DEEP-LEARNING AND ANALYTICAL MODELS GIVE DISTINCT RESULTS FOR THE BRAIN STRUCTURE-FUNCTION RELATIONSHIP IN HEALTH AND IN PSYCHOSIS

Qing Cai[1,2], Hannah Thomas[1], Vanessa Hyde[1,3], Pedro Luque Laguna[1], Carolyn B. McNabb[1], Krish D. Singh[1], Derek K. Jones[1], and Eirini Messaritaki[1]

[1]Cardiff University Brain Research Imaging Centre, Cardiff University, Cardiff, UK
[2]School of Artificial Intelligence, Tiangong University, Tianjin, China
[3]Cambridge University, Cambridge, UK

ABSTRACT

Quantifying the intricate relationship between brain structure and function is of extreme importance in neuroscience. In this work, we present a comprehensive framework for mapping brain structural connectivity measured via diffusion-MRI to resting-state functional connectivity measured via magnetoencephalography, utilizing a deep-learning model based on a Graph Multi-Head Attention AutoEncoder. We compare the results to those from an analytical model that utilizes shortest-path-length and search-information communication mechanisms. The deep-learning model performed well at predicting healthy participant functional connectivity at individual-participant level, in particular in the alpha and beta frequency bands (mean correlation coefficient over 0.8), and better than the analytical model. The two models identified distinct differences in the structure-function relationship in people with psychosis compared to healthy participants, which were highly statistically significant ($p < 2 \times 10^{-4}$ for the deep-learning model, $p < 3 \times 10^{-3}$ in the delta band for the analytical model). Our results imply that human brain structural connectivity and electrophysiological functional connectivity are tightly coupled. They also show that simple analytical algorithms are very good models for communication between brain areas in people with psychosis in the delta and theta bands, while more sophisticated models are required for the alpha and beta bands.

1 Introduction

Quantifying the mapping between structural connectivity (SC) and functional connectivity (FC) in the human brain is a major goal of neuroscience research [1]. Studying the SC-FC relationship in healthy and in patient populations can provide a better understanding of the origins and evolution of neurological disorders by revealing to what extent those are a result of structural damage or of functional defects. Current neuroimaging techniques, such as magnetic resonance imaging (MRI)

and magnetoencephalography (MEG), allow for the non-invasive measurement of SC and FC and have led to large scale studies of the link between the two.

Various methodologies have been used to relate SC to fMRI-measured FC [2, 3, 4, 5], including forward-generating models that link microstructure to FC [6, 7, 8, 9]. Analytical models that assume specific communication mechanisms between brain areas (such as shortest path, search information, navigation efficiency, etc.) have also been used to link SC to fMRI-measured FC [10], confirming that interactions among brain areas are influenced by the broad network of structural connections in addition to shortest paths.

Linking SC to elecrophysiologically-measured FC has also been done [11, 12, 13, 14, 15, 16], including via the use of analytical models [17]. This is of particular interest, given that electrophysiological FC reflects brain connectivity at the milli-second time scale, i.e., the actual time scale of functional interactions in the human brain. Even though analytical models can capture a significant fraction of the SC-FC relationship and can elucidate the mechanisms via which communication happens between brain areas, they cannot capture all aspects of their complex association. Machine-learning approaches, on the other hand, are well-suited for picking up that kind of complexity, as recent work has shown for fMRI-measured FC [18].

In this work we investigate for the first time how well a deep-learning model based on a Graph Multi-Head Attention Autoencoder (GMHA-AE) can predict electrophysiological resting-state functional connectivity measured via magnetoencephalography (MEG) recordings from structural connectivity. The model can learn high-dimensional embeddings of the relationship between brain structural and functional connectomes and provide a robust quantification of it. We also perform a comparison of the results derived via the GMHA-AE to those derived via an analytical model that combines the shortest-path-length and search-information algorithms [10], incorporating communication via both direct and indirect structural connections.

Electrophysiological FC contains rich information about the frequency characteristics of the signals in the brain, and recent work showed that the fidelity of predicting MEG-measured FC via analytical models depends on both the frequency band of the FC and on the structural measure that is used to assign strength to the connections of the SC matrices [17]. In this work, we test whether that is also the case when a GMHA-AE model is used to relate FC to SC.

Because of the similarities of structural connections and of functional connectivity patterns in healthy brains, several studies have used group-averaged structural and functional connectomes when calculating the SC-FC relationship. Although undoubtedly informative, those analyses cannot capture the aspects of the SC-FC relationship that are participant-specific such as, for example, age dependence. Therefore, participant-specific analyses are essential when studying the SC-FC relationship. A question that naturally arises when investigating the SC-FC relationship, and which underlies the group-average analyses, is how specific to a given participant that relationship is. This is also of interest when considering populations that span a wide age range (because the SC-FC relation has been shown to change across the lifespan [19, 20]) or when studying patient populations [21].

In addition to investigating the performance of our proposed GMHA-AE model, we compare its performance to an analytical model that has been previously used to predict FC from SC [17, 22]. Keeping in mind the above-mentioned considerations, in this work we answer the following questions:

1. Which of the two models employed in this work, GMHA-AE or analytical, is better at predicting electrophysiological resting-state FC from SC?
2. Does the predictive ability of each model depend on the MEG frequency band for which the resting-state FC is calculated?
3. Does the predictive ability of each model depend on the structural measure that is used to quantify connection strength in the SC matrices?
4. Is there a difference between the two models in how specific to each participant the predictive ability of their structural connectome is?
5. Is there an effect of participant age in the predictive ability of each model?
6. Is there an effect of disease in the predictive ability of each model?

