Individual structural features constrain the mouse functional connectome

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Abstract

- **Problem**： Whole brain dynamics intuitively depend upon the internal wiring of the brain; **but to which extent the individual structural connectome constrains the corresponding functional connectome is unknown**, even though its importance is uncontested.
- **Method**: After acquiring structural data from individual mice, we **virtualized their brain networks** and simulated in silico functional MRI data. **Theoretical results were validated against empirical awake functional MRI data obtained from the same mice**.
- **Result**: We demonstrate that individual structural connectomes predict the functional organization of individual brains. Using a virtual mouse brain derived from the Allen Mouse Brain Connectivity Atlas, we further show that **the dominant predictors of individual structure–function relations are the asymmetry and the weights of the structural links**. Model predictions were validated experimentally **using tracer injections**, **identifying which missing connections** (not measurable with diffusion MRI) are important for whole brain dynamics in the mouse. **Individual variations thus define a specific structural fingerprint** with **direct impact upon the functional organization of individual brains**, a key feature for personalized medicine.

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Background

- We use **The Virtual Brain (TVB)**, which allows building **individual brain network models based on structural data**. This brain network modeling approach **operationalizes the functional consequences of structural network variations** and allows us **to systematically investigate SC–FC relations in individual human brains**.
- If SC constrains FC, SC-based simulations of FC should match empirical FC within the bounds of validity of the metric.
- However, dMRI **does not provide information on fiber directionality or synaptic details** (distribution and type of neurotransmitter) and suffers from limitations, such as **underestimation of fiber length and misidentification of crossing fiber tracks.**
- Given the imprecision of dMRI-derived SC, it is difficult to estimate the validity of the simulations. However, the currently best gold standard can be derived **in mice from cellular-level tracing of axonal projections**, here named the Allen connectome. Although individuality is lost (the SC is a composite of many mice) and despite other limitations, **the Allen connectome provides details not available otherwise and in particular not available in humans**. Focusing our attention on simulating mouse brain dynamics, we can thus use this detailed connectome to explore which missing features in the dMRI account for individual SC–FC relations. Specifically, **we predict that fiber directionality and fine grain connectivity patterns should be key determinants**.

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Background

- Using dMRI data of 19 mice, we constructed 19 virtual mouse brain models and compared predicted FC with empirical FC data acquired from the same mice during passive wakefulness.
- We found that **individual SC predicts individual FC better than the dMRI-based averaged SC**, and that **predictions can be improved by considering fiber directionality, coupling weights and specific fiber tracks derived from the Allen connectome**. We also found that **hemispherical lateralization in the mouse connectome influences whole brain dynamics**.

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◆ **Structural and Functional Experimental Data**

Nineteen male hybrid nonanesthesized mice were scanned using a 9.4 Tesla MRI to **obtain structural information and resting state functional data**. To obtain the tract streamlines, we integrated the field of orientation probability density using **deterministic and probabilistic processed dMRI-based connectome**. The tracer-based connectome was built through the Allen Connectivity Builder pipeline.

◆ **Surrogate Connectomes**

(1) **dMRI-based averaged connectome** (averaging the 19 dMRI based connectomes),(2) **a filtered tracer-based connectome** (filtering out the connections not detected in the dMRI connectomes), (**3)a symmetrized tracer-based connectome**, (4) **asymmetrized dMRI-based connectomes**, (5) **hybrid connectomes** (dMRI-based connectomes whose connections of 1 area are replaced with the tracer-based connections of that area).

◆ **Simulate Resting State Dynamics**

We simulate resting state dynamics using the connectome-based model approach as implemented in **The Virtual Brain software**. In particular, we used the **reduced Wong Wang model in the bistable configuration in order to reproduce the dynamical switching of the functional connections**. We transformed the simulated synaptic activity in BOLD signal using the Balloon-Windekessel method.

