Accurately predicting functional connectivity from diffusion imaging

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Understanding the relationship between the dynamics of neural processes and the anatomical substrate of the brain is a central question in neuroscience. On the one hand, modern neuroimaging technologies, such as diffusion tensor imaging, can be used to construct structural graphs representing the architecture of white matter streamlines linking cortical and subcortical structures. On the other hand, temporal patterns of neural activity can be used to construct functional graphs representing temporal correlations between brain regions. Although some studies provide evidence that whole-brain functional connectivity is shaped by the underlying anatomy, the observed relationship between function and structure is weak, and the rules by which anatomy constrains brain dynamics remain elusive. In this article, we introduce a methodology to predict with high accuracy the functional connectivity of a subject at rest from his or her structural graph. Using our methodology, we are able to systematically unveil the role of structural paths in the formation of functional correlations. Furthermore, in our empirical evaluations, we observe that the eigen-modes of the predicted functional connectivity are aligned with activity patterns associated with different cognitive systems. Our work offers the potential to infer properties of brain dynamics in clinical or developmental populations with low tolerance for functional neuroimaging.

Understanding the relationship between the dynamics of neural processes and the anatomical substrate of the brain is a central question in neuroscientific research [1]. Modern neuroimaging technologies, such as diffusion imaging [2, 3], allow researchers to track white matter streamlines linking cortical and subcortical structures. This information can be conveniently represented in terms of a structural graph representing direct anatomical connections [4, 5] between distinct brain regions. Complementary information can be acquired with functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) [6, 7], which measures time-dependent neural activity in the form of blood-oxygenation-level-dependent (BOLD) signals [8]. Temporal correlations between BOLD signals (averaged over representative brain parcels) can then be used to build a functional connectivity matrix, which unveils patterns of global coordination among various brain regions [9]. Prior studies offer preliminary evidence that whole-brain functional connectivity is shaped by the structural graph of anatomical connections [10, 11], yet the extent of this relationship in the human brain is not well understood.

An interesting problem in this context is understanding how functional connectivity emerges from the structural brain graph. This is a challenging problem for several reasons. First, the activity of brain regions that are not directly connected by structural links can be strongly correlated due to indirect structural paths along which signals propagate [12]. Second, the propagation of these signals is influenced, in a nontrivial manner, by the length and number of white matter streamlines in these paths [9]. Furthermore, it is unclear how signals propagating over different structural paths interfere or interact with each other to induce a global pattern of temporal correlations. Several studies have attempted to overcome these difficulties by predicting the functional connectivity of the human brain from the structural graph of anatomical connections. These approaches can be classified in three major groups: (i) those performing a direct statistical comparison between the structural graph and the functional connectivity [10, 13, 9, 14]; (ii) those based on numerical simulations of brain activity and connectivity [15, 16, 17, 18]; and (iii) those using graph-theoretical properties of the structural graph as predictors of functional connectivity [12, 19]. While these studies have made important progress, it remains challenging to accurately predict an individual’s functional connectivity from their structural brain graph.

In this article, we introduce a methodology based on spectral graph theory [20] and convex optimization [21] to predict functional connectivity in the resting state (i.e., when a subject is at rest) from the structural graph with high accuracy using a versatile nonlinear predictor. Using our methodology, we are able to systematically unveil the role of indirect structural paths in the generation of functional correlations. In what follows, we describe this predictive methodology and illustrate its performance on neuroimaging data. In our evaluations, we use structural graphs and functional matrices obtained from 84 different subjects measured non-invasively while at rest. In both cases, each node represents an anatomically defined parcel or brain region defined according to the Automated Anatomical Labeling (AAL) atlas [22], which includes 90 cortical and subcortical regions of interest, excluding the brainstem and cerebellar structures. Using diffusion tensor imaging (DTI), we build the edges of the structural graph using the average value of the Fractional Anisotropy (FA) [3] over the white matter streamlines con-
necting brain regions. The topology of the structural graph can be conveniently represented as an adjacency matrix [23], denoted by $S$, where rows and columns are indexed by brain parcels and the entries are the average FA between each pair of brain parcels. On the other hand, the functional connectivity matrix is computed using functional magnetic resonance imaging (fMRI) of blood-oxygenation-level-dependent (BOLD) time signals [8]. For each brain region, we extract a representative time series using the scale 2 wavelet coefficients ($0.06$–$0.125$ Hz) of the mean BOLD signal [9]. An entry $f_{ij}$ in the functional connectivity matrix $F$ is the Pearson’s correlation coefficient between representative wavelet coefficients extracted from regions $i$ and $j$.