2 Methods

A schematic of the analysis pipeline is shown in Fig. 1.

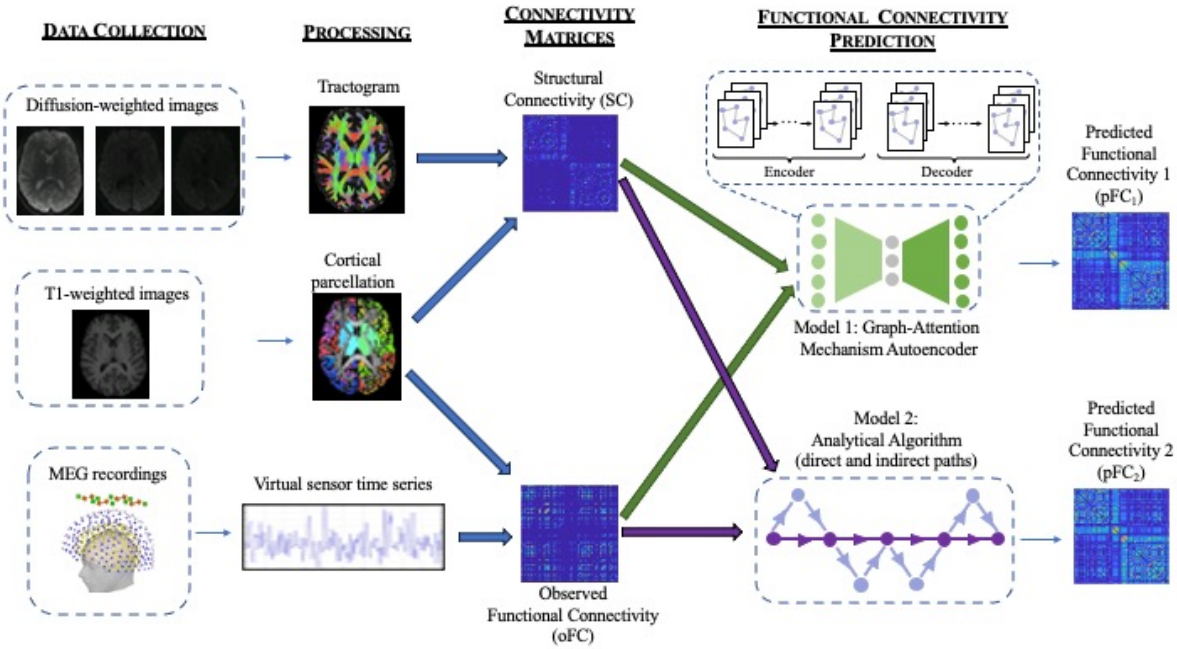

Figure 1: Analysis pipeline.

2.1 Data Acquisition and Processing

Sample

Multi-modal data were collected from healthy participants via the Welsh Advance Neuroimaging Database (WAND) study. In this work, we use data from those participants that have good quality diffusion MRI, mcDESPOT and MEG data. Under these conditions, our sample consists of 126 healthy participants between the ages of 18 and 50 (73 female), 101 of whom were between the ages of 18 and 35 (55 female). The age distributions of the participants are shown in Fig. 2). During

the study, the same data were collected from 5 people with psychosis between the ages of 18 and 35 (3 female). All psychosis participants were diagnosed at least 9 months prior to data collection.

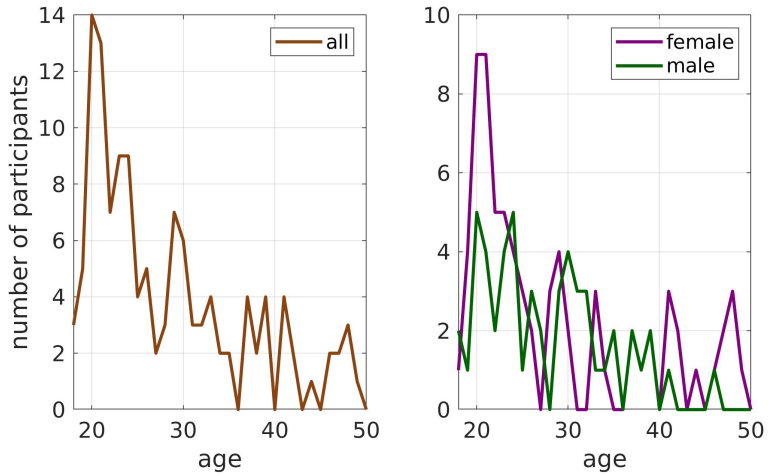

Figure 2: Age distributions of the healthy participants.

MRI Acquisition and Structural Connectivity

T1-weighted images were acquired using magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo (MPRAGE) sequence. MPRAGE sequences were acquired on a Siemens Connectom (300mT/m) 3T scanner, with repetition time (TR) 2300ms, echo time (TE) 2ms, field of view (FOV) 256 x 256 x 192 mm, matrix size 256 x 256 x 192, voxel size 1 x 1 x 1 mm, flip angle 9°, inversion time (TI) 857ms, in-plane acceleration (GRAPPA) factor 2 and phase-encoding direction anterior to posterior (A»P).