SC-FC

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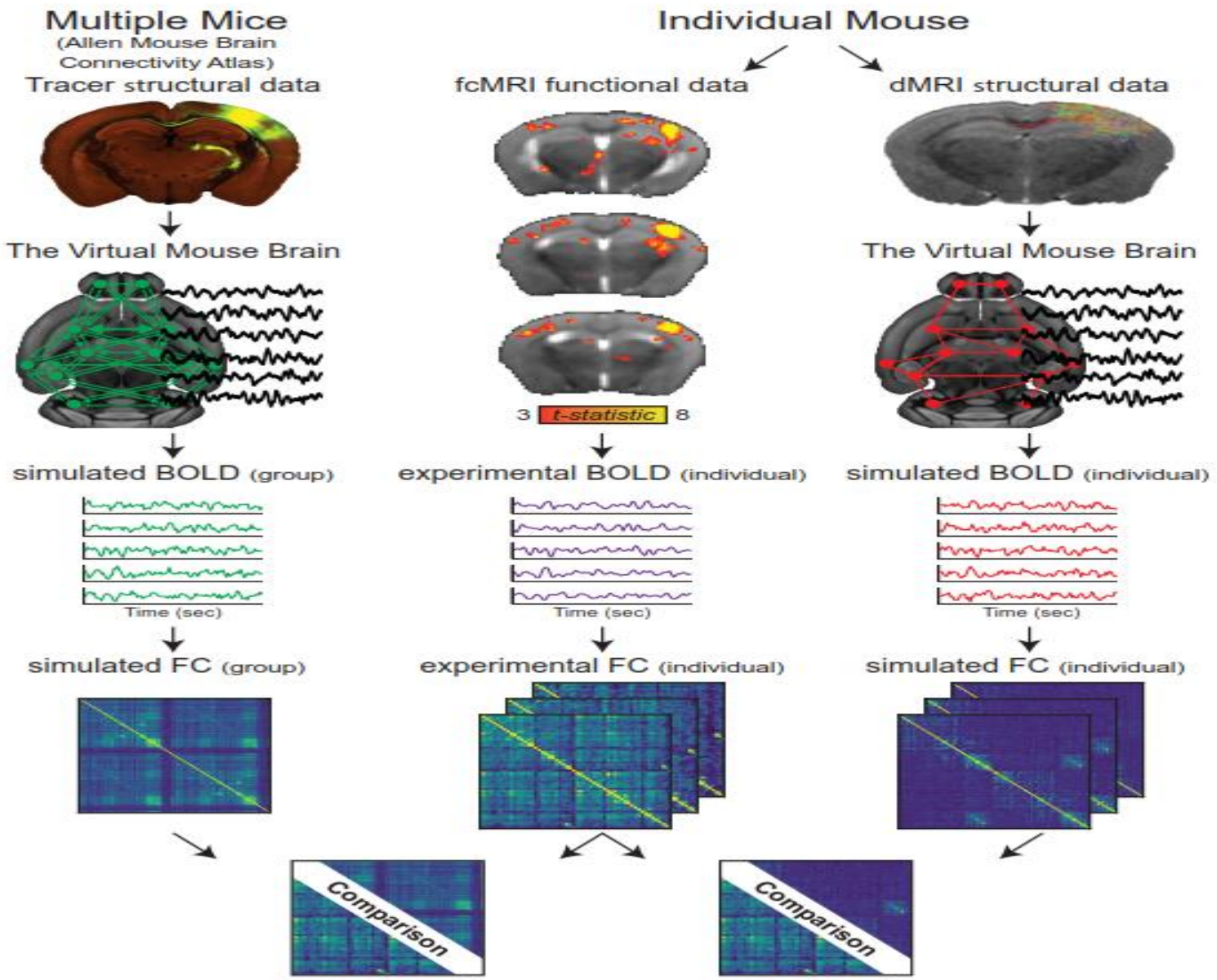

Averaged connectome: the role of individual variability

In order to assess the role of individual variability in dMRI data, we built an averaged connectome, both for deterministic and probabilistic tractography. We defined the averaged connectome as a matrix whose entry w_{ij}, i.e. the connection strength between area *i* and area *j*, is the arithmetic mean of the values of the connection strength w_{ij} of the N individual dMRI connectomes containing both area *i* and area *j*:

$$w_{ij} = \frac{1}{N}\sum_{n=1}^{N} {w_{ij}}^{n} \quad (1)$$

where *n* is the connectome index.

