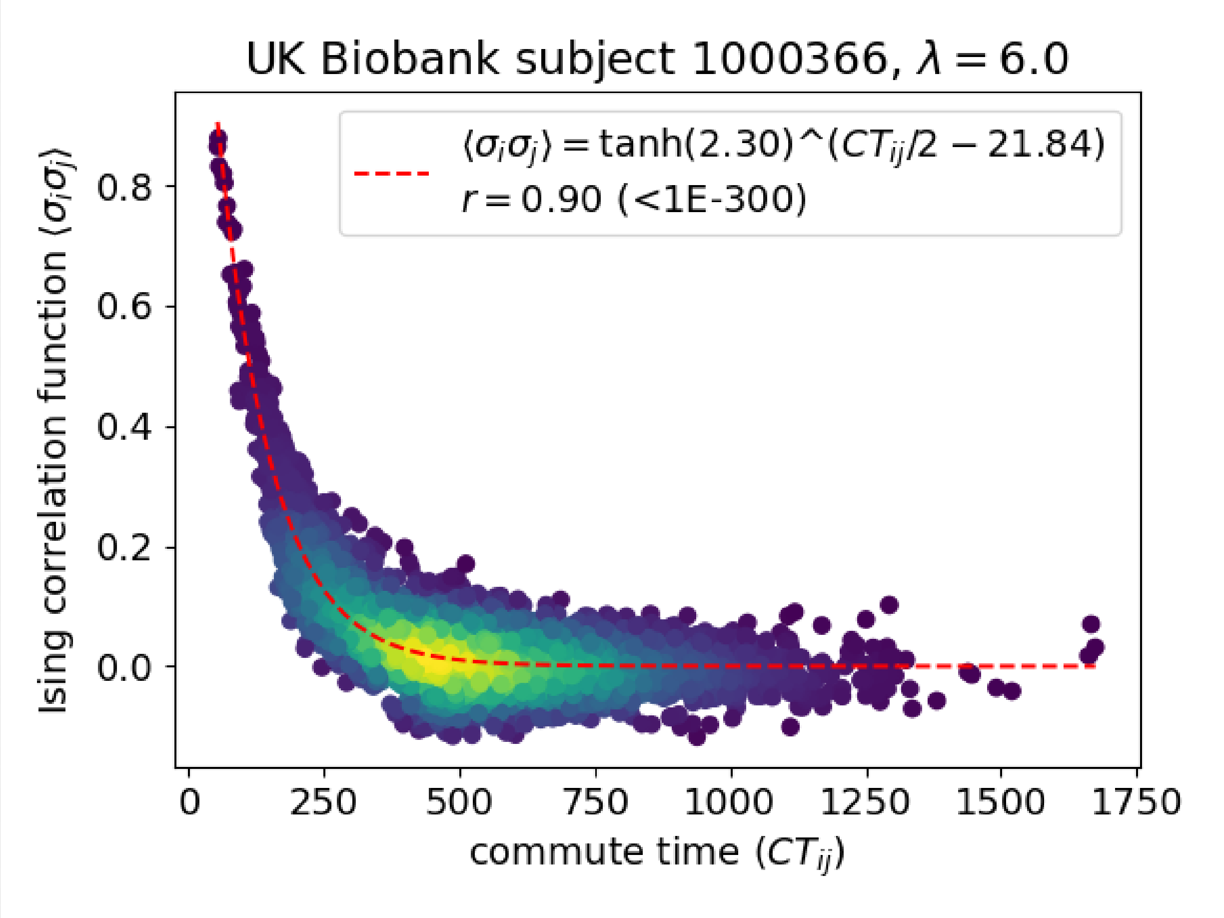
Communicability



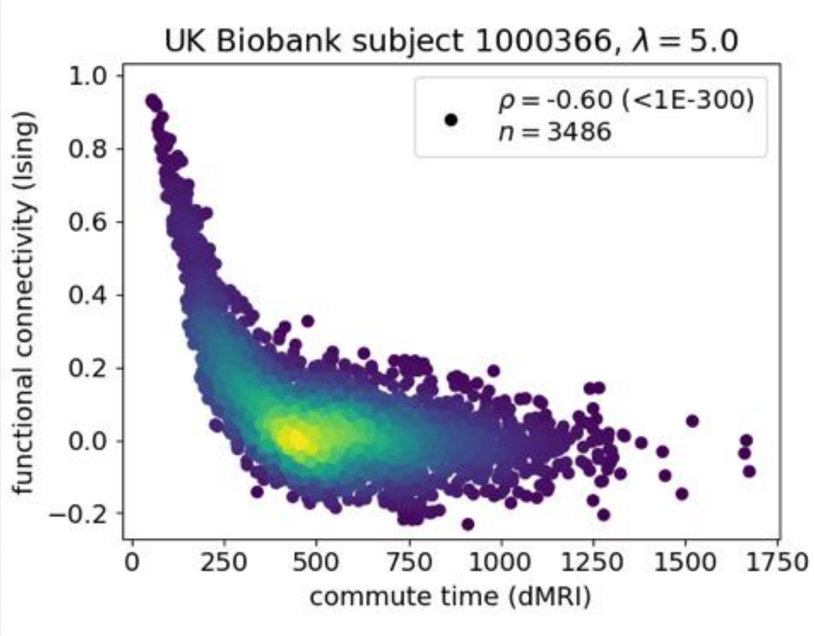
$$CMY_{ij} = \sum_{n} \frac{W'^{n}_{ij}}{n!} = e^{W'_{ij}}; W'_{ij} = \frac{W_{ij}}{\sqrt{\deg(v_i)\deg(v_j)}}$$

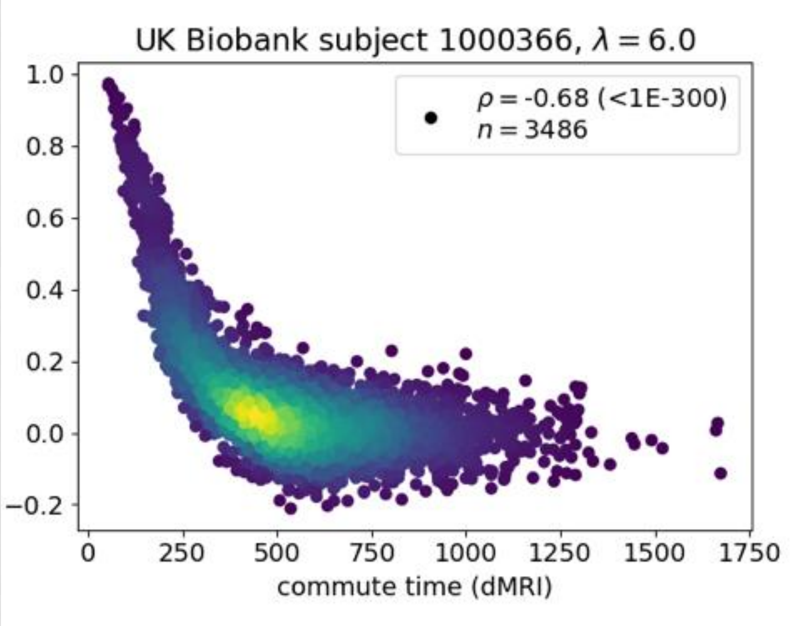
Seguin et al. 2023

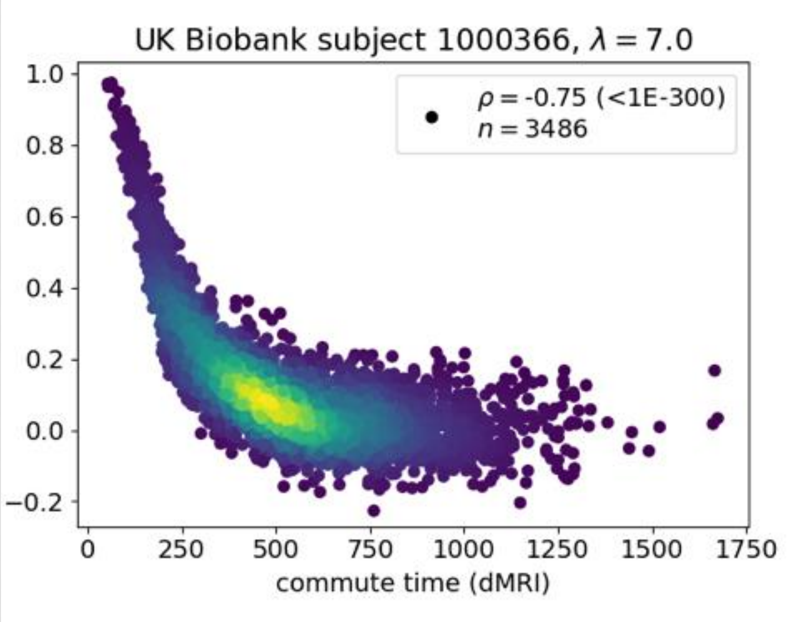
Can derive an analytical theory based on 1D Ising model to capture quantitative relationship