Multi-shell diffusion-weighted MRI data were acquired on the same scanner using protocols described recently for the Microstructural Image Compilation with Repeated Acquisitions (MICRA) dataset [23]. Data were acquired over 18 minutes using a single-shot spin-echo, echo-planar imaging sequence, in both anterior to posterior (A»P) and posterior to anterior (P»A) phase-encoding directions. A»P data comprised two shells of 20 diffusion encoding directions uniformly distributed (Jones et al., 1999) at b = 200 s/mm^2 and b = 500 s/mm^2, one shell of 30 directions at b = 1200 s/mm^2 and three shells of 61 directions each at b = 2400 s/mm^2, 4000s/mm^2 and 6000 s/mm^2. Additionally, two leading non-diffusion-weighted (b = 0 s/mm^2) images and 11 non-diffusion-weighted images were acquired, dispersed throughout (33rd volume and every 20nd volume thereafter). P»A data comprised two leading non-diffusion-weighted images, one shell of 30 directions at b = 1200 s/mm^2 and a final non-diffusion-weighted image. Data acquisition details for all b-values are as follows: TR=3000ms, TE=59ms, FOV = 220 x 200 mm in-plane, matrix size 110 x 110 x 66, voxel size 2 x 2 x 2 mm, with in-plane acceleration (GRAPPA) factor 2. The diffusion gradient duration and separation were 7ms and 24ms, respectively.

McDESPOT (Multicomponent driven equilibrium single pulse observation of T1 and T2) data were acquired using sequences described in [24], including a T1-weighted 3D spoiled gradient-recalled echo sequence (SPGR), an inversion recovery-prepped spoiled gradient-recalled echo sequence (SPGR-IR) and a steady-state free precession (SSFP) sequence. Data acquisition details were as follows: for SPGR – TR=4ms, TE=1.9ms, 8 flip angles (3, 4, 5, 6, 7, 9, 13 and 18°); for SPGR-IR – TR=4ms, TE=1.9ms, flip angle 5°, full k-space acquisition in PE and slice directions; for SSFP –

TR=4.54ms, TE=2.27ms, 8 flip angles (10.00, 13.33, 16.67, 20.00, 23.33, 30.00, 43.33 and 60.00^o). For all mcDESPOT data, the phase-encoding direction was A»P, FOV 220 × 220 × 179 mm^3, matrix size 128 × 128 × 104 and voxel size 1.72 × 1.72 × 1.72 mm^3.

Cortical reconstruction and volumetric segmentation of the T1-weighted images was performed with the FreeSurfer image analysis suite (`https://surfer.nmr.mgh.harvard.edu`). The technical details of the methods used by the FreeSurfer software have been described in other publications [25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37]. The Desikan-Killiany atlas [38] was used to identify the grey matter areas that form the nodes of the structural brain networks. The atlas provides 82 cortical and subcortical areas for the left and right cerebrum.

Data were analysed on a CentOS Linux 7 cluster computing system. The diffusion-MRI data were corrected for thermal noise, signal drift, susceptibility distortions, motion and eddy-current distortions, gradient non-uniformity and Gibbs ringing artifacts using a combination of in-house pipelines, the FMRIB Software Library [39] and MRtrix3 [40]. A brain mask was created using the Brain Extraction Tool [39] to exclude non-brain data. Diffusion MRI noise level estimation and denoising was performed using a Marchenko-Pastur principal component analysis(MP-PCA)-based approach [41, 42]. Within-image intensity drift was corrected by fitting the diffusion-MRI data to temporally interspersed b0 images using in-house code in MATLAB R2017b (MathWorks Inc. Natick, Massachusetts, USA). Slicewise OutLIer Detection (SOLID) [43] was applied, with lower and upper thresholds of 3.5 and 10 respectively, using a modified z-score and a variance-based intensity metric. The susceptibility-induced off-resonance field was estimated from the b0 data collected in opposing phase-encoding directions using FSL's topup [44, 45] and corrected, along with eddy-current induced distortions and participant movement using FSL's eddy tool [46]. In-house code was used to correct for gradient non-uniformity distortions in MATLAB 2017b (MathWorks Inc. Natick, Massachusetts, USA). Gibbs ringing correction was performed in MRtrix3 [40] using the subvoxel-shifts method [47].

Preprocessing of mcDESPOT data included brain extraction of T1-weighted MPRAGE data using HD-BET [48] followed by resampling of MPRAGE and masked brain-extracted data to SPGR-IR resolution using Advanced Normalization Tools [49]. SSFP and SPGR data were corrected for motion using the FMRIB Software Library (FSL version 6.0.1) motion correction tool (mcflirt; [50]) and then SPGR-IR data were registered to the motion corrected SPGR data using FSL's linear registration tool (flirt; [51]). These data were then used to create B1, T1 and B0 maps using functions from QUantitative Imaging Tools (QUIT; [52]), including driven equilibrium single pulse observation of T1 (DESPOT1) with and without high-speed incorporation, as well as DESPOT2 [53, 54]. Finally a three-compartment model [55] was used to separate SPGR and SSFP signals into discrete pools representing myelin water and intra/extra-cellular water or cerebrospinal fluid.