Filtered connectome: the role of long-range connections

Comparing the connectomes in Figure 1B-D it is possible to notice that the number of long-range connections detected with probabilistic, and more dramatically with deterministic, tractography is drastically lower than the one retrieved with the tracer method. It is well known that the accuracy of fiber reconstruction with diffusion-MRI data decreases with fiber distance; however, it is still unclear how to address this methodological limitation.

In order to quantify the impact of long-range connections presence in the simulated system, we filtered down the tracer connectome by removing all the connection not present in the deterministic diffusion-MRI connectomes. The filtered tracer connectome is shown in Figure 2A.

Symmetrized and asymmetrized connectome: the role of fiber directionality

The incapacity to detect fiber directionality is one of the main drawbacks of dMRI method.

In order to understand the influence of this property in the simulated system, we symmetrized the tracer connectome and we asymmetrized the diffusion-MRI connectome.

Symmetrized tracer connectome:

For each asymmetric matrix exists one, and only one, decomposition that enables us to find the corresponding symmetric matrix: each generic matrix A can be decomposed in its symmetric and asymmetric part as:

$$A = A^{sym} + A^{asym} = \underbrace{\frac{1}{2}(A + A^T)}_{\text{symmetric part}} + \underbrace{\frac{1}{2}(A - A^T)}_{\text{asymmetric part}} \quad (2)$$

thus, symmetrizing a matrix means neglecting its asymmetric part.

Following this consideration, the tracer symmetric connectome was defined as the matrix whose entries $\hat{t}_{ij}$ are defined as:

$$\hat{t}_{ij} = \frac{t_{ij} + t_{ji}}{2} \quad (3)$$

where t_{ij} represents the original tracer connection strength between area *i* and area *j*.

The symmetric tracer structural connectivity is shown in Figure 2A.

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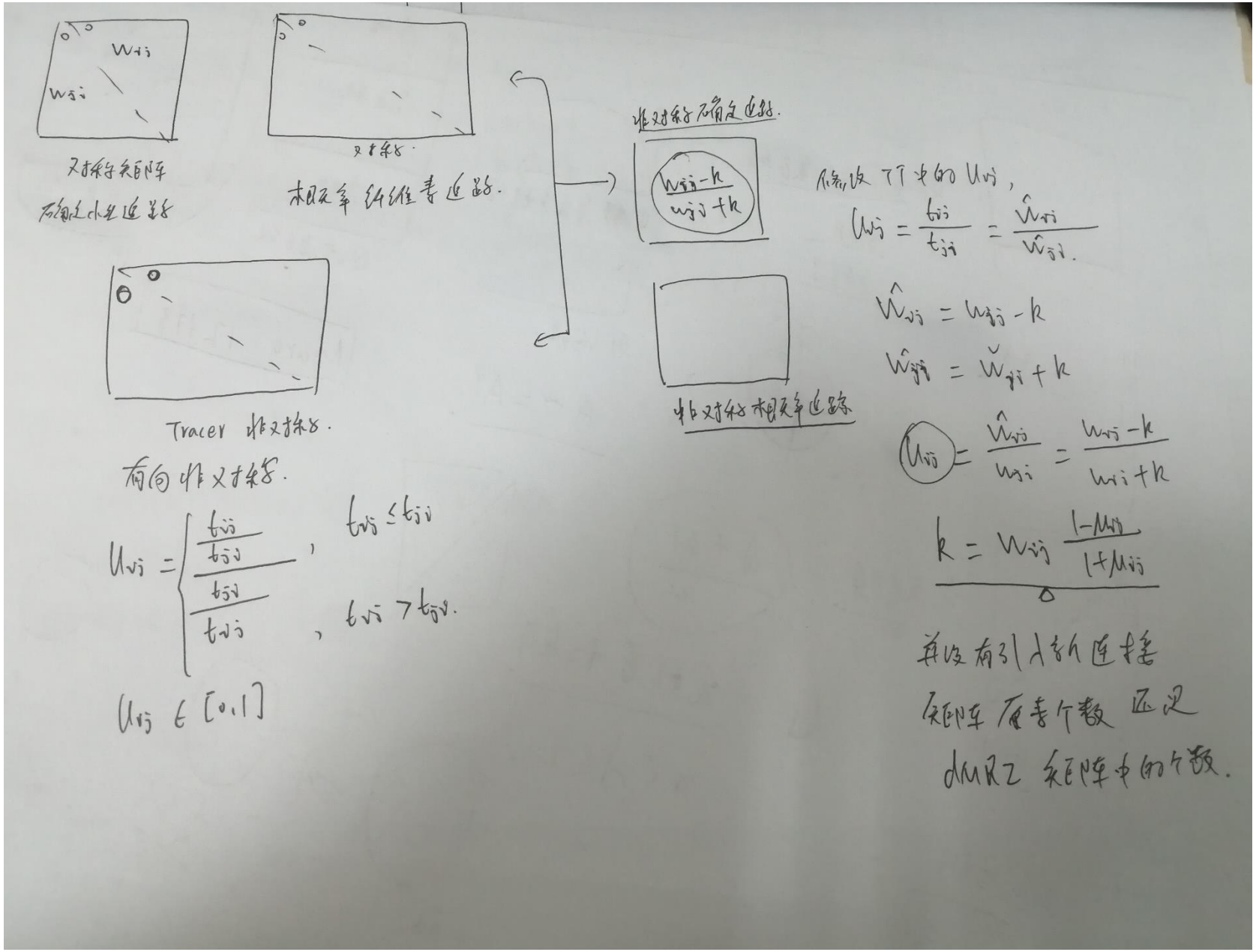
Results