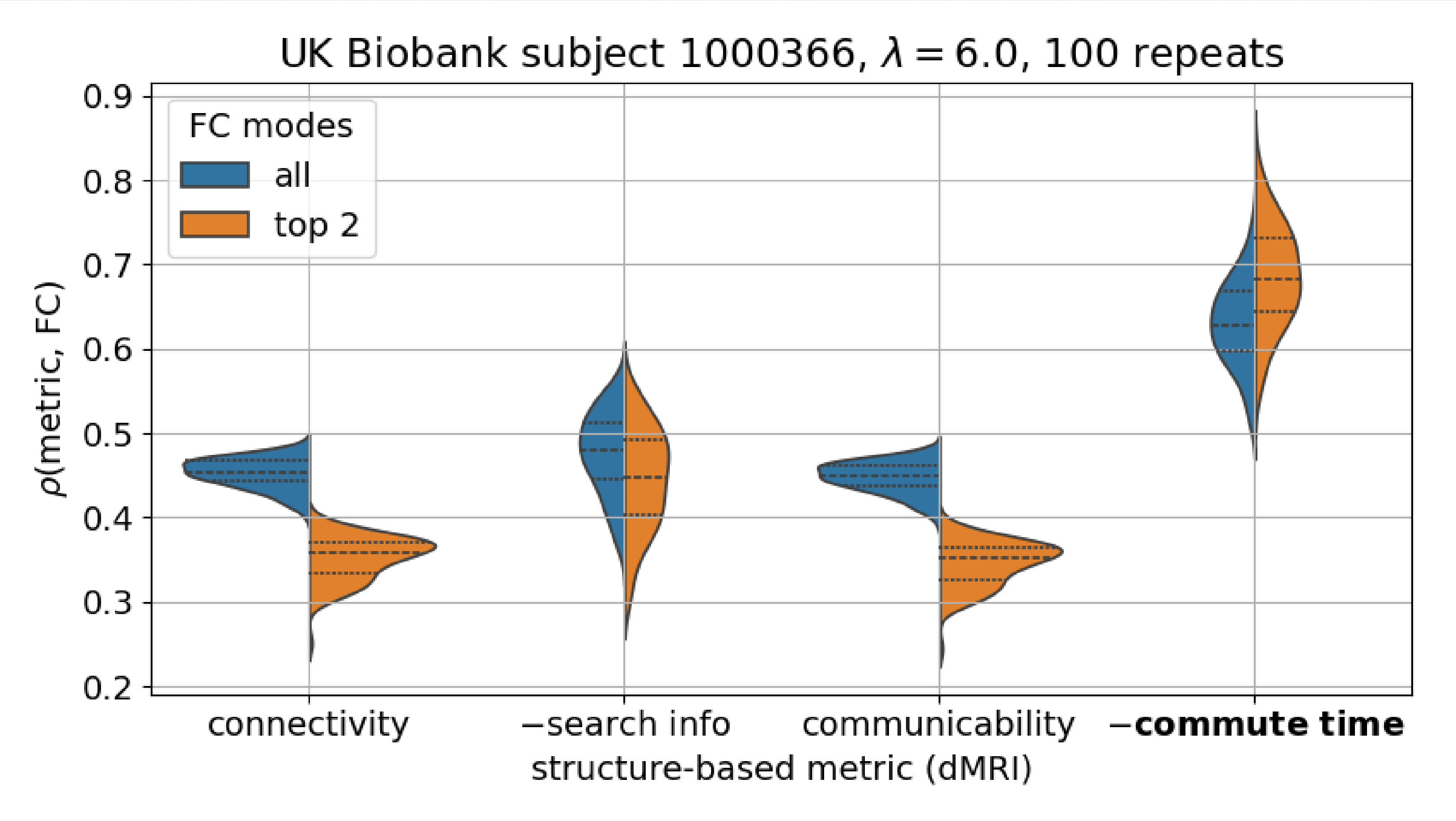
Commute time – FC correlation strengthens with larger coupling constant λ