Using tools from spectral graph theory [20], we propose a technique to predict the functional connectivity matrix $F$ of a subject at rest from his/her structural adjacency matrix $S$. Our predictor is comprised of two stages. In the first stage, we compute a weighted combination of the powers of the structural adjacency matrix $S$ (see Fig. 1). As we discuss in the Online Methods, the $l$-th power of $S$ accounts for structural paths of length $l$ connecting different brain regions. In practice, we truncate this weighted sum of powers at a particular value $k$, which represents the maximum length of the structural paths taken into account in the functional predictor. In the second stage of our prediction process, we perform a change of coordinates aiming to align the eigen-modes of the structural matrix $S$ with the eigen-modes of the functional connectivity matrix $F$. In algebraic terms, this change of coordinates is performed using a rotation matrix $R$ that depends on the eigenvectors of $S$ and the eigenvectors of $F$ (see Fig. 1, and Online Methods). As a result of this eigen-mode alignment, we obtain a functional predictor $\hat{F}$ whose entries are a nonlinear combination of measurements related to structural paths of lengths up to $k$.

We compute the parameters of this two-stage functional predictor by solving an optimization problem [21] aiming to maximize the quality of the functional prediction $\hat{F}$. In our experimental evaluations, we measure the functional prediction quality using the Pearson correlation between the entries of the predicted functional matrix $\hat{F}$ and those of the actual functional matrix $F$ (see the Online Methods). Hereafter, we refer to this optimization problem as the spectral mapping problem. In what follows, we study two different types of spectral mapping problems (represented in Fig. 2). First, we consider the problem of finding a ‘personalized’ functional predictor for each subject. We refer to this problem as the individual spectral mapping problem. Second, we consider the problem of finding a ‘universal’ predictor able to infer the functional connectivity for a whole group of subjects. We refer to this problem as the group spectral mapping problem. In what follows, we solve both spectral problems and illustrate the performance of our approach on neuroimaging data acquired from a large cohort of healthy human participants.

**RESULTS**

**Individual functional connectivity is predicted with high accuracy.** We first focus our attention on the individual spectral mapping problem (pictorially represented in Fig. 2a-d, and mathematically described in the Online Methods). In numerical evaluations, we consider two different BOLD time series for each subject, which we construct as follows. Beginning with a single BOLD time series with 146 time samples, we build one set of samples by randomly selecting half the samples from the original signal. The second set is built by choosing the other half of remaining samples. The first set is then used to generate an in-sample functional connectivity matrix to train the functional predictor (following the methodology described in the Online Methods). The second set is used to generate an out-of-sample functional connectivity matrix to validate the quality of the trained predictor. In a first set of experiments, we train and validate ‘personalized’ functional predictors for each one of the 84 subjects in the dataset. For each individual, we build a hierarchy of predictors with different values of $k$, where $k$ ranges from 1 to 7. In other words, we gradually increase the maximum length of the structural paths being considered in the functional predictor. In Fig. 3a, we plot the average quality of the personalized functional predictor for both the training (in-sample) and the validation (out-of-sample) functional matrices. Using the in-sample data, the correlation level achieved by the functional predictor after training becomes consistently close to 1 as $k$ increases above 5 (red boxes in Fig. 3a). Using the out-of-sample data to validate the trained predictor, we observe that the quality of the prediction consistently increases with $k$, saturating at an average correlation of 0.79 for $k$ above 5. Based on these results, we can quantify the role of structural paths of different lengths in the formation of the functional connectivity pattern. For example, since the average predictor quality for $k = 1$ is 0.562