We defined the asymmetry degree μ_{ij} between connection *i* and connection *j* as:

$$\mu_{ij} = \begin{cases} \frac{t_{ij}}{t_{ji}}, \Lambda\, t_{ij} \leq t_{ji} \\ \frac{t_{ji}}{t_{ij}}, \Lambda\, t_{ij} > t_{ji} \end{cases}$$

so that:

if the *ij* connection is symmetric: $t_{ij} = t_{ji} \Rightarrow \mu_{ij} = +1$

if the *ij* connection is anti-symmetric: $t_{ij} = -t_{ji} \Rightarrow \mu_{ij} = -1$

However, since the connection strengths in the connectome are always positively defined, μ_{ij} is a value always between 0 and 1.

The information on the directionality of the tracer connection between area *i* and area *j*, measured by μ_{ij}, are inserted in the diffusion-MRI connectome by modifying the original connection w_{ij} in $\check{w}_{ij}$:

$$\mu_{ij} = \frac{t_{ij}}{t_{ji}} = \frac{\check{w}_{ij}}{\check{w}_{ji}} \qquad (5)$$

Specifically, we defined $\check{w}_{ij} = w_{ij} - k$ and $\check{w}_{ji} = w_{ji} + k$, where k is defined as:

$$\mu_{ij} = \frac{\check{w}_{ij}}{\check{w}_{ji}} = \frac{w_{ij}-k}{w_{ji}+k} \Rightarrow k = w_{ij}\frac{1-\mu_{ij}}{1+\mu_{ij}}$$

if wij = wji, then uij = 1-2k/(1+k)

It is important to notice that the asymmetrization of the connectome does not imply the introduction of new connections: if the original diffusion-MRI connection w_{ij} is absent it follows, from the last equation, that also the increment k will be zero.

The asymmetrized deterministic connectome is shown in Figure 2B.

Hybrid connectome: the role of individual connections

We aimed to study the influence of the technique, the dMRI or the tracer one, in reconstructing the connections of a specific brain area. For this purpose, we built surrogate connectomes where all the brain wirings were reconstructed with deterministic dMRI except the connections of the region under examination that were measured with anatomical tracing.

In particular, for each deterministic dMRI connectome *W*, composed of N brain areas, we generated *N* different connectomes W^k by substituting the incoming and outgoing non-zero dMRI connections of area *k* with the corresponding tracer connections. The entry w_{ij}^k of the hybrid connectome W^k are defined as:

$$w_{ij}^k = \begin{cases} w_{ij} \text{ if } i, j \in [1,2,\dots,k+1,k-1,\dots,N] \\ t_{kj} \text{ if } i = k \text{ and } w_{ij} \neq 0 \\ t_{ik} \text{ if } j = k \text{ and } w_{ij} \neq 0 \end{cases}$$

where w_{ij} and t_{ij} represent the connection strength of the original-individual deterministic dMRI and the original tracer connectome, respectively.