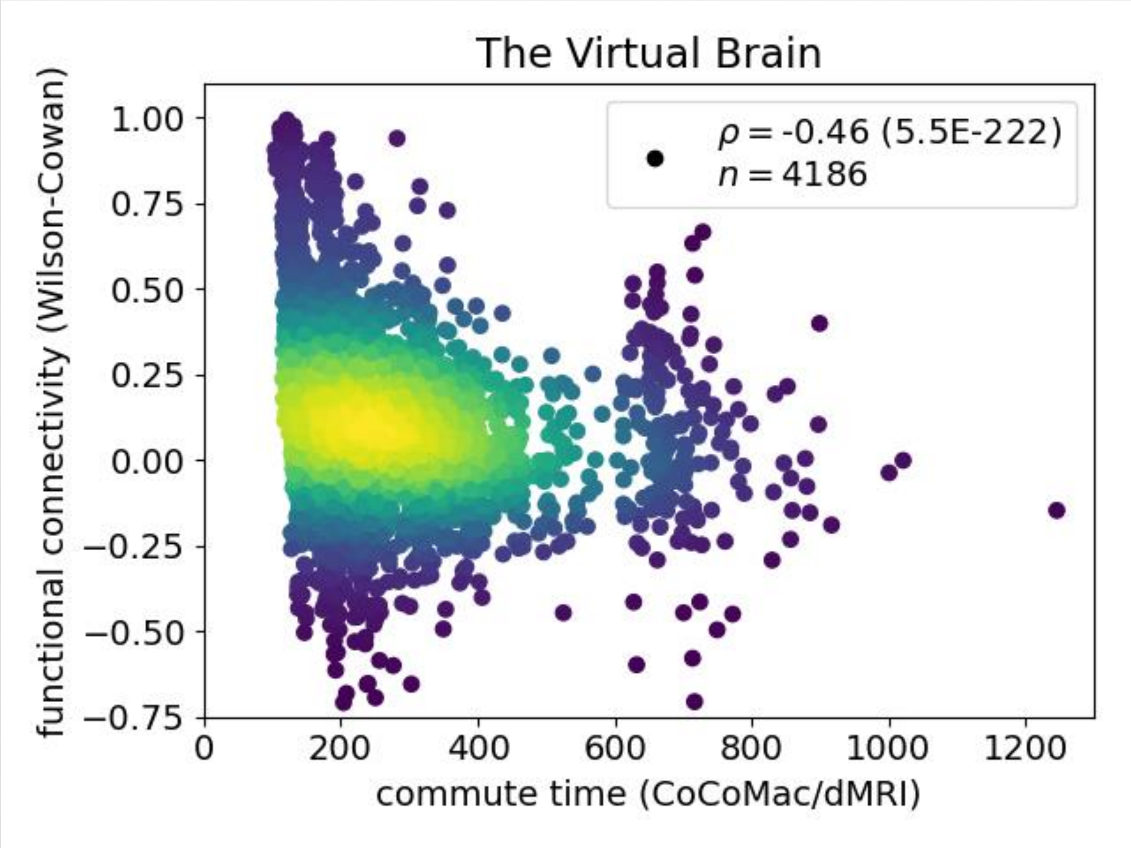


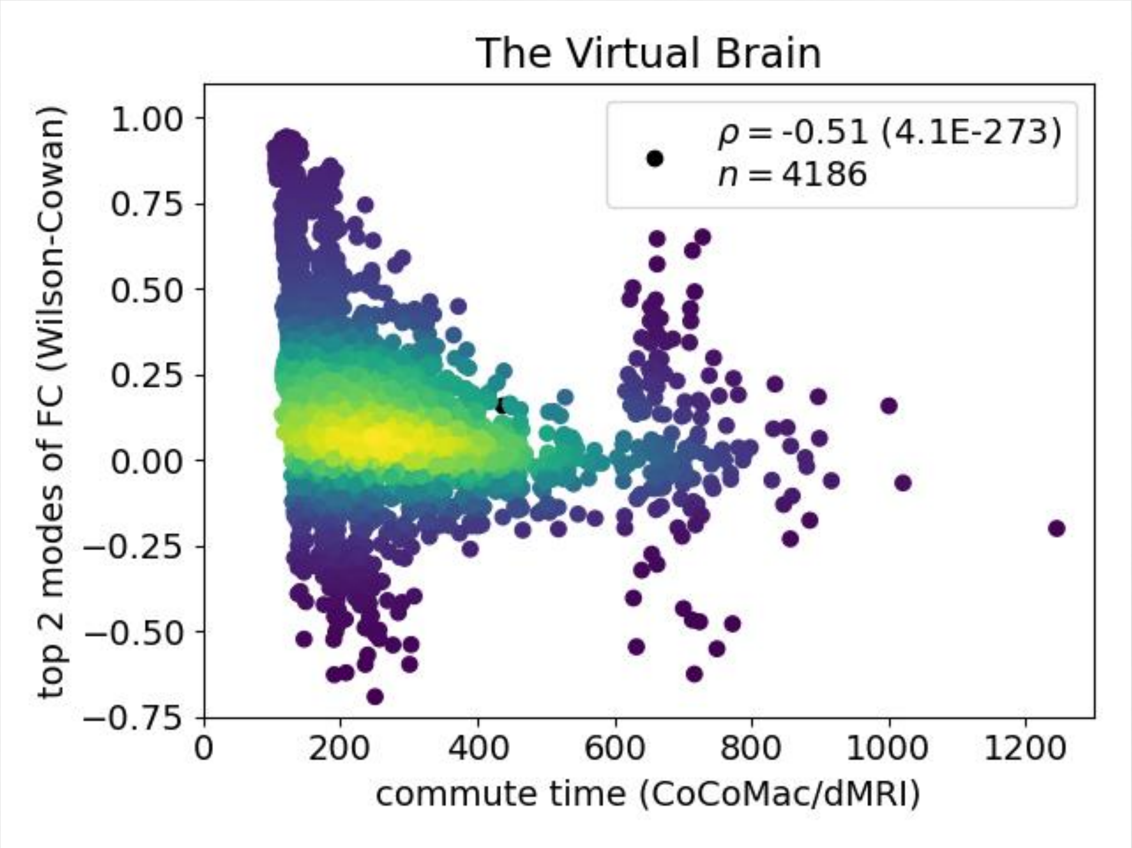


Comparing commute time for Ising simulations

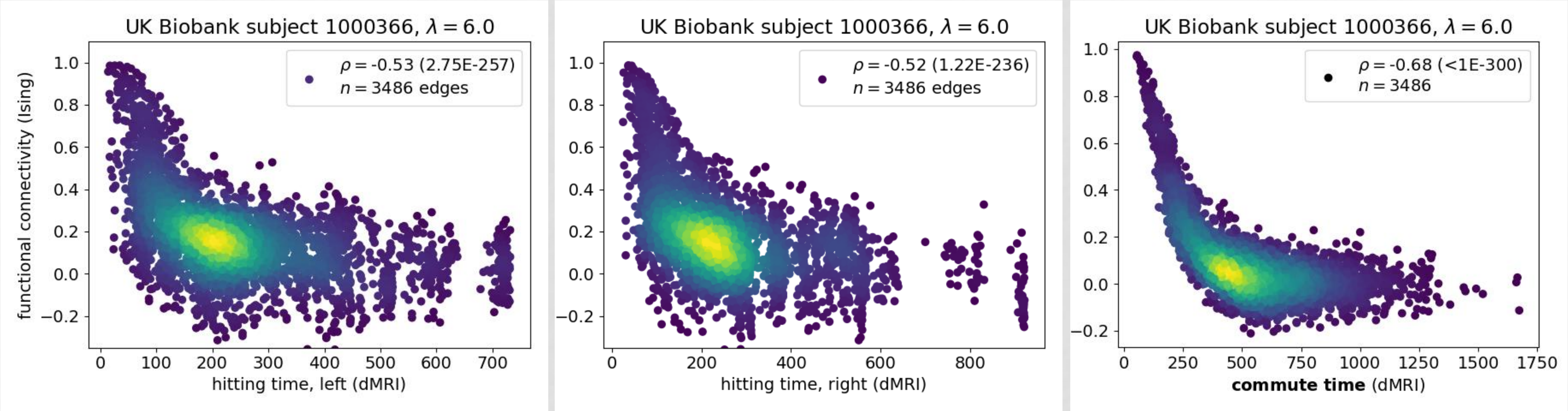


Commute time captures function in Wilson-Cowan simulation

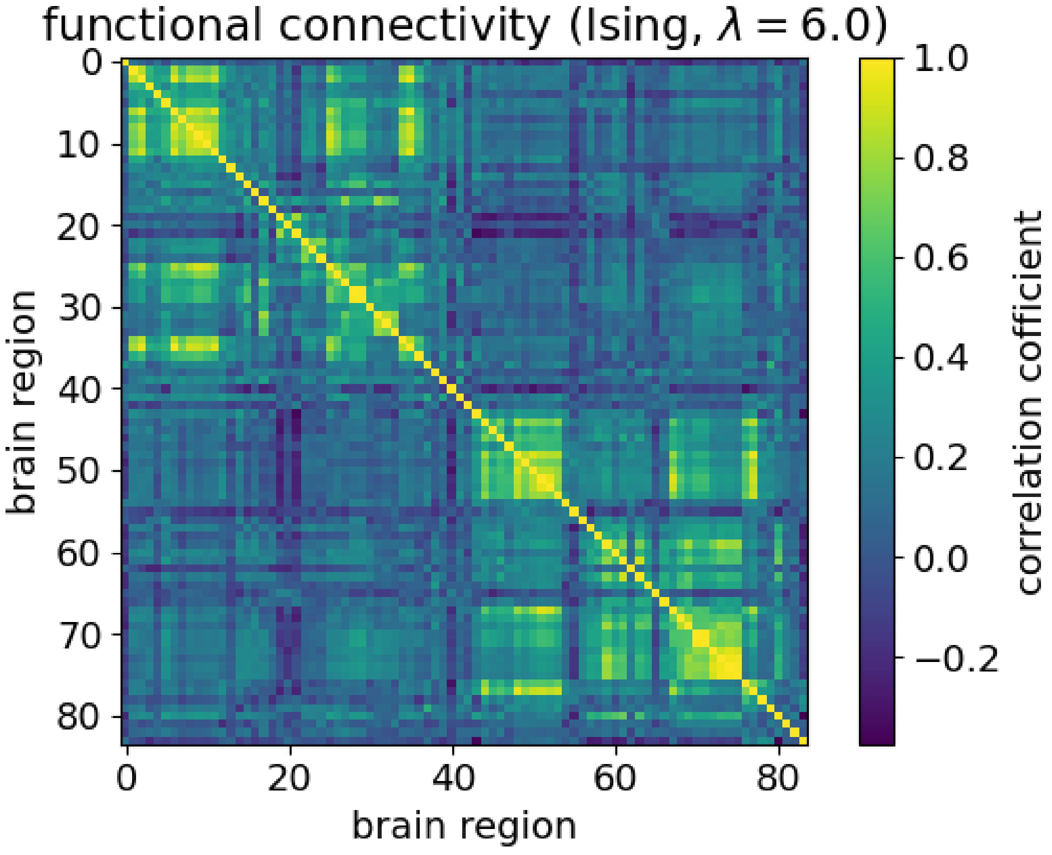