![Figure 1](image-url)
in the validation dataset, we conclude that direct structural paths of length 1 account for 56.2% of the personalized prediction quality, on average. Furthermore, the average prediction quality increases to 0.686 when we also consider paths of length $k = 2$. Hence, we conclude that structural paths of length 2 account, on average, for a 12.4% increment in the prediction quality (i.e., $100 \times (0.686 - 0.562) = 12.4$). Similarly, as we gradually include structural paths of length 3 to 7 in the predictor, the quality increases according to the following incremental percentages: 3.7%, 4.7%, 1.9%, 0.27%, and 0.12%. Notice how the propagation of neural signals through short structural paths has the strongest influence in the resulting functional connectivity. We also observe that the average prediction quality saturates at $k \geq 5$. Therefore, paths of length up to 5 in the structural graph contain most of the information needed to predict functional correlations, offering fundamental insight into the lengths of paths used for neural computations. In the inset in Fig. 3a, we include a scatter plot to compare the entries of the actual functional connectivity matrix $F_j$ (values in the abscissae) with those of the predicted functional matrix $\hat{F}_j$ (values in the ordinates) when we choose $k = 5$ for the individual with the median correlation quality. The ordinates of the red (respectively, blue) dots correspond to the entries of the functional connectivity matrix used for training (respectively, validation).

**Group spectral mapping partially predicts individual connectivity from common parameters.** In addition to the individual spectral mapping problem, we also consider the *group spectral mapping problem*, in which we aim to find a ‘universal’ predictor able to estimate a representative functional connectivity matrix for a group of subjects. In other words, given the structural graphs and functional connectivity matrices of a group of individuals, we aim to find a common predictor to estimate the functional connectivity matrix for any individual in the group with the maximum possible overall correlation quality (see the Online Methods for a technical description of this problem). From a neuroscientific perspective, this problem corresponds to understanding the common role of structural paths of differing lengths in neural computations performed in many individuals. To evaluate the performance of the method, we partition the set of 84 subjects into two subsets: an in-sample subset
of 42 individuals whose structural graphs and functional connectivity matrices are used to train the universal predictor, and an out-of-sample subset of 42 individuals used to evaluate the prediction quality. In this setup, we find the optimal parameters of the universal predictor for the in-sample training set when the maximum length of structural paths under consideration ranges from \( k = 1 \) to 7. In Fig. 3 b, we plot the performance of the universal functional predictor for both the in-sample training set (yellow boxes) and the out-of-sample validation set (green boxes). Overall, the performance in the validation set is well aligned with the training set, and both tend to increase as we increase the value of \( k \). As expected, the universal predictor presents a lower performance when compared with the personalized predictors, highlighting the existence of meaningful individual differences in how structural paths inform functional dynamics. In particular, when the out-of-sample prediction case is considered, the best average performance stabilizes at around 0.62 for the group case (while in the personalized case, it saturates at around 0.79).

It is interesting to speculate that differences between the predicted and actual functional connectivity matrices may be related to individual differences in cognitive abilities in healthy individuals, or to individual differences in symptomatology in clinical populations.

**Spectral mapping exhibits robustness to the number of nodes in the parcellation.** It is important to understand whether or not the mappings from structure to function are invariant across spatial resolutions of brain dynamics. To address this question, we performed the same analyses described above using a different anatomical atlas. More precisely, we considered an upsampling version [9] of the Automated Anatomical Labeling Atlas, which we refer to as the AAL-600, developed to create equally-sized regions that still obey gross anatomical boundaries [5, 4]. This upsampled version contains 600 regions created via a series of steps in which regions are bisected perpendicular to their principal spatial axis. Following this process, the resulting atlas contains regions comprised of approximately 268 voxels each. In Fig. 3 c-d we present the results for the individual and group spectral mappings in the AAL-600 atlas. Observe that the results are similar to those obtained for the AAL-90 atlas, as illustrated in Fig. 3 a-b. In particular, we notice that the performance of the predictor increases as longer structural paths are considered and its performance saturates for structural paths longer than 5.

**Functional eigen-modes are revealed by group spectral mapping.** To investigate the neurophysiological drivers of these predictions, we depict in Fig. 4 brain surface activation maps representing the first four eigen-modes of the predicted functional connectivity \( \hat{F} \) (i.e., the eigenvectors of \( \hat{F} \) associated with the four largest eigenvalues). We observe that these eigen-modes are aligned with activity patterns in distinct cognitive systems. In particular, the first eigen-mode (Fig. 4 a) represents the so-called Bonacich centrality of the functional connectivity matrix, which measures how ‘well-connected’ or ‘central’ a region is in the functional graph [24].

