Supplementary Information for
A large-scale high-density weighted structural connectome of the macaque brain acquired by predicting missing links

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A. Supplementary Methods
I. Macaque brain connectome and data processing

The two datasets applied in this work contain the binary network of dataset 1 \((D_1)\) from CoCoMac (Kotter R 2004) and the weighted \(91 \times 29\) sub-network \((D_2)\) recently acquired by systematic experiments (Markov NT, MM Ercsey-Ravasz, et al. 2014).

Compared with \(D_1\), \(D_2\) has partial coverage yet higher binary connectivity density of 61.2% than that of 26.3% in \(D_1\). To guarantee that \(D_2\) is not biased to certain function domain, the 29 target regions were distributed broadly across different function domains (Markov NT, MM Ercsey-Ravasz, et al. 2014), including 4 in occipital, 6 in parietal, 6 in temporal, 5 in frontal, 7 in prefrontal, and 1 in limbic regions. The projection weights span five orders of magnitude, statistically decaying with projection distance. Since many weak projections have been discovered in the experiment, the binary connectivity density reaches 61.2%. Although this newly obtained weighted connectivity dataset \(D_2\) is the most accurate one for primate brain until now, it only covers less than 1/3 of all pairs of regions. Further studies of brain networks require a dataset with more complete coverage and connectivity.

To calibrate our predictive model based on the high-resolution weighted \(91 \times 29\) dataset \(D_2\), in this paper, we have applied the same M132 architectonical atlas for both datasets \(D_1\) and \(D_2\) and the new predicted network \(P_b\). Since the two atlases
corresponding to $D_1$ and $D_2$ are both recorded in CoCoMac, we have mapped the 103 regions in $D_1$ onto the template of M132 atlas in $D_2$ based on the statistical table of regions recording the overlap ratio for each individual region between the two different atlases from CoCoMac ("http://CoCoMac.g-node.org/services/f99_region_overlap.php"). From this table, for each of the 103 regions, we identified the corresponding region in the M132 atlas with the highest overlap ratio. Based on the correspondence, a $91 \times 91$ binary network from $D_1$ is obtained from the CoCoMac dataset with connectivity density of 26.3%, which is far lower than 61.2% of the high-resolution $91 \times 29$ dataset $D_2$. In a word, the binary network $D_1$ will be used to predict both the missing links and their strength, calibrated by the high-resolution weighted $91 \times 29$ network $D_2$.

II. Predictive model

1. Prediction score with three factors for pairs of regions

To predict the missing links in the macaque brain, we mainly considered three representative factors for pairs of regions, including spatial proximity, topological similarity, and cytoarchitectural similarity, which are measured respectively by the spatial closeness based on Euclidean distance, the similarity of topological connections to other regions and similarity in neuron density of two different regions. There are previous studies on the high-resolution $91 \times 29$ experimental network $D_2$ revealing relationships between the three factors and connectivity probability of projections in the macaque brain, as listed in the Method part of the main text. In this work, the three factors will be combined to generate prediction scores $P_{ij}$ for potential link for each pair of regions. This score can be viewed as a measure indicating the connectivity probability from region $i$ to $j$. We then look for pairs of regions, which are not connected yet but have the highest connectivity probabilities (prediction scores) (Lü L et al. 2012). These pairs of regions are more likely candidates for missing connections. In this paper, the prediction score $P_{ij}$ is calculated by the combination of the three factors, (i) topological similarity $T_{ij}$, (ii) spatial proximity $D_{ij}$, and (iii) cytoarchitectural similarity $C_{ij}$, which will be described in more details in the following.

a) Topological similarity $T_{ij}$ In this work, we have applied 13 representative methods to measure topological similarity $T_{ij}$ between each pair of areas from existing links (Lü L et al. 2012). Given 91 regions, $A$ is the corresponding adjacency matrix, where $A_{ij} = 1$
represents a projection from region \(i\) to region \(j\), otherwise \(A_{ij} = 0\). \(K_i^{\text{out}}\), the out-degree of region \(i\), is the number of connections from \(i\) to other regions. Conversely, \(K_i^{\text{in}}\) is the in-degree of region \(i\), representing the number of other regions projecting to region \(i\).