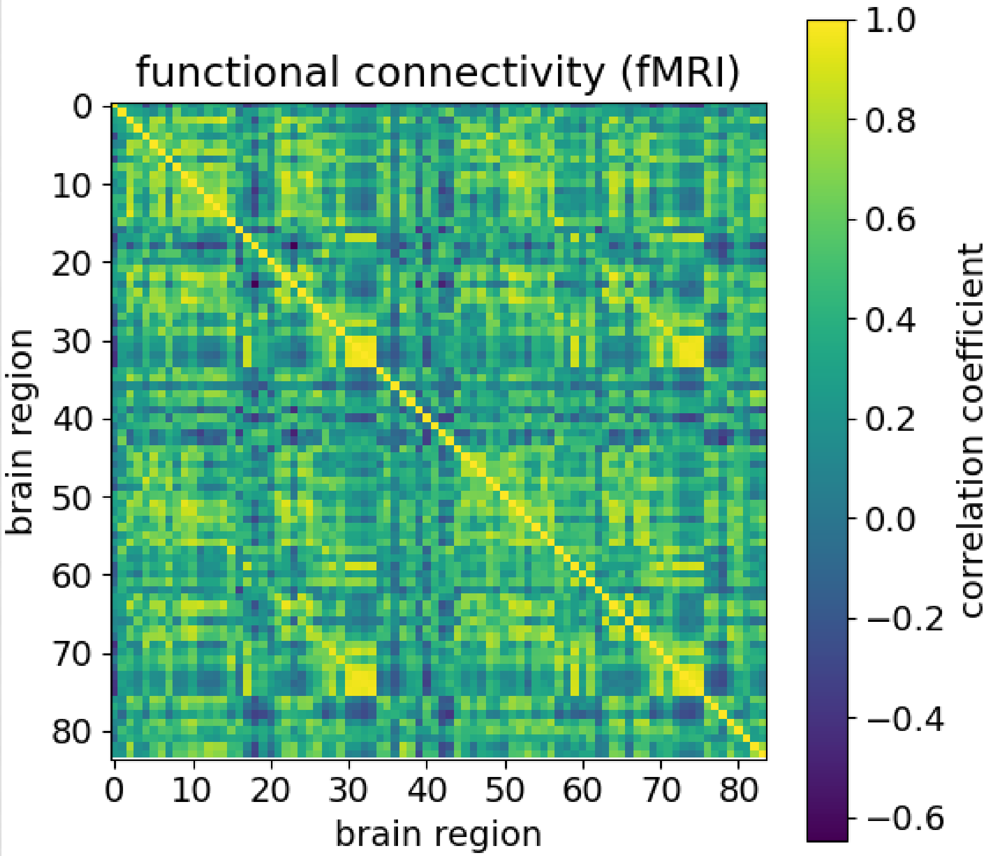


Hitting time does not capture function as well

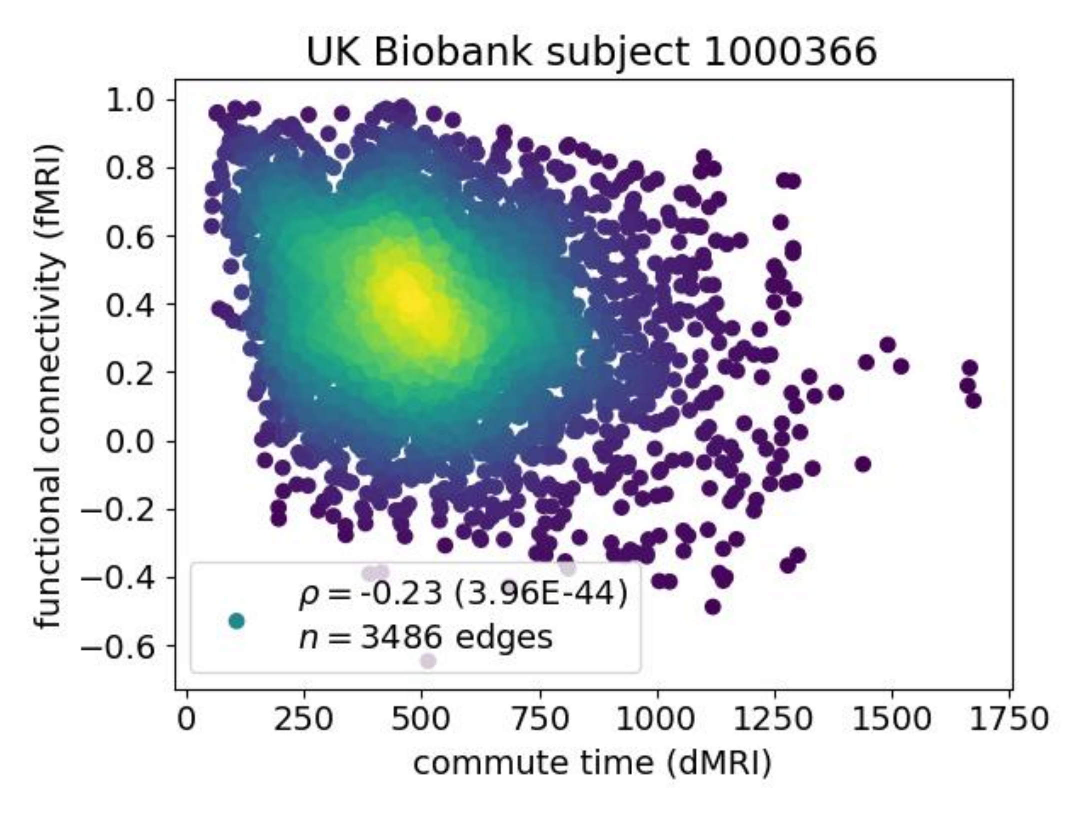


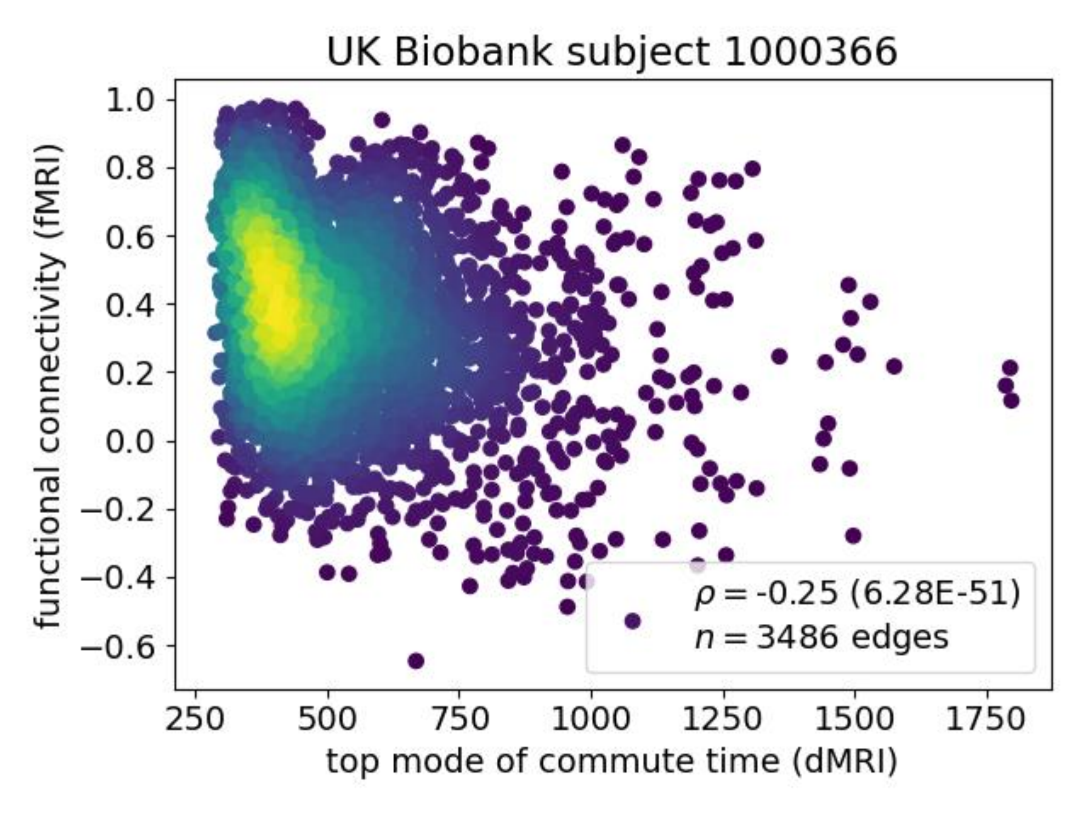
Simulated FC matrix still does not resemble a brain's FC