**Figure 3** Spectral mapping performance. We represent the evolution of the correlation quality between the predicted and the actual functional connectivity matrices when we vary the maximum length of the paths under consideration (denoted by the parameter \( k \)) for the individual and the group spectral mappings. These cases are evaluated for the AAL-90 parcellation in a-b, and for the AAL-600 parcellation in c-d. In a (respectively c), we plot the evolution of the correlation quality evaluated over 10 different splits of the BOLD signal time-series wavelet coefficients in the training (in red) and validation (in blue) sets. The inset plot in a (respectively c) includes two scatter plots of the entries of the predicted functional matrix \( \hat{F} \) (values in the ordinates) versus the actual connectivity matrix \( F \) (values in the abscissae) when \( k = 5 \) for the individual with the median correlation quality. The ordinates of the red (respectively, blue) dots in the scatter plot correspond to the entries of the functional connectivity matrix used for training (respectively, validation). In b and d, we plot the evolution of the correlation quality evaluated over 10 different splits of the BOLD signal time-series in the training (in yellow) and validation (in green) sets.

The second eigen-mode (Fig. 4 b) takes high values (depicted in yellow) over primary sensory and motor cortices, as well as the adjacent premotor areas and inferior parietal lobule, classically associated with sensorimotor control processes. The third eigen-mode (Fig. 4 c) presents high values over primary and secondary visual cortex, as well as the posterior parietal cortex, which are regions associated with visually and somatosensory guided action. Finally, the fourth eigen-mode (Fig. 4 d) presents high values over the prefrontal cortex and temporoparietal junction, which are regions associated with high level cognition, attention and the control of behavior.

**Similarity of spectral characteristics across individuals.** From a mathematical perspective, the effectiveness of the group spectral mapping method is, in part, explained by
the similarity of spectral characteristics across subjects in the dataset. In particular, as we illustrate below, the eigenvalues of the functional (respectively, structural) matrix present a high level of similarity across individuals. Furthermore, the most relevant eigenvectors of these matrices (i.e., those associated with the largest eigenvalues) are also well aligned among individuals. To evaluate spectral similarities in the data, we start by plotting the eigenvalues of the structural matrix (in decreasing order) in Fig. 5c. In this figure, we include a box plot for the eigenvalues in the dataset. More precisely, for each eigenvalue number (i.e., the $i$-th eigenvalue number of each matrix, in decreasing order), we represent the average value, as well as the first and third quartile for the 84 values corresponding to the $i$-th eigenvalues of all the individuals in the dataset. We observe how the distribution of eigenvalues is very concentrated; in other words, the eigenvalues of the structural matrices in our dataset are very similar across individuals. Similarly, in Fig. 5f, we plot the histogram of correlations for the first and second eigenvectors of the functional matrices, respectively. From a mathematical perspective, these spectral similarities allow us to find a high-quality ‘universal’ predictor able to map the adjacency matrix of structural brain graphs into functional connectivity matrices using tools from spectral graph theory. From a neurophysiological perspective, such similarities indicate that healthy human subjects display a similar organization of paths in structural graphs, as well as functional connectivity matrices.

**Stability of spectral mapping.** In what follows, we examine the stability of our predictor to ensure that the spectral mapping method is not overfitting the data. In this
Figure 6 Stability of spectral mapping. Thin lines denote the evolution of the functional correlation quality for each one of the 84 individuals in the dataset, whereas bold lines indicate the average over all thin lines. In a-b, we plot the evolution of the quality for FA-type structural matrices as we vary the value of the hyper-parameters $k$ and $r$. Similarly, c-d display this evolution for Connect-type structural matrices.

direction, we vary the number of degrees of freedom in the functional predictor using two hyper-parameters. The first hyper-parameter is the order of the maximum power of $S$, denoted by $k$, included in the first stage of our functional predictor (see Fig. 1 and Online Methods). As previously mentioned, this value is equal to the maximum length of the structural paths considered by the functional predictor. The second hyper-parameter is the rank $r$ of the rotation matrix $R$ used in the second stage of the functional predictor (see Fig. 1 and Online Methods). By reducing the rank of the rotation matrix, we restrict the number of eigen-modes of $S$ that we aim to align with the eigenmodes of $F$. Computationally, this has the effect of reducing the number of free parameters associated with the rotation matrix $R$. In Fig. 6, we plot the influence of these hyper-parameters on the quality of the solution of the individual spectral mapping problem. This quality is measured as the correlation coefficient between the entries of the functional matrix $F$ and the entries of the predicted functional matrix $\hat{F}$. Fig. 6 contains subplots displaying the evolution of the functional correlation quality for all the 84 individuals in the dataset as we vary the hyper-parameters. In particular, in Fig. 6 a (respectively, b), we plot the evolution of the quality when the structural matrix is based on the Fractional Anisotropy (FA) as we vary the value of the hyper-parameter $k$ (respectively, $r$). Similarly, in Fig. 6 c-d, we plot the evolution of the functional correlation quality when the structural matrix is built according to an alternative method based on the number of streamlines connecting the regions associated to each pair of nodes [9].