It is important to notice that this operation does not imply the introduction of new connections.

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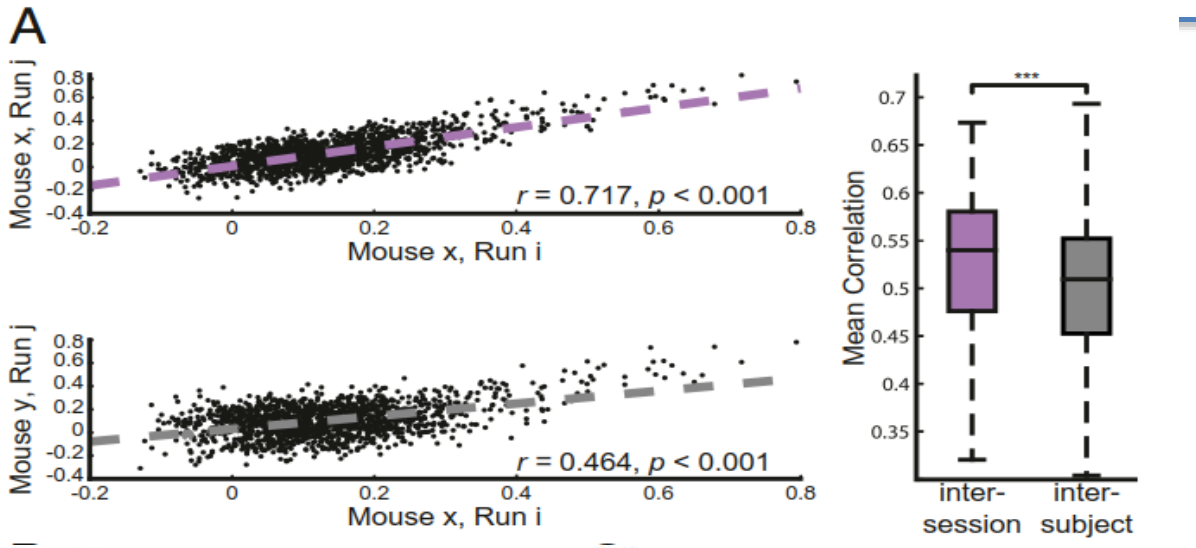