Top modes of commute time are better at explaining fMRI





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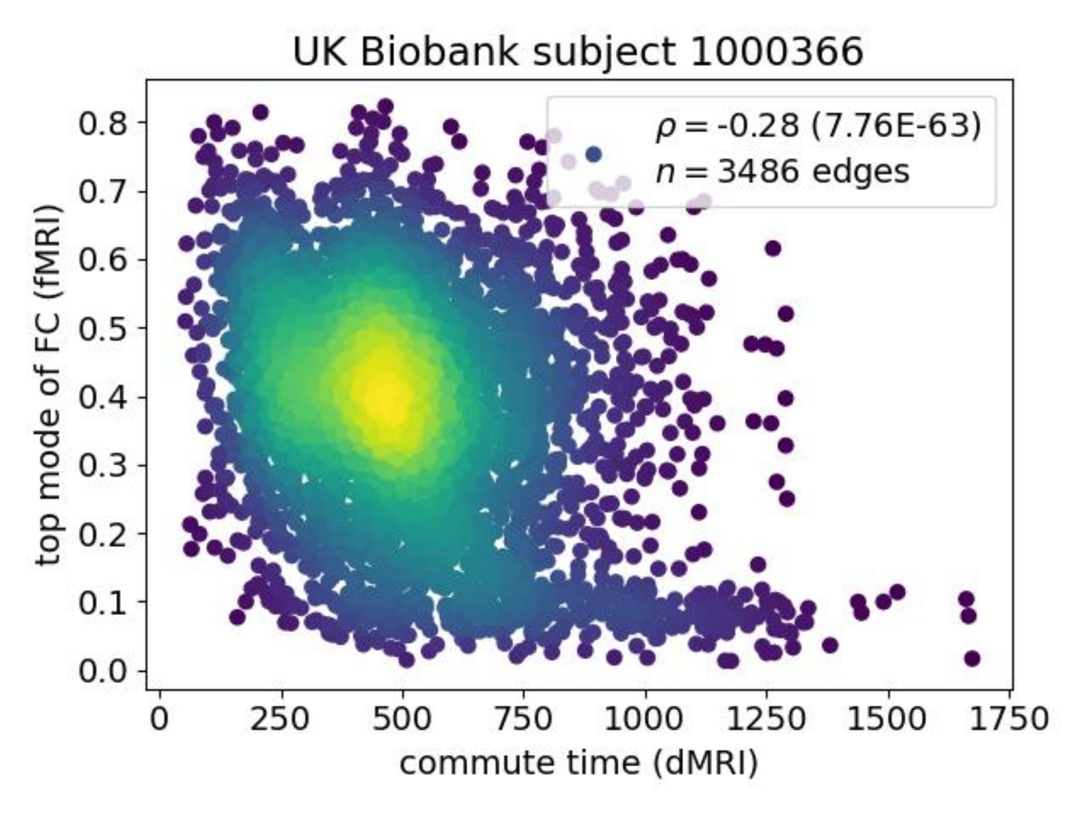
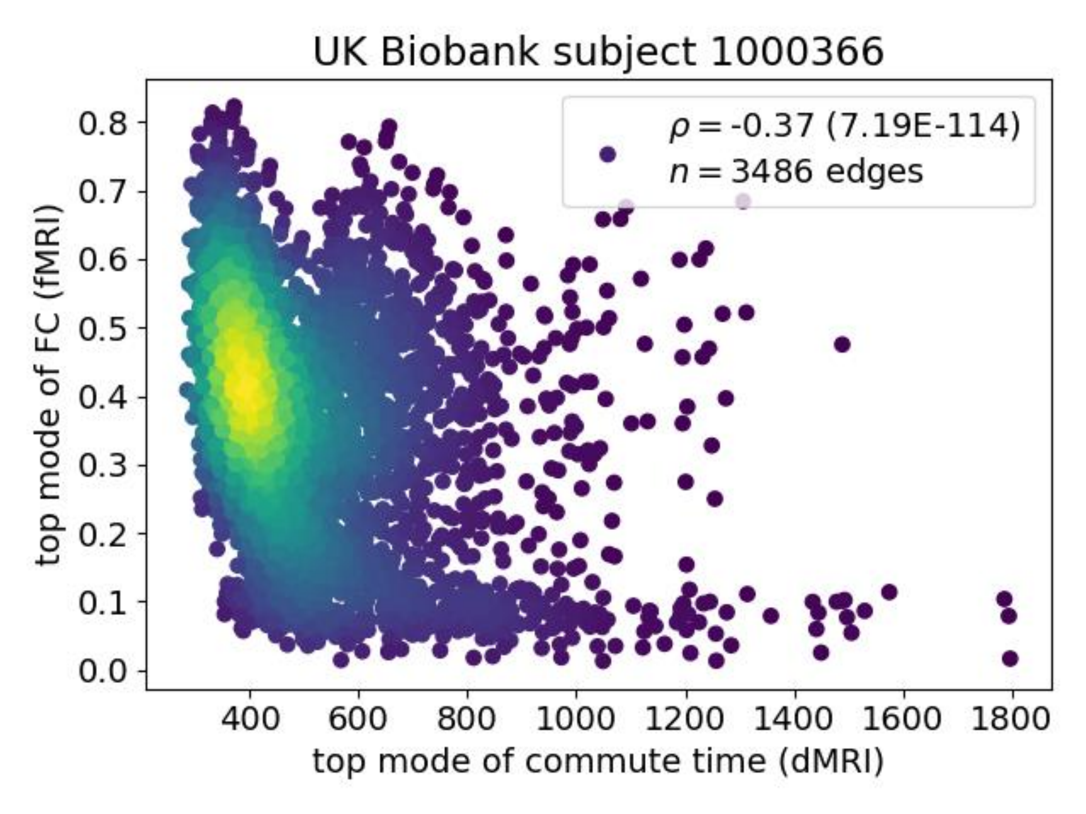
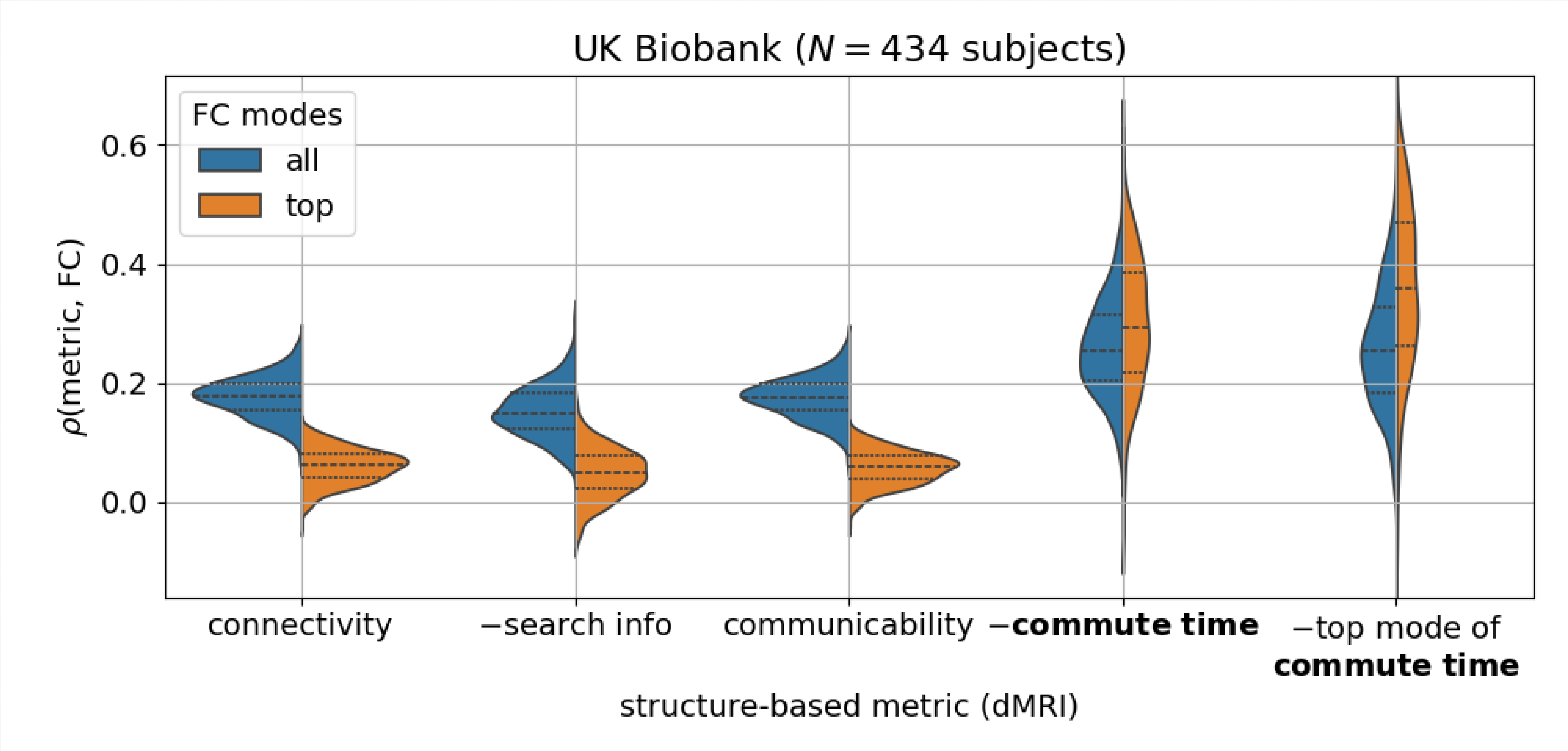
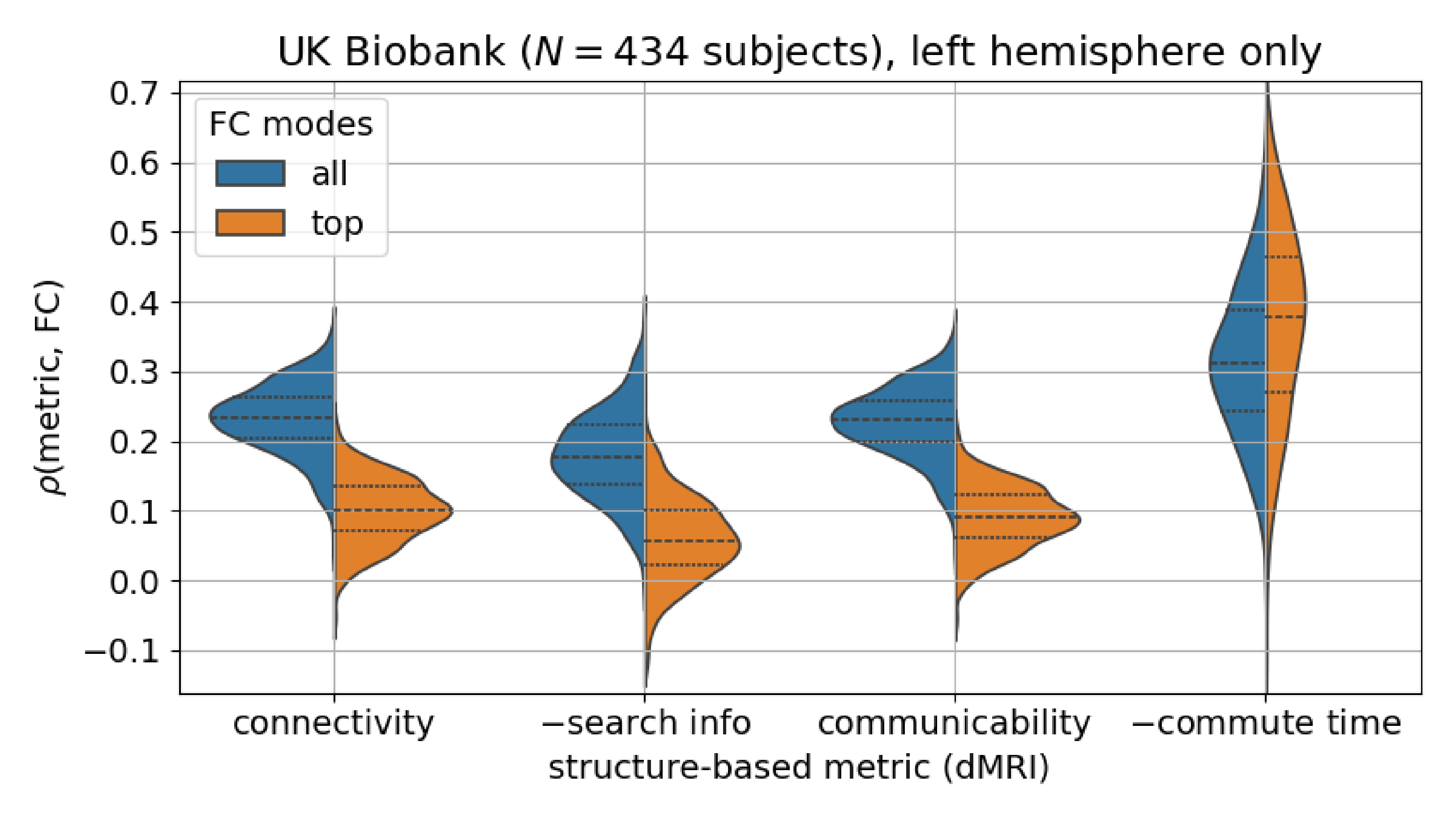