Detailed description of \(T_{ij}\) from 13 methods that account for different combinations of input and output projections, are shown as Table S1, measuring the degree of shared neighbours in the network for a pair of regions. The different predictive models using these different measures of topological similarity then will be compared and the best one will be selected at each iteration step.

**Table S1.** Metrics of topological similarity.

| NO. | Metrics | Descriptions |
|-----|---------|--------------|
| #1  | \(T_{ij} = \sum_{m=1}^{N} \delta_{im} \delta_{jm} / k_{j}^{\text{out}}\) | Measuring the number of common output neighbors of areas \(i\) and \(j\), relative to the total output neighbor of area \(i\). \(N\) is the number of all areas. |
| #2  | \(T_{ij} = \sum_{m=1}^{N} \delta_{im} \delta_{jm} / k_{j}^{\text{out}}\) | Measuring the number of common output neighbors of areas \(i\) and \(j\), relative to the total output neighbor of area \(j\). |
| #3  | \(T_{ij} = \sum_{m=1}^{N} \delta_{mi} \delta_{mj} / k_{i}^{\text{in}}\) | Measuring the number of common input neighbors of areas \(i\) and \(j\), relative to the total input neighbor of source area \(i\). |
| #4  | \(T_{ij} = \sum_{m=1}^{N} \delta_{mi} \delta_{mj} / k_{j}^{\text{in}}\) | Measuring the number of common input neighbors of areas \(i\) and \(j\), relative to the total input neighbor of target area \(j\). |
| #5  | \(T_{ij} = \frac{1}{k_{j}^{\text{out}}} \sum_{z \in \Gamma_{i} \cap \Gamma_{j}} \frac{1}{k_{z}^{\text{out}}}\) | In order to depress the connecting effect of large areas (that is to say, as nodes with larger degree connect to many nodes, hence may contribute less information in measuring the similarity of other nodes), this method measures the reverse output-degree of common neighbors that areas \(i\) and \(j\) both connect to, relative to the total output neighbor of source area \(i\). \(\Gamma_i\) and \(\Gamma_j\) are respectively the set of nodes that region \(i\) and \(j\) connect to, and \(z\) is the common
node that both $i$ and $j$ connect to.

### Measuring the reverse output-degree of common neighbors that areas $i$ and $j$ both connect to, relative to the total output neighbor of target area $j$.

$$T_{ij} = \frac{1}{k_j^{\text{out}}} \sum_{z \in \Gamma_i \cap \Gamma_j} \frac{1}{k_z^{\text{out}}}$$

### Measuring the reverse in-degree of common neighbors that areas $i$ and $j$ both connect to, relative to the total input neighbor of source area $j$.

$$T_{ij} = \frac{1}{k_i^{\text{in}}} \sum_{z \in \Gamma_i \cap \Gamma_j} \frac{1}{k_z^{\text{in}}}$$

### Measuring the reverse in-degree of common neighbors that areas $i$ and $j$ both connect to, relative to the total input neighbor of target area $j$.

$$T_{ij} = \sum_{m=1}^{N} \delta_{im} \delta_{mj}$$

### Feedforward interaction (Junker BH and F Schreiber 2011). $m$ is the intermediate area of regions $i$ and $j$, which consists of an $i \rightarrow m \rightarrow j$ triple.

### Feedback interaction (Guyton AC et al. 1955; Hegger R et al. 1998)

$$T_{ij} = \sum_{m=1}^{N} \delta_{jm} \delta_{mi}$$

### Feedback interaction normalized by the in-degree and out-degree of intermediate area $m$ of regions $i$ and $j$.

$$T_{ij} = \sum_{m=1}^{N} \frac{\delta_{jm} \delta_{mi}}{k_m^{\text{in}} k_m^{\text{out}}}$$

### Katz similarity (Katz L 1953) is a path-dependent similarity which including all paths. $c$ is a damping factor controlling the path weights and $l$ is the path length. Since $A$ is the adjacency matrix. $A^c$ is equal to the number of distinct paths between respective pairs of nodes.