MRtrix3 [40] was used to calculate the response function (using the Dhollander algorithm [56, 57] which is appropriate for multi-shell acquisitions) and the fiber orientation distributions (using Multi-Shell-Multi-Tissue constrained spherical deconvolution [58] which allows estimation of multiple crossing fibers within each voxel), in order to perform anatomically-constrained tractography. The MRtrix function 5ttgen [59, 60, 61, 45, 62] was used to segment anatomical images into cortical grey matter (GM), subcortical grey matter, cerebrospinal fluid, white matter (WM) and abnormalities. Anatomical images were coregistered to the diffusion-weighted images using FSL [50, 39, 51, 45, 63]. The interface between grey and white matter was identified using function 5tt2gmwmi of MRtrix3 [60, 40]. Anatomically-constrained streamline tractography [60, 64, 40] was used to generate whole-brain tractograms with seeds in the GM-WM interface. Streamlines

were of minimum/maximum length of 30/250mm, cutoff of 0.06, and maximum angle between successive steps of 50°. Twenty million streamlines were generated for each participant. The sift2 algorithm [65] was used to provide tractograms that have a density of reconstructed connections proportional to the fibre density within each voxel as estimated by the diffusion model. This ensures that the number of streamlines connecting two regions of grey matter provides an estimate of the cross-sectional area of the white matter axons connecting those regions, which is a biologically-relevant measure of structural connectivity. Each participant's tractogram was overlayed on the participant's fractional anisotropy map and visually inspected to ensure that the tractogram provided good coverage of the white matter and that no streamlines extended into unphysical regions.

The structural connectivity matrices representing the structural networks of the participants have the cortical and subcortical areas identified from the Desikan-Killiany atlas as the nodes, and the white matter tracts linking those areas as the edges (connections). In order to evaluate the impact that different white matter characteristics have on predicting electrophysiological resting-state FC, we used six different structural measures as edge weights for the white matter tracts.

The first such measure was the number of reconstructed streamlines (NS), for which the resulting SC matrices have been shown to be good at predicting functional connectivity from both fMRI [10, 2] and MEG [17]. Because the absolute number of streamlines of a connection depends on the size of the connected brain areas (i.e., pairs of larger brain areas are connected by more streamlines because of their size rather than because of stronger connectivity) a second measure we used was the volume-normalized NS (NS/vol), namely the number of streamlines divided by the sum of the volumes of the connected brain areas. We also used the fractional anisotropy (FA) of the diffusion tensor [10, 17, 66, 67] and the inverse radial diffusivity (iRD) [17, 68], both of which have been used in studies that investigate the relationship between brain structure and function in health and disease. These metrics are related to the myelination and axonal characteristics of white matter tracts, and therefore are good proxies for structural connectivity [69]. They have also been shown to provide good reproducibility for the structural connectivity matrices and their graph theoretical properties when used as edge weights [70, 71].

Despite the sensitivity of the FA and iRD to changes in tissue microstructure, these measures are inherently non-specific when it comes to describing biological attributes of the brain's WM, such as myelination and axonal diameter. For example, a reduction in FA could reflect reduced neurite density, increased neurite orientation dispersion, both, or various other changes to tissue microstructure [72]. Radial diffusivity can be influenced by both myelination and axonal density of the white matter tracts, and therefore higher values can indicate lower myelination or axonal density [73, 74, 75].

The total restricted signal fraction derived from the CHARMED model [76] is attributed to water within the intra-axonal space and therefore is related to axonal characteristics of the WM tracts. We use this fraction, FRtot, as an edge weight in the SC matrices. Finally, the myelin water fraction (MWF) derived from the mcDespot data is used as an SC edge weight to reflect the myelination of the white matter tracts.

With these 6 measures as edge weights (NS, NS/vol, FA, iRD, MWF, FRt) we have 6 SC matrices for each participant. These 6 matrices all represent the participant's structural substrate that underlies FC, but each relies on a different aspect of the brain's microstructure to depict structural connectivity strength. The SC matrices were normalized so that the values for each SC matrix of each participant were in the range of 0 to 1.

The Euclidean distance (ED) between centers of the Desikan-Killiany brain areas was calculated for all participants. Specifically, MRtrix [40] was used to locate the coordinates of the center of each brain area, and in-house Matlab code was used to calculate the distances between those. Structural matrices were then calculated in which the values of structural connections were the Euclidean distances between the centres of the DK brain areas.

MEG Acquisition and Functional Connectivity

Ten-minute whole-head MEG recordings were acquired in a 275-channel CTF radial gradiometer system, at a sampling rate of 1,200 Hz. Twenty-nine additional reference channels were recorded for noise cancellation purposes and the primary sensors were analyzed as synthetic third-order gradiometers [77]. Participants were seated upright in a magnetically shielded room with their head supported with a chin rest to minimize movement. They were asked to rest with their eyes open and to fixate on a central red point presented on a PROPixx LCD projector (Vpixx Technologies Inc). Horizontal and vertical electro-oculograms (EOG) were recorded to monitor eye blinks and eye movements. Recordings were also acquired while the participants performed tasks after the completion of the resting-state paradigm, but those recordings were not used in the analysis presented here.