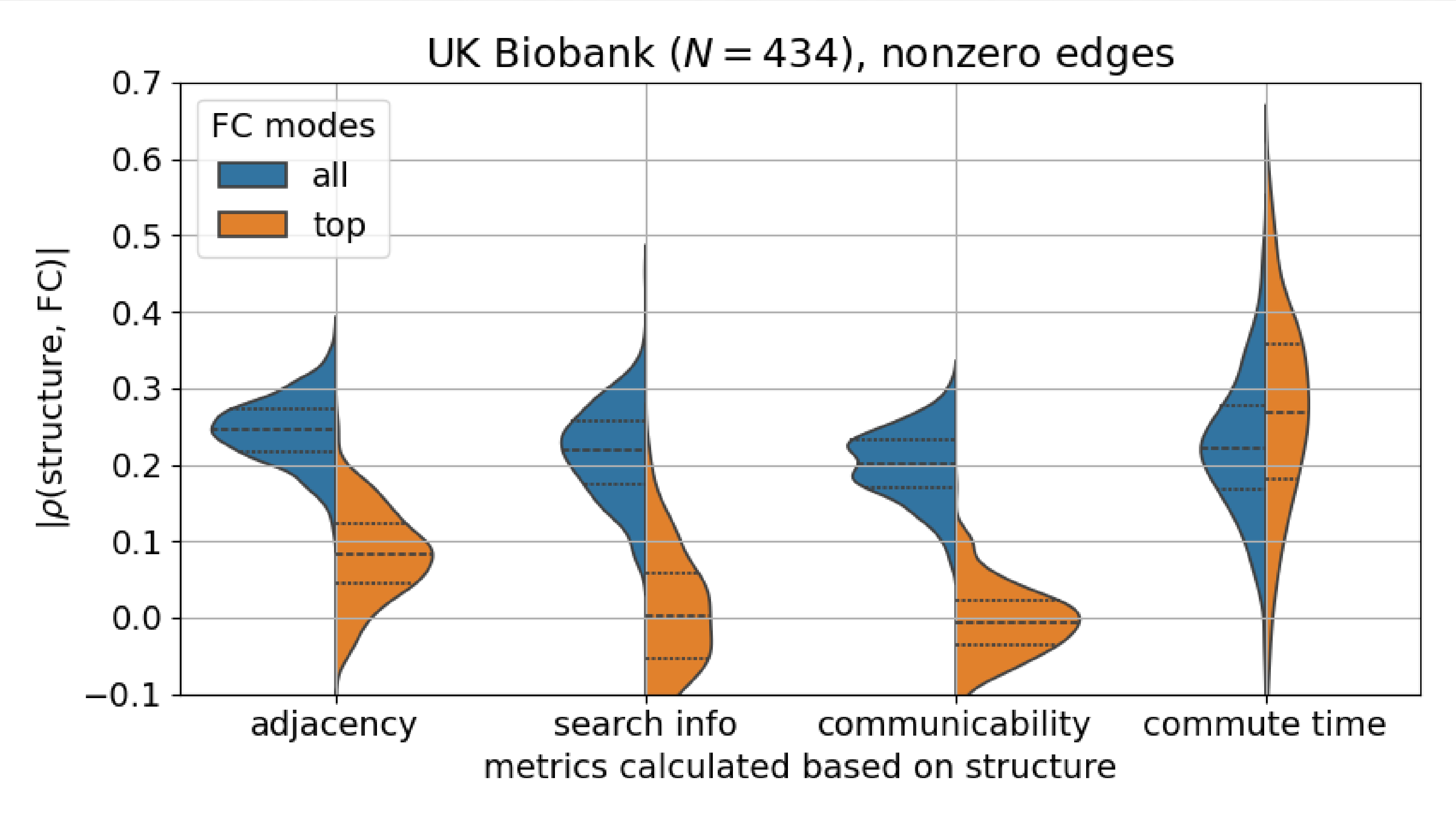
Top modes of commute time and FC perform stronger