$$T_{ij} = \sum_{l=1}^{\infty} c^l \cdot | \text{path}_{i,j}^{(l)} |$$

$$= cA_{ij} + c^2(A^2)_{ij} + c^3(A^3)_{ij} + L$$

### RWR (Random walk with restart) (Pan J-Y et al. 2004; Tong H et al. 2008) index is a direct application Random walk. $T_i$ is the similarity vector for area $i$, with the $j$-th element $T_{ij}$ as the similarity between area $i$ and $j$. $P^T$ is the transition matrix with element $p_{ij} = \delta_{ij} / k_i^{\text{out}}$, $e_i$ is an $N \times 1$ vector with the $i$-th element equal to 1.

$$\vec{T}_i = cP^T \vec{T}_i + (1 - c)e_i$$
and others all equal to 0, and c is a tunable damping parameter.

b) Spatial Proximity $D_{ij}$. Based on previous studies that the connectivity probability and connection weight both follow exponential decay with the spatial distance between regions (Ercsey-Ravasz M et al. 2013; Markov NT et al. 2013), we also take the spatial proximity $D_{ij}$ as an exponential form

$$D_{ij}(\alpha) = e^{-\alpha d_{ij}} \quad (S1),$$

where $\alpha$ is the decay parameter and $d_{ij}$ represents the distance between region $i$ to $j$, measured by the Euclidean distance of their respective spatial position. Since $D_1$ was registered to M132 atlas of $D_2$ covering the whole hemisphere shared by CARET database (http://sumsdb.wustl.edu/sums/index.jsp), we have adopted 3-D coordinate of all voxels in the M132 atlas (Paxinos G et al. 2008; Saleem KS and NK Logothetis 2012). Thus, the spatial position of each brain region in the atlas is taken as the mass center by averaging surface 3-D coordinates based on surface atlas downloaded from CARET database.

c) Cytoarchitectural Similarity $C_{ij}$. Previous work (Beul SF et al. 2015) has found that cytoarchitecture similarity based on neuron density could distinct the connected and unconnected pairs of regions in the weighted 91x29 experimental network $D_2$. By staining to mark neurons and with help of the microscope-computer interface, the neuron density in different regions of macaque brain has been well studied in previous studies (Dombrowski SM et al. 2001; Barbas H et al. 2005; Collins CE et al. 2010; Elston GN et al. 2010; Beul SF et al. 2017). Therefore, we can acquire the neuron density of 91 regions in the macaque brain based on the public dataset (as shown in Fig. S1 for the cortical map of neuron density). As in the previous study (Beul SF et al. 2017), the similarity of neuron density as cytoarchitectural measure is defined as

$$C_{ij} = ND_i/ND_j \quad (S2),$$

where $ND_i$ and $ND_j$ represent the neuron density of source region $i$ and target region $j$, respectively.

Taking these three factors together into account, the connectivity probability $P_{ij}$ (prediction score) in the predictive model is subsequently defined as

$$P_{ij} \propto T_{ij}(\gamma)^{D_{ij}(\alpha)^{C_{ij}}^\beta} \quad (S3),$$

where $\alpha$, $\beta$ are tuneable parameters and $\gamma = 1,2,...,13$ represents measure index for
topological similarity in Table S1, and will be calibrated by the high-resolution 91×29 experimental network $D_2$. In addition, we also compared the results combing the three factors together to those with only single factor, where $P_{ij} \propto T_{ij}(\gamma)$, $P_{ij} \propto D_{ij}(\alpha)$, or $P_{ij} \propto C_{ij}^\beta$, respectively.

![Image](image.png)

**Fig. S1.** The map of the neuronal density for 91 regions from M132 atlas across the whole macaque brain.

2. **Evaluation metrics**

In this work, we propose the multiple iteration predictive model to predict the missing links in $D_1$. As a consequence, a hemisphere-wide binary network (91×91) with high connectivity density is obtained ($P_b$). The parameters in the predictive model is calibrated and validated by the dataset $D_2$. The performance is evaluated by comparing the connectivity matrix entries (both existent and non-existent links) in the same 91×29 sub-region of $P_b$ and $D_2$. Here, we mainly apply four measures to evaluate the predictive model.