To achieve MRI/MEG co-registration, fiduciary markers were placed at fixed distances from three anatomical landmarks identifiable in the participant's T1-weighted anatomical MRI scan, and their locations were manually marked in the MR image. Head localization was performed at the start and end of the MEG recording and continuously through the recording. The data were subsequently pre-processed in a manner similar to that described in [78]. Specifically, all datasets were downsampled to 600 Hz, and filtered with a 1 Hz high-pass and a 150 Hz low-pass filter. The datasets were then segmented into 2-s epochs, and were visually inspected. Epochs exhibiting large head movements, muscle contractions, or other large artefacts were excluded from subsequent analysis.

The functional networks were constructed in a manner similar to that described in [78] but with some important differences. Specifically, the MEG sensor data were downsampled to 300Hz, before being source localized using FieldTrip (RRID:SCR_004849) version 20190219 [79]. The source-reconstruction grid for each participant was constructed using Freesurfer to segment the individual's T1 anatomical scan to yield the set of gray-matter voxels at a resolution of 2 mm isotropic. All these voxels were automatically labelled using the Desikan-Killiany parcellation [38] and matched to the MEG-coregistered MRI for the individual using FSL-flirt. All of these coregistered and parcellated gray-matter voxels were used for LCMV beamformer source-localisation using a single-shell forward model [80], where the covariance matrix was constructed in each of the four lower frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz). For each band, the beamformer weights were normalized using a vector norm [81]. Epochs were concatenated to generate a continuous dataset that was projected through these weights to yield a virtual-sensor time course for each voxel and then band passed to the above-mentioned frequency bands. For each of the 82 Desikan-Killiany regions, the virtual channel at the centroid of the region was chosen as a representative voxel.

The resulting 82 time series were orthogonalized in order to avoid spurious correlations, using symmetric orthogonalization [82]. A Hilbert transform was used to obtain the oscillatory amplitude envelope. The data were subsequently despiked using a median filter in order to remove artifactual temporal transients, downsampled to 1 Hz, and trimmed to avoid edge effects (removing the first two and the last three samples). Amplitude correlations were calculated by correlating the downsampled

Hilbert envelopes to each other, and the resultant correlation coefficients were converted to variance-normalized z-scores. This choice was motivated by the fact that such correlations have been shown to be one of the most robust and repeatable electrophysiological connectivity measures [83, 84].

Through this process we obtained 4 FC matrices for each participant.

2.2 Prediction of FC

Our aim was to achieve a mapping from a participant's SC to that participant's FC. We used two methods to predict the FC from the SC: a deep learning model that employs an attention mechanism and a model that is based on analytical measures of communication between brain areas.

For each of the two models, the resting-state FC from each frequency band was predicted for each participant individually, using that participant's structural connectome, for each of the 6 edge weightings separately. The ED matrix of each participant was also used as input, as described below. Thus we ended up with 24 predicted FC matrices (pFC) for each participant, one for each frequency-band/edge-weight combination.

GMHA-AE Model

We constructed a model based on a Graph Multi-Head Attention Autoencoder (GMHA-AE), the structure of which is depicted in Fig. 1. Autoencoders, first introduced in [85], are a type of neural network that consists of an encoder and a decoder. The encoder compresses the input data into a latent representation, while the decoder reconstructs the original data from this representation.

To effectively utilize the complex information present in brain connectivity data, we require a model that can naturally express these connectivity relationships. Graph Neural Networks (GNNs) are specifically designed for this purpose. GNNs are neural networks tailored for graph-structured data, where nodes represent entities and edges denote the relationships between them [86]. For example, in social networks nodes represent individuals and edges denote their friendships or interactions; in molecular biology nodes represent atoms and edges depict chemical bonds within a molecule. GNNs excel at handling these graph structures by iteratively aggregating information from neighboring nodes, thereby creating enriched representations of each node. This process captures the complex interactions within the graph and enhances the model's understanding of the underlying relationships.

In our model, we leverage node attributes and local topological information derived from SC matrices to generate high-dimensional representations that capture the functional and structural properties of the underlying connectome. These representations encompass both the characteristics of individual brain areas as well as their connections. To achieve this, we employ multi-head attention mechanisms. Attention mechanisms allow the model to selectively focus on the most relevant parts of the input data during predictions, much like humans concentrate on the most relevant details when processing complex information. Multi-head attention extends this concept by enabling the network to focus on multiple parts of the input simultaneously, capturing diverse patterns in the data.

In our GMHA-AE model, the encoder, equipped with multi-head attention, processes the input data SC (which include the ED structural matrices) to generate a latent representation that captures both direct and indirect connections within the brain. This representation is then used by the decoder to reconstruct the FC matrix. By reconstructing the FC matrix, the decoder implicitly models the

mapping from SC to FC, completing the autoencoder's function. Throughout this process, the multi-head attention mechanism provides a flexible approach that captures the complex relationships inherent in brain connectivity data. More details on the encoder, decoder and objective function are provided in appendix A.

We used a five-fold cross-validation methodology as follows: The sample was randomly divided into five equal sets. In each iteration, one set was selected as the validation set, and the remaining sets were used as the training set. This process continued until each set had been used as the validation set once. Parameters were optimized and selected using grid search based solely on the training data. The total number of training epochs was set to 200, with a batch size of 32, a learning rate of 1×10^{-3}, and γ in the objective function set to 0.01.