**Comparison to null models.** To gain critical understanding on the effectiveness of our method, we perform a series of tests considering several null models. In our evaluations, we use the function $\text{ucorr}(A,B)$, which is defined as the correlation between the upper-triangular entries of two square symmetric matrices $A$ and $B$ of the same dimension. Using this function, we first evaluate $\text{ucorr}(F_i,S_j)$ for each individual $i$ in the dataset. This correlation measures the inherent similarities between structural and functional modalities for the same subject. In Fig. 7a, we display in green a box plot summarizing the distribution of correlations, which yields a mean (and a standard deviation) of 0.190 (0.042). Apart from similarities between structural and functional matrices for the same subject, we also measure inherent similarities for different subjects. In this direction, we evaluate $\text{ucorr}(F_i,S_j)$ for all pairs $(i,j)$ of individuals in the dataset. In Fig. 7a, we display in purple a box plot summarizing the distribution of correlations, which yields a mean (and a standard deviation) of 0.188 (0.041). These numerical results suggest that the functional matrices $F_i$ in our dataset are poorly correlated with the structural matrices $S_i$; in fact, the average correlation between $F_i$ and $S_i$ is similar to the average correlation between $F_i$ and $S_j$ for $j \neq i$. Furthermore, we also analyze similarities among the functional (respectively, structural) matrices in the dataset by evaluating

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ucorr($F_i, F_j$) (respectively, ucorr($S_i, S_j$)) for all pairs ($i, j$) of individuals in the dataset. In Fig. 7b, we display box plots summarizing the distribution of correlations for the structural and functional modalities, whose means (and standard deviations) are 0.461 (0.112) and 0.582 (0.045), respectively. From these results, we observe that, as expected, structural matrices present a significant level of correlation across individuals, while functional matrices present a lower average correlation.

In the above experiments, we have examined inherent similarities in the dataset by studying correlations between structural and functional matrices for the same, as well as different, individuals. In the following set of experiments, we evaluate the similarity between the ‘personalized’ functional predictor and functional matrices. As previously described, the ‘personalized’ functional predictor for the $i$-th individual in the dataset is trained using the pair of matrices ($S_i, F_i$) and characterized by the set of parameters $a_i$ and $R_i$. The input of this predictor is a structural matrix $S$ and its output, denoted by $\hat{F}_i(S)$, is a functional matrix predicted from $S$. In the next experiment, we first compute the functional matrix predicted when the input is the $j$-th structural connectivity $S_j$ using the ‘personalized’ predictor corresponding to the $i$-th individual. We denote this matrix as $\hat{F}_j^i = \hat{F}_i(S_j)$. We then compare this matrix with $F_i$ and $F_j$ by computing ucorr($\hat{F}_j^i, F_i$) and ucorr($\hat{F}_j^i, F_j$) for all pairs of individuals ($i, j$) in the dataset. In Fig. 7c, we display in gray a box plot summarizing the distribution of ucorr($\hat{F}_j^i, F_i$), whose mean (and standard deviation) is 0.479 (0.174). This relatively high value is, in part, explained by the inherent similarity among structural matrices of different subjects, as pointed out in the previous paragraph. Similarly, in Fig. 7c, we display in brown a box plot summarizing the distribution of ucorr($\hat{F}_j^i, F_j$) for all $i \neq j$, whose mean (and standard deviation) is 0.226 (0.112). These values should be compared with ucorr($\hat{F}_j^i, F_i$), i.e., the correlation between the predicted and actual functional matrices for the $i$-th individual. As plotted in Fig. 3a, the average correlation in this case is much higher (above 0.99 (< 0.001) for the in-sample case, and at 0.79 (0.06) for the out-of-sample case). From these comparisons, it is possible to conclude that the spectral mapping method captures features that are specific to each individual’s structural and functional connectivity matrices, since such mapping is not reproducible (on average) by swapping either the matrices or the parameters associated with the mapping.