a) **Sensitivity**: Describes the ratio of all links in $D_2$ that have been correctly predicted. It was defined by the fraction of correctly predicted links (*True Positive*, $TP$) (connected links both in $P_b$ and $D_2$) over all the binary links in $D_2$, $TP + FN$, where $FN$ denotes the number of existing links in $D_2$ but not correctly predicted (*False Negative*).
Sensitivity = \frac{TP}{TP+FN} \quad (S4)

b) **Specificity**: Describes the ratio of all unconnected pairs of regions in $D_2$ that are also not predicted. It is defined by the fraction of the number of unconnected pairs of regions (True Negative $TN$) (unconnected pairs of regions neither in $P_b$ and $D_2$), over the number of all unconnected pairs of regions in $D_2$ ($FP+TN$, where $FP$ denotes false positive, i.e., those pairs without connections in $D_2$, but incorrectly predicted as connections in $P_b$), namely,

\text{Specificity} = \frac{TN}{FP+TN} \quad (S5)

c) **Precision**: Describes the ratio of all predicted link in $P_b$ that are real connections (true positive) in $D_2$. It is defined by the fraction of correctly predicted links ($TP$) to all predicted links in $P_b$ ($FP+TP$), namely,

\text{Precision} = \frac{TP}{FP+TP} \quad (S6)

d) **Weight recovery rate** ($r_{weight}$): Denoted as the ratio between the sum of weights for the correctly predicted links (connected links both in $P_b$ and $D_2$, $TP$) and the total sum of weights in $D_2$, defined as

\[ r_{weight} = \frac{\sum TP W_{ij}}{\sum TP+TN W_{ij}} \quad (S7) \]

where the weight $W_{ij}$ refers to the experimental values in $D_2$.

III. Model validation

1. Method of model validation

In this work, we validate the reliability of the model about the prediction of binary connection and connection weights. We take the high-resolution $91 \times 29$ experimental
network \((D_2)\) as the validation data to train the predictive model and evaluate the prediction performance. Firstly, we generate 500 groups of training and testing sets, which are derived by randomly separating \(D_2\) into two subsets for 500 realizations. For each realization, we randomly select 14 target regions from the 29 regions, and use \(91 \times 14\) matrix as training sub-network and the remaining \(91 \times 15\) sub-network as testing set. Secondly, the parameters \((\alpha, \beta, \gamma)\) in the model at each iteration step are selected by optimizing its performance (i.e., the highest precision) in the \(91 \times 14\) training experimental sub-network. At the end of multiple-iteration process, we can obtain a \(91 \times 91\) prediction network \(P_b\) according to the predictive model. Finally, we check the prediction power by comparing the corresponding subset in the predicted network to the \(91 \times 15\) testing sub-network.

Here, we first calculate sensitivity (Eq. S4) and specificity (Eq. S5) to quantify the performance of the predictive model. In addition, we apply receiver operating characteristic (ROC) analysis (Fawcett T 2006) to evaluate the performance with parameters calibrated by the training \(91 \times 14\) sub-networks, with respect to the prediction power of random benchmarks. The ROC curve, which is represented by true-positive rate (sensitivity) vs. false-positive rate (1-specificity), is obtained using sequentially thresholding different connectivity density of prediction network during iterations. Since our initial iteration step starts from \(91 \times 91\) CoCoMac-based network \((D_1)\) with density of 26.3%, the random networks also start from \(D_1\) by adding or deleting links randomly. That is to say, the sensitivity and specificity in the predicted networks stay as the same as that in the random networks, when the connectivity density varies from 0% to 26.3%. Then, we continue the iteration processing to add more predicted links into the predicted network till the complete network is obtained. Apparently, as more links are added to the predicted network, the sensitivity will increase and the specificity decreases. The area under the ROC curve (Fig. S2A) (AUC) indicates the prediction power of the model, with a larger AUC representing stronger prediction power. We compare the AUC of the predictive model to the random benchmark (Fig. S2B), of which the mean ROC curve of the benchmark is shown in Fig. S2A. Furthermore, we compare the sensitivity of the predicted network at the termination condition of the predictive model to that in the random networks, with the same connectivity density of 61.2% in the subset \(91 \times 29\) (Fig. S2C).
Fig. S2. AUC and sensitivity in the predicted links compared with that in the 91×15 sub-network sampled from $D_2$. (A) ROC curves in the predicted network (red line) and random benchmark (black line, averaged over large number of realizations) starting from zero predicted links till all pairs of regions are connected. The AUC for the predictive model is calculated by the area below the red line, and for the random benchmark below the black line. (B) The distribution of the AUC among the realizations of random benchmark (gray bars) and AUC in the predicted network (red vertical line). (C) Distribution of sensitivity of the random networks and sensitivity of the predicted network. Here, all the networks have the same connectivity density of 61.2% as the $D_2$ (red star in A), which satisfies the termination condition of the predictive model.