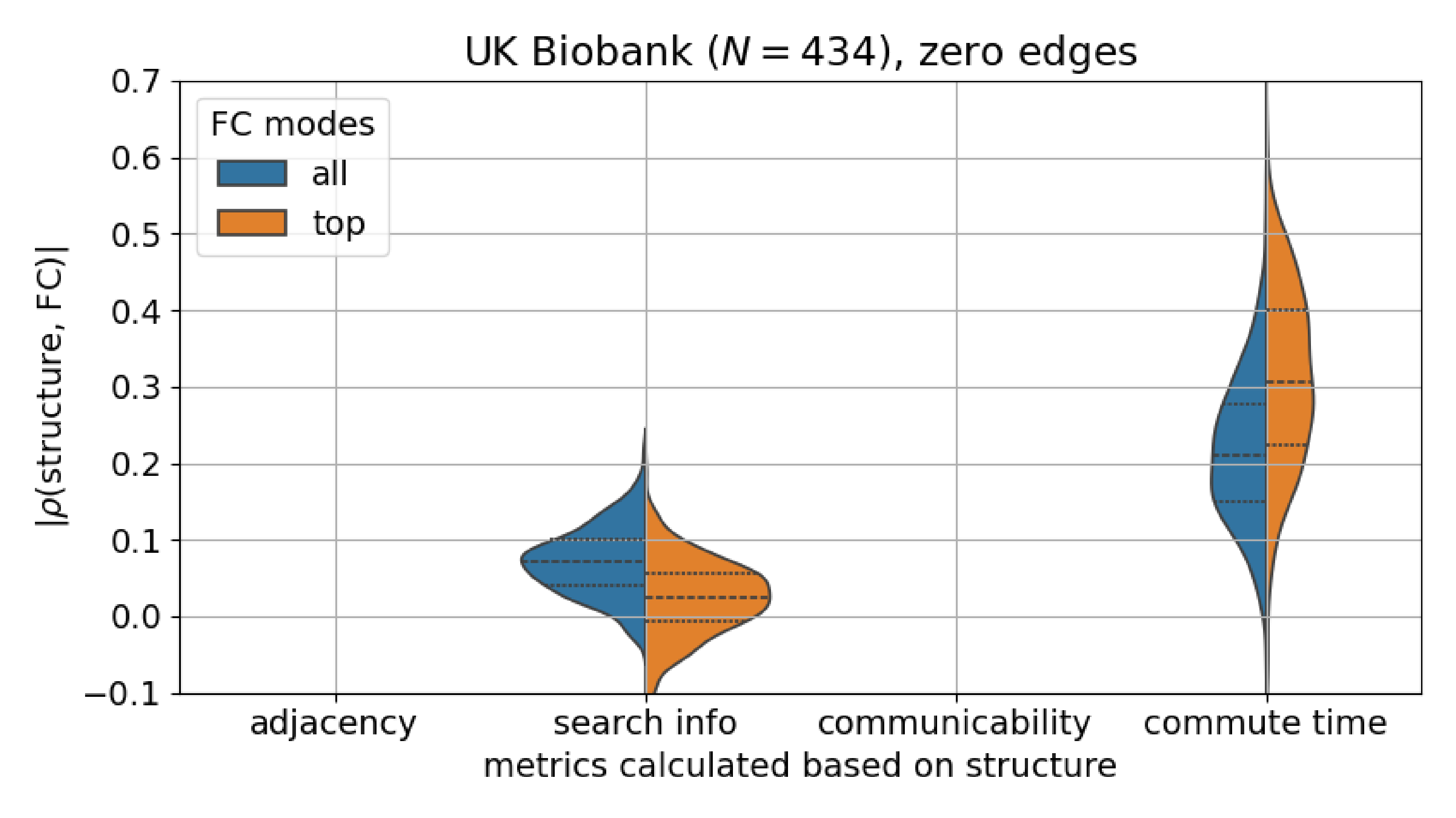
Comparing commute time to leading metrics, left hemisphere only



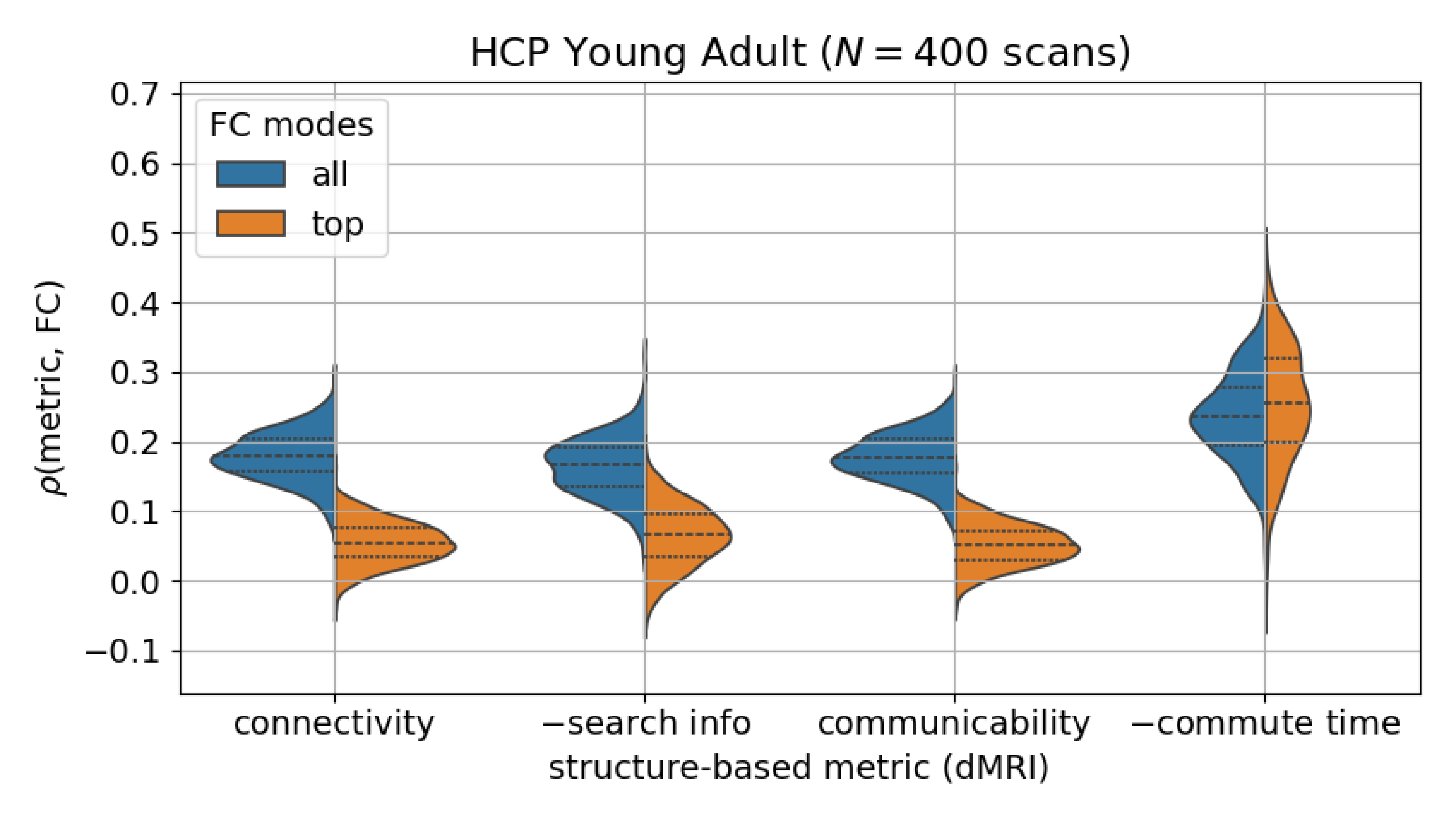
Comparing commute time to leading metrics, exclude edges with no connection in structural connectivity matrix