**DISCUSSION**

**Broader implications for cognitive neuroscience.** Our results have important implications for cognitive neuroscience. First, it is striking that paths of length up to $k = 5$ offer maximal prediction accuracy, even across structural brain networks constructed from very different spatial resolutions (from 90 to 600 brain regions). This surprisingly low value of $k$ suggests that relatively parsimonious polysynaptic connections impose critical constraints on brain dynamics and observed functional connectivity. The disproportionate contribution of short paths (of length up to 5) to the functional prediction may be due to energy considerations: it is intuitively plausible that processing information along longer paths may require more energy than processing information along shorter paths. An alternative explanation could lie in the temporal constraints imposed by our environment: over evolutionary time scales, the time it takes an organism to respond to threats or opportunities is negatively correlated with the organism’s reproductive success. Assuming longer paths require more time and more energy; it is then reasonable that relatively short paths in the structural graph can predict the observed functional dynamics. However, this line of argument also begs the question of why the functional connectivity matrices cannot be predicted with high accuracy using only paths of length $k = 1$ or $k = 2$. To address this question, it is important to note that paths of increasing length offer a greater dimensionality to the dynamic range of the system. Systems that only utilize structural paths of length $k = 1$ necessarily have an impoverished ensemble of possible states in comparison to those that utilize structural paths of longer lengths. Thus, it is intuitively plausible that the prediction accuracy obtained from $k = 5$ is an indirect indication of a careful balance between the competing requirements for a broad dynamic range and an energetically and temporally efficient system.

**Broader implications for clinical neuroscience.** Our results are also more broadly relevant for clinical neuroscience. Critically, the ability to predict a subject’s functional connectivity from their structural connectivity opens the door to inferring brain dynamics even in individuals with low tolerance for functional neuroimaging. Such an ability is particularly relevant in the context of clinical populations with increased motion, anxiety, or proneness to seizures, as well as in developmental populations that have difficulty staying still in the MRI scanner for long periods of time. The principled and accurate inference of brain dynamics from these populations supports the development of personalized therapeutics based on neural markers.

**A generalizable methodological tool.** Finally, it is important to note that the methods we develop here are more generally applicable to other problems in which one wishes to predict one set of matrices from another set of matrices. In the context of neuroimaging, we could use these same tools to ask how structural graphs prior to an injury relate to structural graphs after an injury. We could also ask whether and how functional connectivity matrices change over time, either during learning or as a function of normal aging. It will be interesting in future to determine whether features of the rotation matrix (the mapping from structure to function) are related to individual differences in cognitive abilities in healthy subjects, symptomatology in diseased cohorts, or genetic variability.

**METHODS** Methods and any associated references are
available in the online version of the paper.

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COMPETING INTERESTS The authors declare that they have no competing financial interests.

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ONLINE METHODS

Connectivity Matrices. Structural brain graphs were estimated via deterministic tractography applied on diffusion tensor imaging (DTI) scans [3]. Each region in the structural graph corresponds to a localized brain area in the Automated Anatomical Labeling (AAL) atlas [22]. In our experiments, we consider structural graphs with weighted edges using two types of connectivity: Connect and Fractional Anisotropy (FA).

In the Connect type, the weight of an edge is given by the total number of white matter fiber tracts connecting a pair of brain regions. In the FA type, edge weights are computed using the fractional anisotropy of all voxels in the DTI scan, which is a scalar value describing the degree of anisotropy of the diffusion of water molecules in the voxel.

The weight of an edge connecting two regions is, thereby, defined as the average value of the fractional anisotropy over the white matter streamlines connecting them [3]. Apart from structural graphs, we also consider functional connectivity matrices, built as follows. For each brain region in the AAL atlas, we extract a representative time-series signal in each region [4]. The brain region in the AAL atlas, we extract a representative time-series corresponding to a localized deterministic tractography applied on diffusion tensor imaging (DTI) scans [3]. Each region in the structural graph corresponds to a localized deterministic tractography applied on diffusion tensor imaging (DTI) scans [3]. In our experiment, we partition this group into two subgroups of equal size. We use the pairs of nodes and weighted edges. We denote by $S$ the set of all such pairs.