To further confirm the reliability of the model, we also evaluate the similarity between the sensitivity in the 91×14 training sub-network and the sensitivity in the 91×15 testing sub-network. If the sensitivity in both training and testing subsets are not significantly different, the sensitivity of links in the predictive model can be considered reliable. Otherwise, if the model over-fits to the training set to lose the generalization ability, its performance should be clearly poorer in the testing set. Therefore, in order to test the reliability of sensitivity, we repeat the prediction process on the 500 realizations of the training and testing sub-network, and compare the sensitivity across the 500 realizations (Fig. S3) by
double-sample t-test. The results show that the sensitivity of the 500 training sub-networks is no significantly different from that of the 500 testing sub-networks. Furthermore, we also apply the Kolmogorov-Smirnov statistics (KS) to quantify the discrepancy of the sensitivity distributions between the training and testing sub-networks. Smaller KS value indicates the two distributions are more similar, and vice versa. Results of model validation will be presented below. Moreover, we compare the sensitivity in the predicted networks acquired for different iteration steps \( t \), and select optimal one according to the largest sensitivity of the final predicted network. After confirming the reliability of the model, all the 29 target regions are used as the training set to search for the optimal parameters of the predictive model to acquire the prediction network \( P_b \) for the whole hemisphere.

![Fig. S3. Distributions of sensitivity of the predicted results from the training and test sets.](image)

We also validate the assignment of connection weight for all the links in \( P_b \). For this part, we examine the influence of number of distance bins \( n \) to search for the optimal parameters for weight assignment. For a given number of distance bin \( n \), we train the parameters of Eq. (S1) for each distance bin based on the training \((91\times14)\) samples, then test in the rest \((91\times15)\) samples from \( D_2 \).

2. Results of model validation

In this section, we shall test the reliability of the predictive model to predict missing binary links from \text{CoCoMac}-based network across the hemisphere. 500 random groups of training and testing sets are generated from the \( 91\times29 \) experimental network \( D_2 \). We here
take one group as an example to present the results. Firstly, $91 \times 14$ subnetwork from $D_2$ is taken as the training sub-network, which has 801 experimentally identified links. The parameters at different iteration steps of the model are calibrated by the training set. The remaining $91 \times 15$ sub-network is used as the testing set, which has 814 experimentally identified links. Secondly, we apply operating characteristic (ROC) analysis to evaluate the performance of the model. As we predict more and more links during the multiple-iteration process, the connectivity density of the predicted network will accordingly increase. The true positive and false positive rates of the prediction networks are recorded at different connectivity density (Fig. S2A). The area under the ROC curve (AUC, Fig. S2A) indicates the prediction power of the model, with a larger value of AUC representing better prediction power (Fawcett T 2006). We obtain the AUC (AUC=0.75) after comparing with test sample as shown in Fig. S2A. Thirdly, we examine whether the AUC and sensitivity are significantly higher than the random benchmark. We acquired 1000 realizations of random networks by randomly shuffling links in the predicted network. The mean values of sensitivity and specificity for the random benchmark are shown as black line Fig. S2A. Finally, we calculate AUC (Fig. S2B) as well as sensitivity (Fig. S2C) of the random networks and compare them with the predicted network, which have the same connectivity density 61.2%. It can be clearly seen that AUC and sensitivity in the predicted network after comparing with the testing sample is significantly higher than the random benchmarks (AUC=0.75 for the predictive model, mean AUC=0.5 for the random benchmark, $P<1.0 \times 10^{-19}$; sensitivity=0.74 for the predictive model, and mean sensitivity=0.58 for the random benchmark, $P<1.0 \times 10^{-19}$).