The GMHA-AE model was first trained on the 126 healthy participants and used to predict their FC. For the analysis that pertains to the people with psychosis, it was first trained on the 101 healthy participants that were 18 - 35 years old (for a detailed explanation of this choice, please see Section 2.3 below). Once trained and validated, the data of the people with psychosis were passed through it, and their FC was predicted.

Analytical Model

A number of algorithms that model communication between brain areas were described in [10] and implemented in the Brain Connectivity Toolbox [87]. These algorithms calculate the potential predictors of FC based on a SC matrix, employing different methods to identify the optimal structural links between brain areas, and then use regression to generate a predicted FC (pFC) that best matches the observed FC (oFC). They favor structural connections that are stronger and several of them take into account both direct and indirect structural connections between brain areas. The Euclidean distances between brain areas can also be incorporated in the model.

In this work we combined the shortest-path-length (SPL) and search-information (SI) algorithms, i.e., our analytical model takes into account both direct and indirect structural connections between the cortical and subcortical areas. This was used for the healthy participants and the people with psychosis. The Euclidean distance matrices of the participants were used in the analytical model, because these have been shown to increase the model's predictive ability [10, 17].

2.3 Statistical analysis

Characteristics of the connectivity matrices

The 6 SC matrices derived for each participant, each weighted with a different structural measure, are all intended to represent the structural connectome of that participant. We wanted to quantify how different these 6 matrices are, and whether they should be expected to result in appreciable differences when it comes to predicting FC from SC. For each of the 6 structural measures, we vectorized the SC matrix of each participant, keeping all unique connections, and concatenated the vectors for the 126 participants. This resulted in one vector for each structural measure. We then calculated the correlation coefficients between vectors for each pair of structural measures in order to quantify how correlated the matrices resulting from each structural measure are across the group of healthy participants.

Prediction accuracy

In order to assess the accuracy of the predictions, we calculated the correlation coefficients between the oFC for each frequency band and the pFC generated for that frequency band with each of the 6 SC matrices, for the GMHA-AE model and the analytical model. We also wanted to quantify whether using different structural measures as edge weights results in different ability of the structural connectome to predict functional connectivity. To do that, we used a paired t-test to compare the distributions of the oFC-pFC correlations for the 6 different SC edge weights, for each frequency band. This was done for the pFC from the GMHA-AE model and from the analytical model.

Individuality of the SC-FC relationship

We are also interested in how "individual" (i.e., specific to each healthy participant) the relationship between FC and SC is. To test this, we repeated the FC prediction with the the GMHA-AE model and the analytical model, but after shuffling the order of the SC matrices of the 126 healthy participants while keeping the order of the FC matrices the same. This way, the FC of each healthy participant was predicted using the SC matrix of another healthy participant. For each such prediction of FC, we calculated the correlation coefficient between predicted and observed FC. We repeated this process 1000 times, and derived the mean of the correlation coefficients for each healthy participant. The process was repeated for each MEG frequency band and each SC edge weight, for both the GMHA-AE and the analytical model.

Age dependence

In order to evaluate the impact of participant age on the relationship between SC and FC, we calculated the correlation coefficients between the participant age and the oFC-pFC correlation coefficients, for both the GMHA-AE and the analytical model, for the 126 healthy participants.

Psychosis

We wanted to test the hypothesis that the SC-FC relationship is altered as a result of psychosis in comparison to healthy participants. People with psychosis have been shown to exhibit age-related brain alterations such as cognitive dysfunction [88], dendritic spine loss [89, 90] and cortical atrophy [91]. In order to prevent any results from that comparison being diluted by those aging effects, we compared the people with psychosis to the healthy participants that matched the ages of the people with psychosis, i.e., were in the age range of 18 to 35 years. This left us with 101 healthy participants to perform the comparison on.

In order to compare the matrices of people with psychosis to those of the healthy participants we calculated correlations between those matrices, for each frequency band for the FC matrices and for each edge weight for the SC matrices. These correlations were then compared with the correlations of the SC matrices and the FC matrices between the healthy participants.

We used a Mann-Whitney U test to compare the distributions of the total connection strength (sum of all edges) of the healthy participants to those of people with psychosis, for the 6 edge weights for the SC matrices and the 4 frequency bands for the FC matrices.

Finally, we wanted to quantify any differences in the SC-FC relationship between healthy participants and people with psychosis. To do this, we used a Mann-Whitney U test to compare the

	NS	NS/vol	FA	invRD	MWF
NS/vol	0.8877				
FA	-0.1960	-0.2558			
invRD	-0.0707	-0.1170	0.7746		
MWF	-0.0084	-0.0643	0.4187	0.5337	
FRtot	-0.1161	-0.1817	0.7799	0.8289	0.6769

Table 1: Correlation coefficients between the SC matrices of the healthy participants for different edge weights. All p-values were less than 10^{-5}.

distributions of the oFC-pFC correlation coefficients between people with psychosis and healthy participants, for each of the FC-frequency-band/SC-edge-weight combinations.

In the above analysis, p-values were corrected for multiple comparisons using the false-discovery-rate (FDR) algorithm [92, 93].

3 Results

Characteristics of the connectivity matrices

The distributions of edge weights for the SC matrices weighted with different structural metrics (Fig. 3) indicate the distinct nature of the SC networks they represent. This is also evident by the fact that the correlation of the edge strengths for all participants is generally low and always under 0.9 (Table 1, Fig. 4). The highest correlations are between SC matrices weighted with NS and NS/vol, FA and iRD, FA and FRtot, and iRD and FRtot.