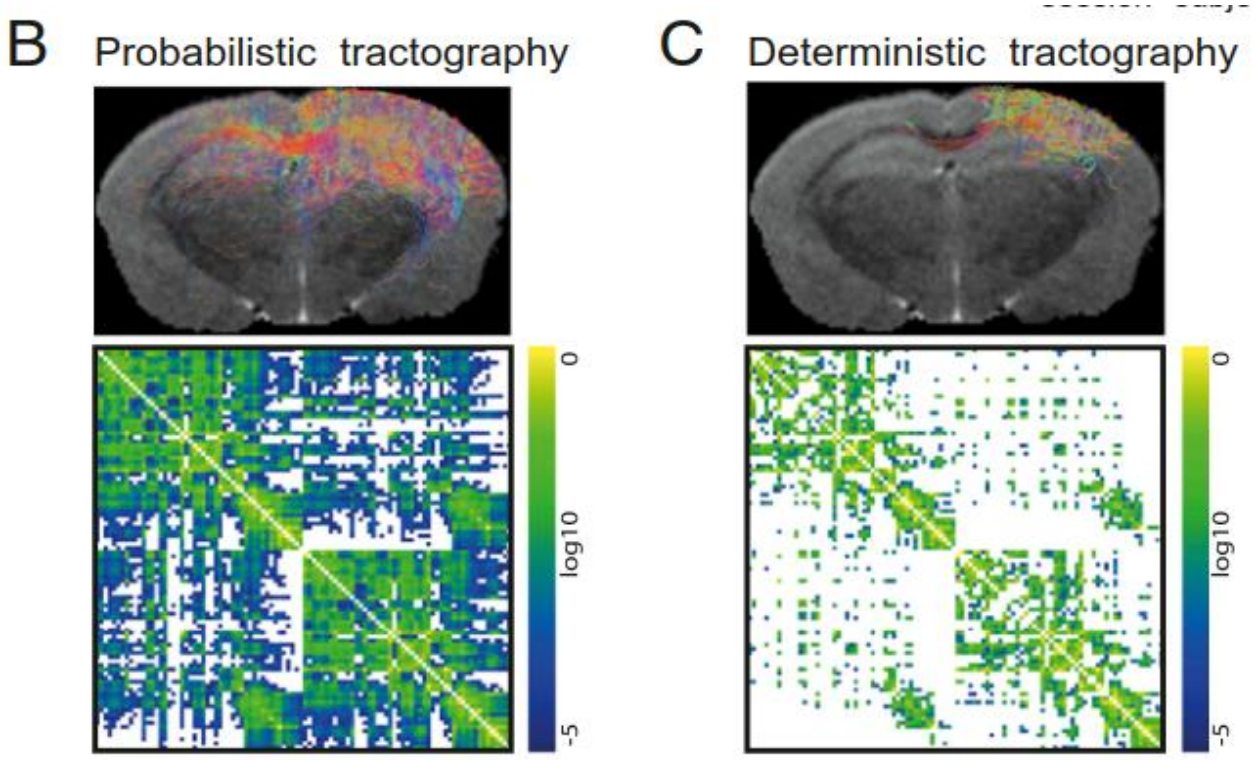
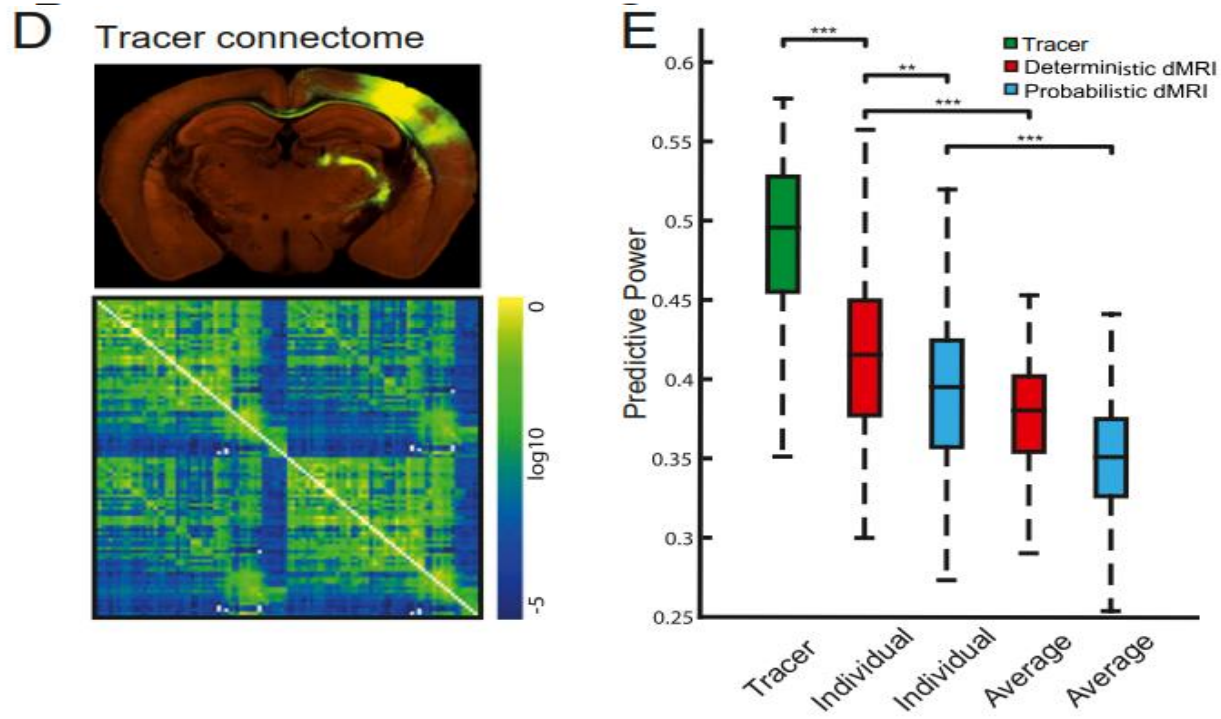
- SC Obtained with a Deterministic Algorithm Is a Better Predictor of FC
- Individual SC Is the Best Predictor of Individual FC