In order to test the reliability of sensitivity of the training and testing sub-network, we compare the distribution of sensitivity of the predicted network at the termination condition in the 500 training sub-networks to that in the corresponding 500 testing sub-networks (Fig. S3). We apply the double-sample t-test analysis on the two distributions of sensitivity, and find that the mean values of sensitivity are significantly close (double-sample T-test: $P<1.0 \times 10^{-19}$). Moreover, the distribution of sensitivity in training sample is close to that in testing sample using Kolmogorov-Smirnov statistics (KS=0.36). These results show that using $D_2$ as data training indeed has generalizability. This is possibly because the 29 target regions are rather uniformly distributed among different functional modalities, hence are not biased (Markov NT, MM Ercsey-Ravasz, et al. 2014).

To further compare the 3-factor model with other models, we compared the precision curve and AUC from the model by the three factors, to that from models by two factors and single factor. The precision for the newly predicted links remains at a high level of 74.1% for the 3-factor model, which is higher than the models using three types of two factors, namely
topological similarity and spatial proximity (71.8%), cytoarchitecture similarity and spatial proximity (72.1%), cytoarchitecture similarity and topological similarity (72.1%) (Fig. S4). The precision of the models using only a single factor is even smaller (spatial proximity 67.3%, topological similarity 65.0%, and cytoarchitectural similarity 67.4%; see Fig. 1A and Fig. S4). Compared to AUC=0.75, $P<1.0\times10^{-19}$ when compared to random network) from the 3-factor prediction model (Fig. S2), AUC for the 2-factor model or 1-factor model is clearly smaller (AUC=0.69, $P<1.0\times10^{-19}$ for two factors of topological similarity and spatial proximity; AUC=0.72, $P<1.0\times10^{-19}$ for cytoarchitecture similarity and spatial proximity; AUC=0.72, $P<1.0\times10^{-19}$ for cytoarchitecture similarity and topological similarity; AUC=0.67, $P<1.0\times10^{-19}$ for single factor of spatial proximity; AUC=0.67, $P<1.0\times10^{-19}$ for cytoarchitecture similarity and AUC=0.61, $P<0.001$ for topological similarity) (Fig. S5).

**Fig. S4.** The precision (correctness of predicted links) in the predicted network based on different predictive models (three factors vs. single factor, as well as three types of two factors of topological similarity and spatial proximity, topological similarity and cytoarchitecture similarity, cytoarchitecture similarity and spatial proximity) with respect to connectivity density for the 91*29 subsystem. The gray
dashed line is a random benchmark (including error bars from 5,000 independent realizations of randomly adding links).

Next, we search for the optimal number of iteration steps by comparing the sensitivity of the predictive model acquired at different iteration steps $t$. The predicted networks are trained by $91 \times 14$ subnetwork from $D_2$. The corresponding sensitivity is calculated by comparing

**Fig. S5.** ROC curve and AUC in the model with two factors or single factor. Red line represents the ROC curve. The back dashed line is for the random benchmark, averaged over large number of realizations. The AUC for all these models is calculated by the area below the red line.
with the 91×15 testing subnetwork from $D_2$. Both training and testing subnetworks are acquired by 500 realizations. The mean value of sensitivity in the testing samples is largest when the number of iteration step is $t=15$ (see Fig. S6).

We then evaluate weights assignment when choosing different number $n$ of distance bins. The parameters of Eq. (S1) to assign weights are calibrated at various distance bins in the training 91×14 sets, by maximizing the correlation between the assigned and experimental weights for the true positive predicted links in the training sets from $D_2$. This procedure is repeated for various number $n$ of distance bins. Clearly, as $n$ increases, the correlation between the assigned and experimental weights in the 91×15 testing sets will increase accordingly and then decrease due to over-fitting to the training sets. Specially, the correlation between the estimated and experimental connection weights achieves maximal value ($r=0.49$, $P<1.0 \times 10^{-12}$) when $n=12$ (Fig. S7). Thus, by the training and testing validation, the optimal number of distance bins $n$ is set to 12.