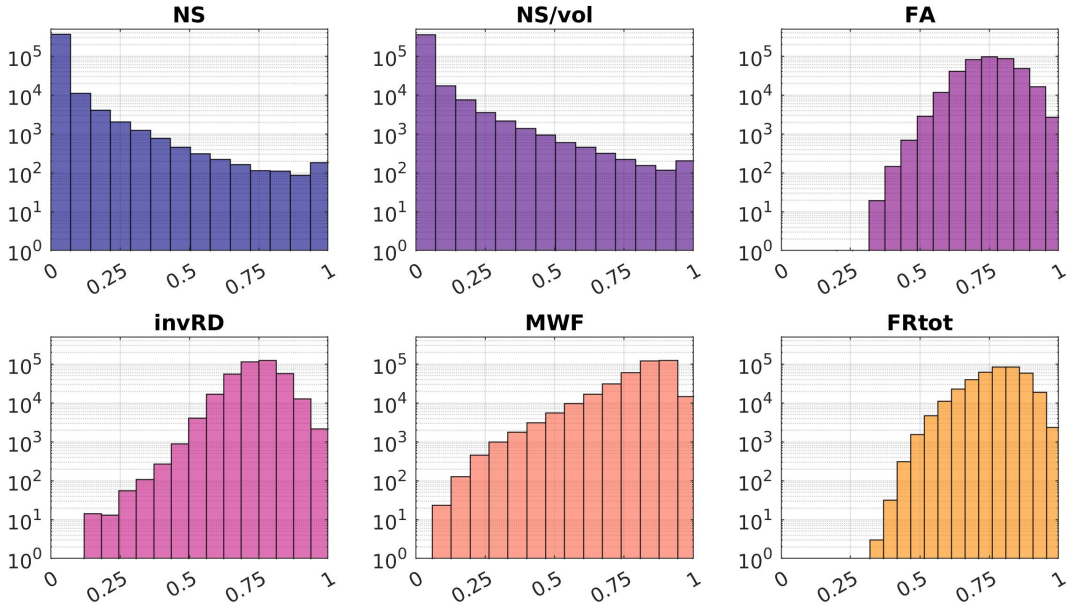

Figure 3: Histograms of the number of edge weights of the normalized SC matrices for the 6 different choices of edge weight.

Comparison of connectivity matrices of people with psychosis to those of the healthy participants

The SC and FC matrices of the participants with psychosis were compared to the matrices of the 101 healthy participants who were between the ages of 18 and 35 years. The NS-weighted and