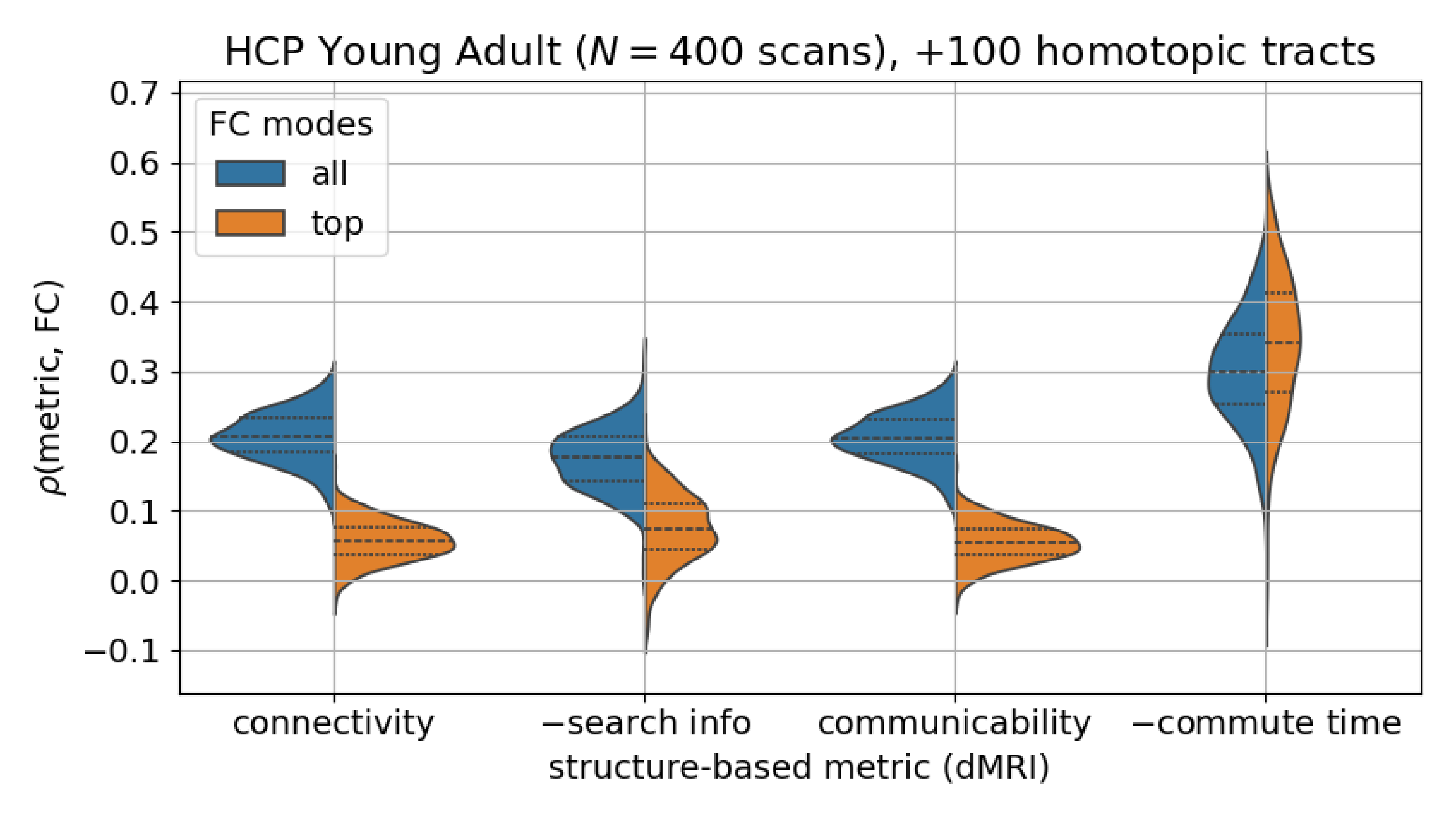
Comparing commute time to leading metrics, only include edges with no connection in structural connectivity matrix



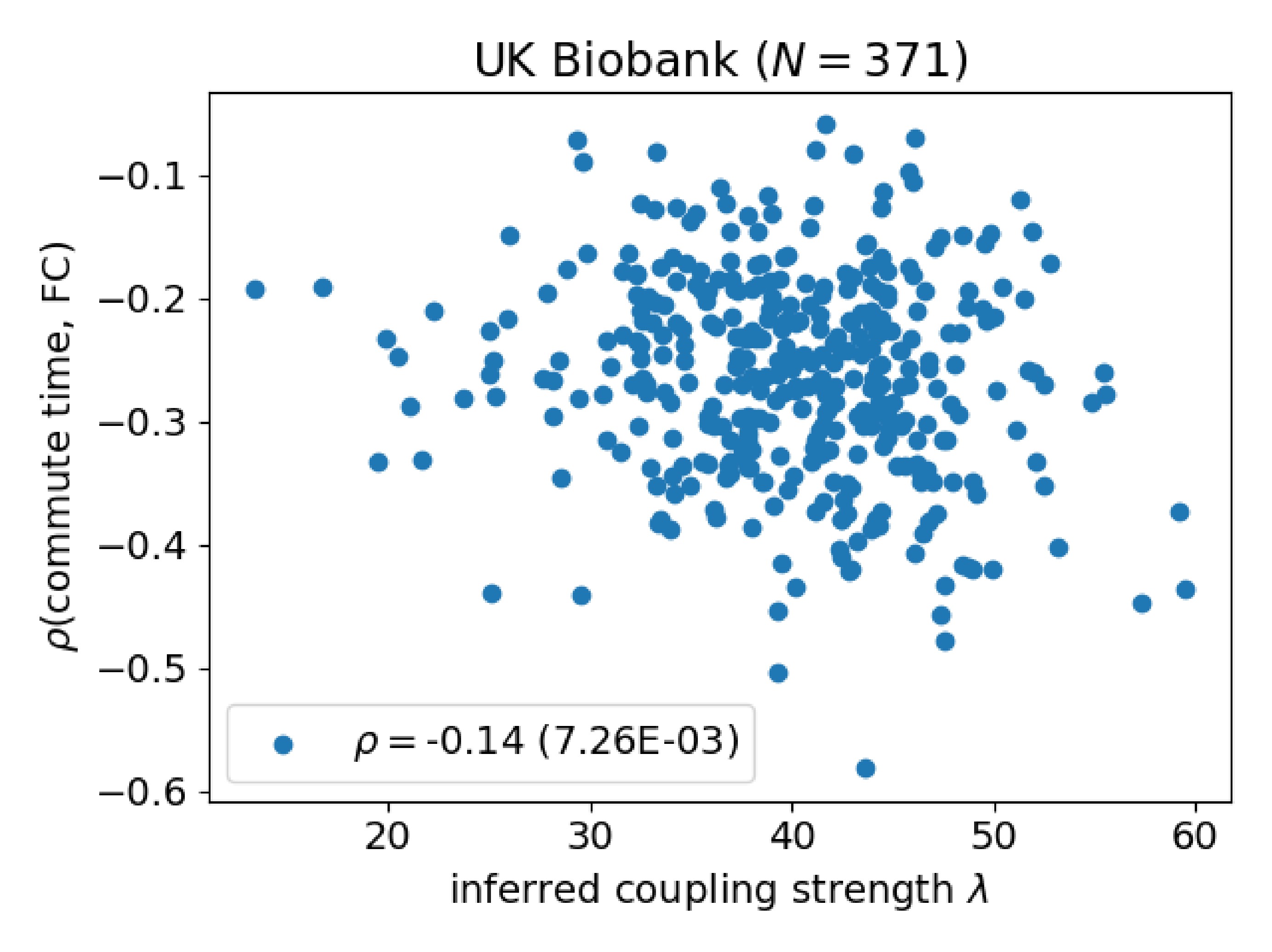
Commute time leading performer in another dataset



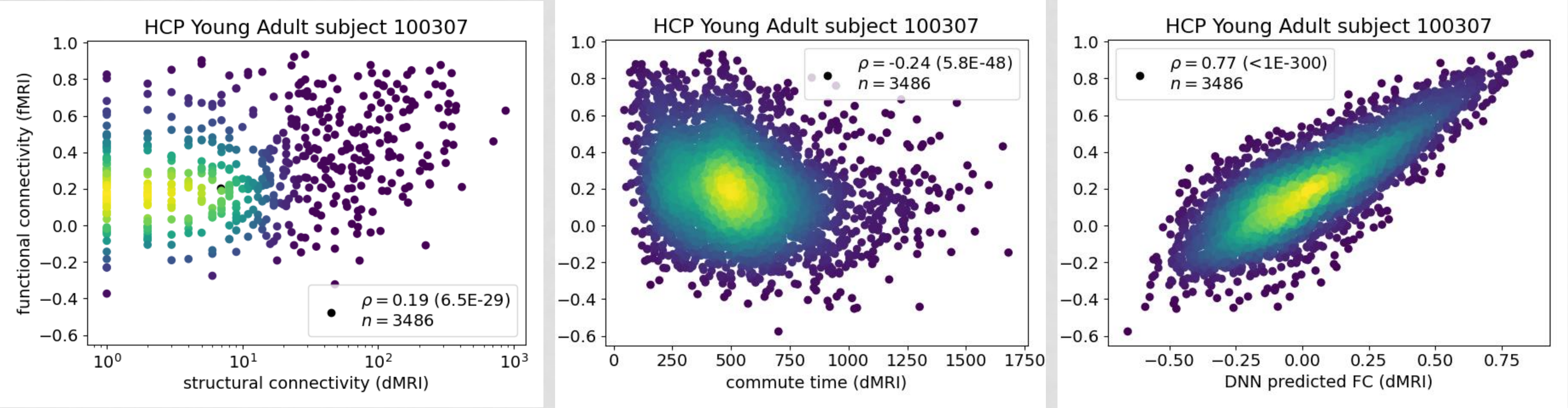
Artificially adding edges between the same region across hemispheres improves results



Coupling strength does not strongly underly structure-function



Machine learning does much better



Sarwar et al. 2021