![Fig. S6. Sensitivity of predicted binary links compared with links in the test groups varies as iteration steps increasing in the predictive model.](image-url)
B. Supplementary Results

Here we provide more results supplemental to those in the main text. First, we present a more detailed comparison of the predicted networks with binary connectivity density of 61.2% and 40% to $D_1$ and $D_2$, supplementary to Fig. 2 in the main text. Clearly, both predicted networks with different densities have relatively high correctness of predicted links (red dots in Fig. S8A and S8B) and small ratio of wrongly predicted links (blue dots in Fig. S8A and S8B) in the 91×29 subsets.

![Fig. S7. Correlation between the assigned weights and experimental weights varies as the number of distance bin $n$ changes in the predictive model.](image-url)
Fig. S8. Supplementary to Fig. 2 in the main text. The predicted networks from the multi-iteration predictive model with three factors with the overall all connectivity density of 59% (A) and 40% (B). Each dot presents each link in the predicted network including the existing links from CoCoMac dataset. In (A) and (B), red dots represent correctly predicted links in the final predicted network belong to the 91×29 experimental subsystem $D_2$ (Markov, et al. 2012). Blue dots show the wrongly predicted links in the predicted network. Grey dots exhibit the links in the predicted network in the rest (91-29)×29 subsystem that is not covered by the experimental data $D_2$. The index of the cortical areas is the same as Fig. 2 in the main text, which follows the index list in (Markov, et al. 2012).

Fig. S9. Prediction performance for links with different weights and distance. (A) and (B) compare the
sensitivity for different classes of links after applying predictive models with three factors or a single factor. (A) The sensitivity for the links with high (FLNe>0.0015, black bars) or low (FLNe<0.0015, white bars) experimental weights that are predicted by different models. (B) The sensitivity separately for the four classes shown in Fig. 3A by different models. Long (short)-distance links correspond to the pairs of connected regions with distances greater than 31.3 mm (less than half of the distance range).

As shown in Fig. 1 in the main text, the final predictive network $P_b$ has the sensitivity of 74.1% in the 91×29 subsets compared to $D_2$. In the main text we also compared the sensitivity for all predicted links and for the high weighted links (FLNe>0.0015 in $D_2$) that are within and between different functional systems (Fig. 4). Here we presented more details for the sensitivity within and between these different functional systems (Fig. S10).

Except for the temporal functional domain, which involves only a small number of regions, all the other intra-functional and most inter-functional connections generally have high sensitivity (larger than 0.8) (Fig. S10A). Only inter-functional connections of visual system have relatively low sensitivity. If just considering the high weight links (FLNe>0.0015 in $D_2$), the sensitivity of different functional domains largely increases (Fig. S10B).

**Fig. S10.** Supplementary to Fig. 4 in the main text. Comparison between sensitivity for the intra- and inter-functional links involving all the predicted links (A) or just including the high weight links (B) in the 91×29 subsystem of the predicted network $P_b$. For both subfigures, the letters in x-axis or y-axis refer to the corresponding functional systems (visual (V), somatosensory (S), motor (M), temporal (T), and frontal (F)).

Compared with the predictive model with only a single factor, the predictive model with the combination of three factors has the largest sensitivity of 0.97 for intra-functional links (Fig. S11A), while the sensitivity for inter-functional links are nearly the same for different predictive models. For the high weight links (FLNe>0.0015 in $D_2$), the intra-functional
sensitivity for the predictive model with three factors is still highest (0.98) compared to other predictive model with only a single factor (Fig. S11B). The sensitivity increases from 0.68 for all inter-functional links to 0.75 for high weight inter-functional links, which is close to that from the model with spatial proximity, and higher to that from the predictive model with the other single factor.

**Fig. S11.** Supplementary to Fig. 4 in the main text. Comparison of sensitivity for the intra- and inter-functional links in the 91 × 29 subsystem of the predicted network by four different predictive models with three factors or just a single factor. (A) The sensitivity for all predicted links. (B) The sensitivity for the high weight links (FLNe>0.0015).