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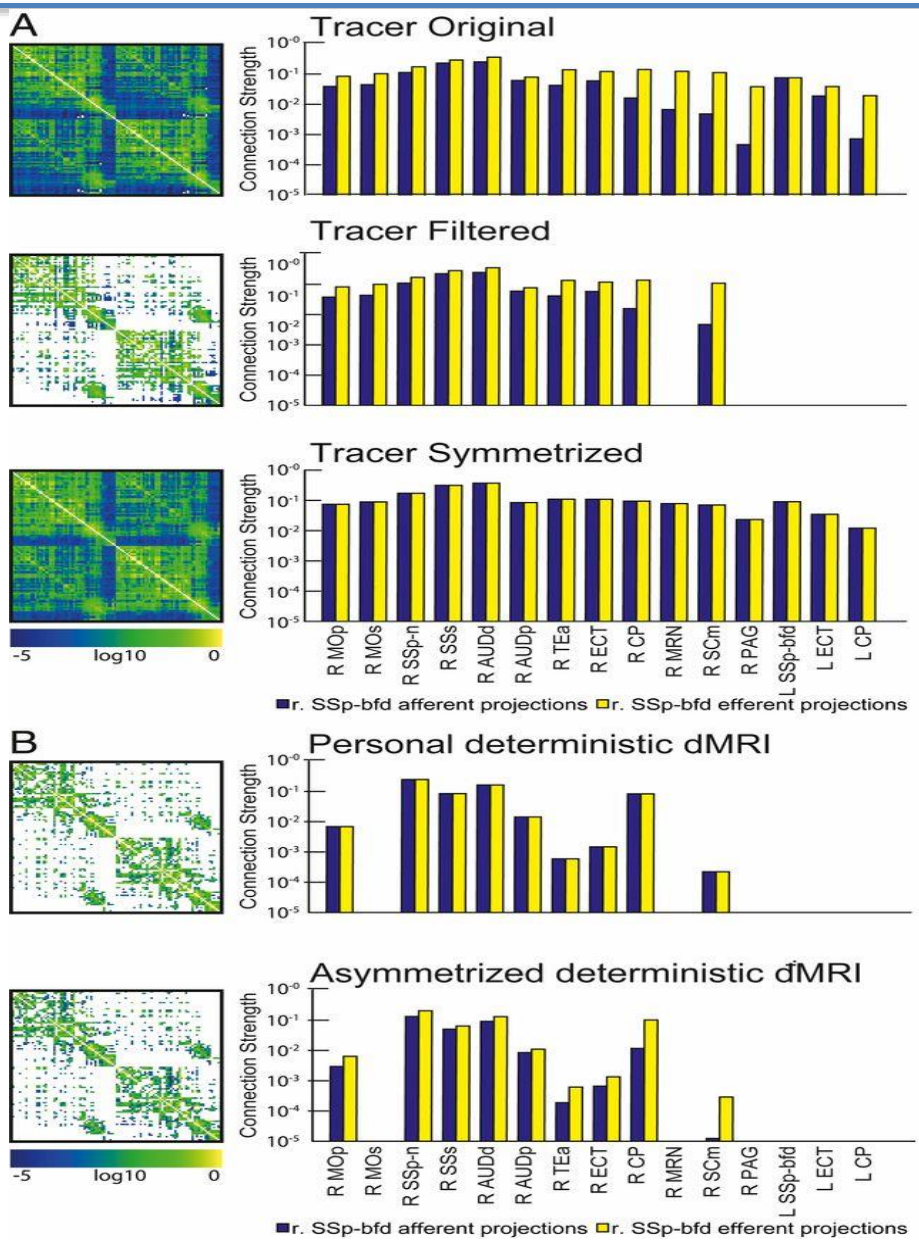
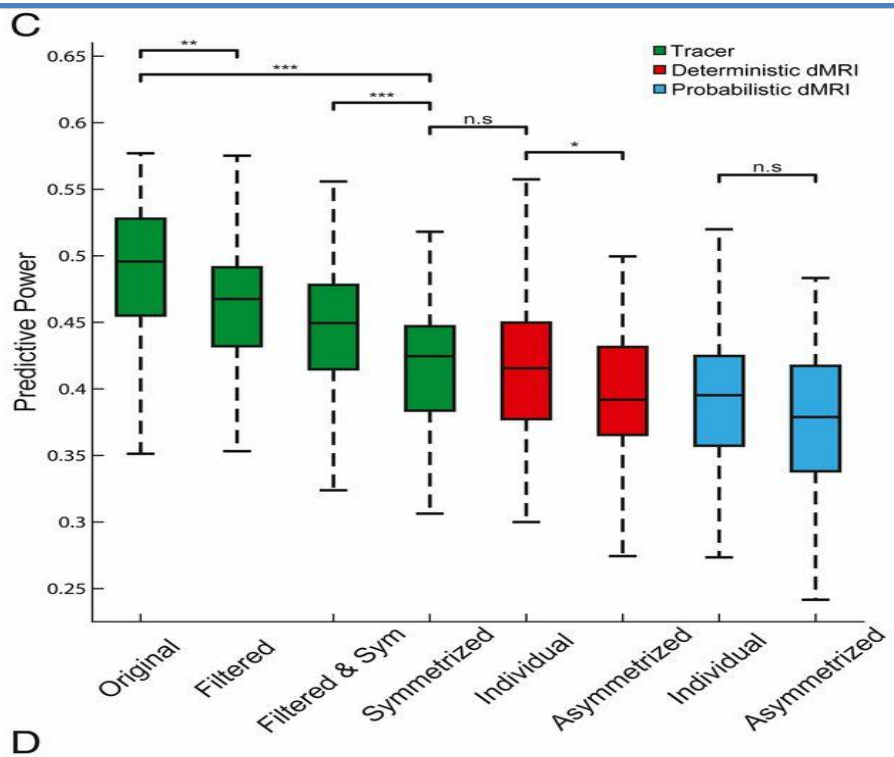
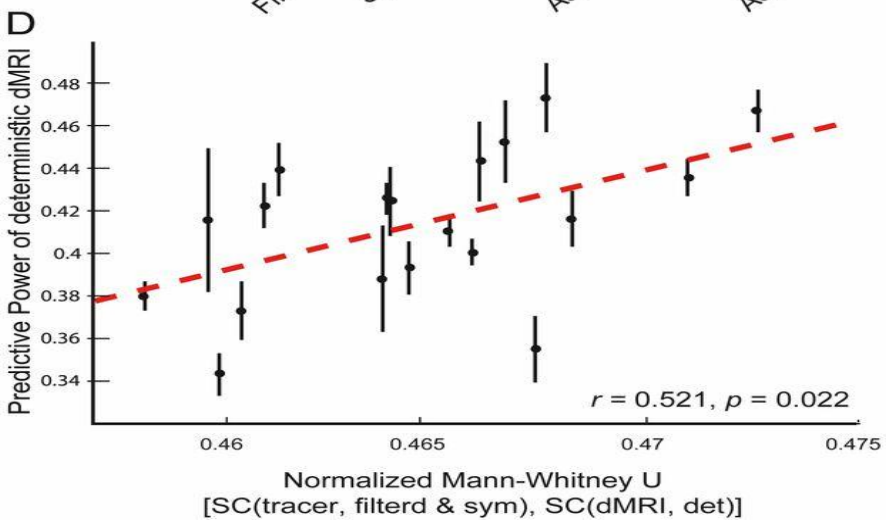
Importance of Long-Range Connections and Directionality

把TT矩阵去除DT追踪中不存在的连接

(A+A')/2







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Significance

- The structural connectome is a key determinant of brain function and dysfunction. The connectome-based model approach aims to understand the functional organization of the brain by modeling the brain as a dynamical system, then studying how the functional architecture rises from the underlying structural skeleton. Here, taking advantage of mice studies, we systematically investigated the informative content of different structural features in explaining the emergence of the functional ones. We demonstrate that individual variations define a specific structural fingerprint with a direct impact upon the functional organization of individual brains stressing the importance of using individualized models to understand brain function. We show how limitations of connectome reconstruction with the diffusion-MRI method restrict our comprehension of the structural–functional relation.

THANK YOU !

感谢大家批评指正！