To find the values of the parameters $\lambda_i$ and $\phi_i$, we use a weighted sum of powers of $l_i$ connecting nodes $i$ of the structural graph, i.e., the entry $(i,j)$ of $S$ is given by:

$$S[i,j] = \sum_{p \in \sigma(i,j)} \omega(p),$$

where $\sigma(i,j)$ is the set of all paths of length $l$ from $i$ to $j$ in the structural graph. Given a path $p=(i_0,i_1,...,i_l)$, we define the weight of the path as the following product:

$$\omega(p) = \sum_{i \in \sigma(p)} \omega_i,$$

where $\omega_i$ is the weight of the edge $i$.

A fundamental result in spectral graph theory relates the eigenvalues and eigenvectors of $S$ to the optimization problem in (2) is given by:

$$F = R^T \left( \sum_{i=0}^{N} \omega_i S \right) R.$$

In what follows, we explain how to generate in-sample and out-of-sample functional matrices to train our predictor and assess its quality. We start with a collection of bold signals $b_i = (b_i(1),...,b_i(146))^T$ of dimension 146, where $b_i(s)$ denotes the $s$-th time sample of the average BOLD signal in the $r$-th brain region (according to the AAL atlas with either 90 or 600 regions). We then compute the scale-2 maximum-overlap wavelet transforms [26] of $b_i$ for all $r$, which we denote by $w_r = (w_r(1),...,w_r(146))^T$. For each region $r$, we partition the wavelet vector $w_r$ into two: one first vector $w_{r1}^{(1)}$ including 73 entries of $w_r$ (chosen uniformly at random without repetition), and $w_{r2}^{(1)}$, which includes the remaining entries of $w_r$. Using the sets of vectors $w_{r1}^{(1)}$ and $w_{r2}^{(1)}$, we compute two functional correlation matrices; the in-sample matrix $F^{(1)}$ and the out-of-sample matrix $F^{(2)}$, where $F^{(1)} = (\omega_{ij}^{(1)})$ as well as the out-of-sample matrix $F^{(2)} = (\omega_{ij}^{(2)})$. In our numerical experiments, we use $F^{(1)}$ to find the optimal set of parameters for the predictor $\hat{F}$ (i.e., we use $F^{(1)}$ to solve the optimization problem in (2)). In the main document, we use the out-of-sample matrix $F^{(2)}$ to assess the quality of our predictor.

Since an $n \times n$ rotation matrix $R$ has $n(n-1)/2$ degrees of freedom [27], the solution to (2) may result in overfitting due to the additional number of parameters in the predictor. To validate that this is not the case, we consider a version of the optimization problem (2) in which we constrain the rank of $R$ to be equal to a given integer $p$ (see Supplementary Information for more details). In our numerical experiments, we compute the predictor for different values of $p$ and plot our results in Fig. 6. Our results support our claim about the absence of overfitting in $\hat{F}$.

Group Spectral Mapping. Consider a group of $N$ individuals whose structural and functional matrices are given by the set of pairs $[S_i,F_i]$. In this mapping problem, our objective is to find a common predictor able to generate an approximation of $F_i$ from $S_i$. Our predictor is parameterized as follows: $F_i = R[S_i]^T R^T$, where $S_i = \sum_{j=0}^{N} a_i S^j$ and $R$ is an orthogonal rotation matrix. To find the parameters $[a_i]_{i=0}^{N}$ and $R$ in the common predictor, we propose to solve the following optimization problem: given $N$ pairs of matrices $[S_i,F_i]$, we aim to express $R$ and $\{a_i\}_{i=0}^{N}$ as well as the value of the maximum order $k$, find the solution pair $[a_i]_{i=0}^{N}$ and $R$ that solves

$$\min_{a_i} \left\| R \left( \sum_{j=0}^{N} a_i S^j \right) R^T - F_i \right\|_F^2$$

subject to

$$R^T R = I_N.$$
of structural and functional matrices in the first subgroup (which we refer to as the in-sample set) to train the common predictor, and validate our results with the second subgroup (the out-of-sample set).

Matrix Correlation Quality. In our empirical evaluations, we measure the similarity between two $n \times n$ square matrices $X$ and $Y$ using the matrix correlation function, denoted by $\text{ucorr}(X,Y)$, and defined as the entry-wise correlation between the upper-triangular entries (excluding diagonal elements) of $X$ and $Y$. In other words, if we build two vectors $x$ and $y$ of dimension $n(n-1)/2$ by ‘vectorizing’ the upper triangular entries of $X$ and $Y$, the matrix correlation function is simply the correlation between these two vectors.