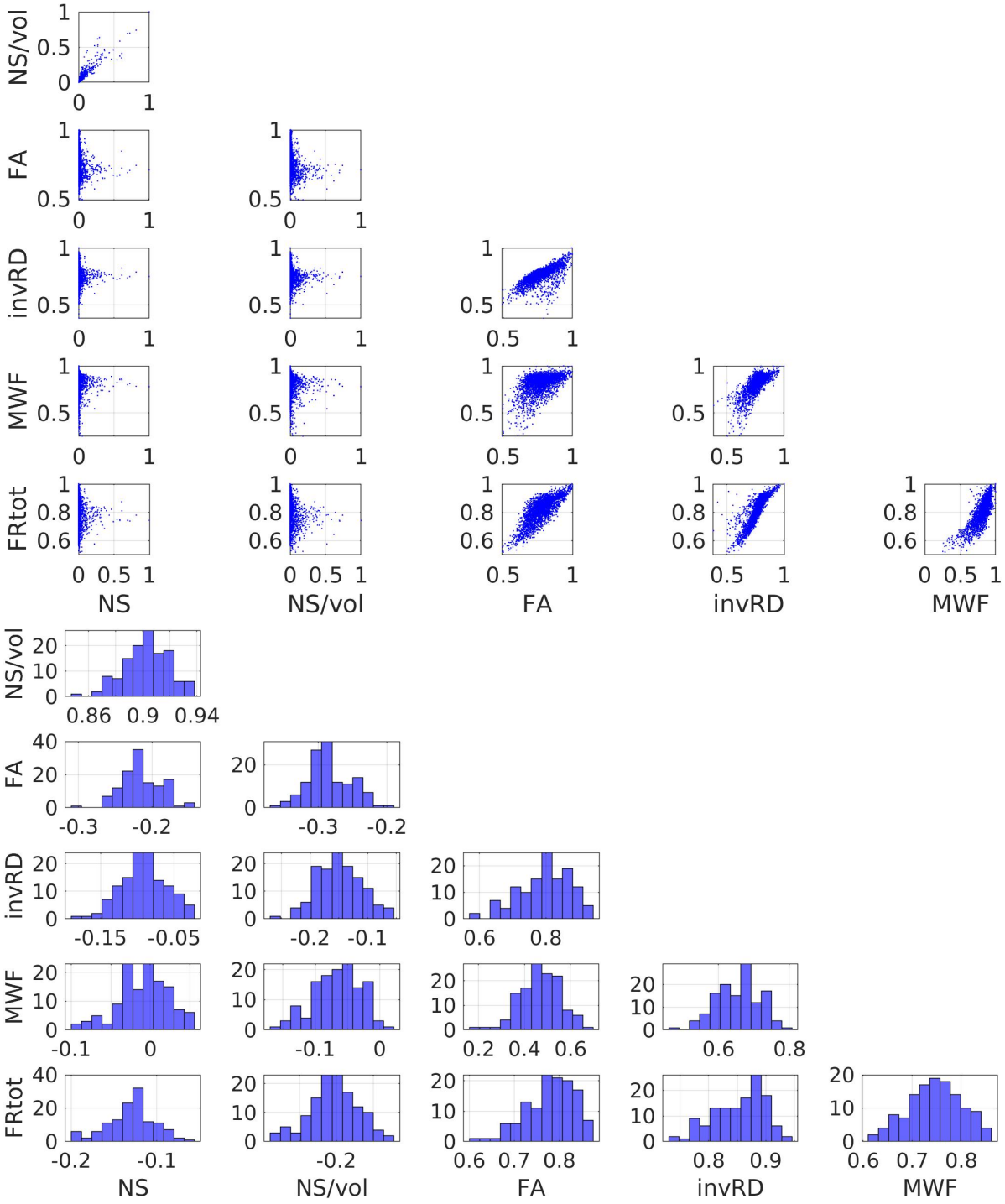

Figure 4: Top panel: Scatter plots of the edge weights for the SC matrices. Bottom panel: Distributions (across participants) of the correlations between edge weights for the SC matrices.

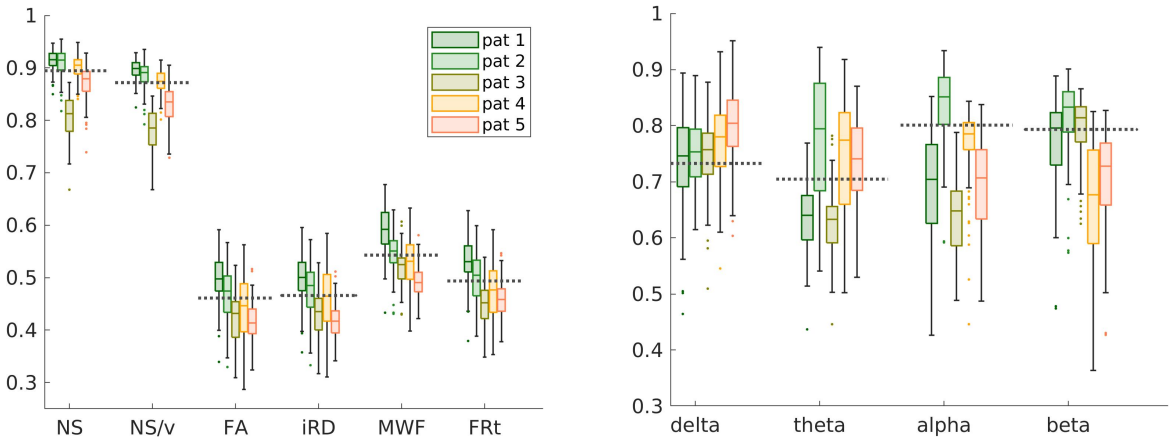

Figure 5: Distributions of correlations between SC (left panel) / FC (right panel) matrices of people with psychosis to those of the healthy participants, for each edge weight / frequency band. The dashed lines show the mean of the correlations between the matrices of the healthy participants for comparison.

NS	NS/vol	FA	invRD	MWF	FRtot	delta	theta	alpha	beta
0.53	0.82	0.60	0.25	0.28	0.14	0.47	0.55	0.17	0.026

Table 2: p-values resulting from the Mann-Whitney U test for the total edge strength distributions between healthy participants and those with psychosis. None of the values survived FDR multiple-comparison correction.

NS/vol-weighted SC matrices of the people with psychosis exhibited high correlations with those of the healthy participants, while the ones for the other edge weights did not (left panel of Fig. 5). However, those correlations were comparable to the correlations between SC matrices of the healthy participants (the means of the correlations for healthy participants are shown in the same figure as dashed lines for comparison.)

The FC matrices of the people with psychosis exhibited moderate correlations with the FC matrices of the 101 healthy participants aged 18 - 50 years (right panel of Fig. 5) but those correlations were mostly comparable with those between FC matrices of healthy participants.

We also compared the total connectivity strength of the matrices of the people with psychosis to those of the healthy participants. The results are shown in Fig. 6. The p-values resulting from the Mann-Whitney U tests between the distributions of the connectivity strength for the healthy participants and those with psychosis are shown in Table 2. The only p-value that was under 0.05 is the one for the beta band FC, but it did not survive FDR multiple-comparison correction.

We looked at individual connections and how those behave for the participants with psychosis in comparison to the healthy participants. For each psychosis participant, we calculated how

psychosis participant	1	2	3	4	5
NS	49	31	359	19	569
NS/vol	115	22	109	11	346
FA	11	31	86	183	89
iRD	11	26	73	182	30
MWF	13	27	104	183	90
FRtot	11	28	70	183	44

Table 3: Number of SC connections of the psychosis participants that are outside of the 99% of the distribution over the 101 healthy participants of matching ages, for each edge weight.

psychosis participant	1	2	3	4	5
delta	0	0	1	1	1
theta	1	0	0	0	0
alpha	12	9	5	0	14
beta	1	3	0	1	5

Table 4: Number of FC connections of people with psychosis that are outside of the 99% of the distribution over the 101 healthy participants of matching ages, for each frequency band.

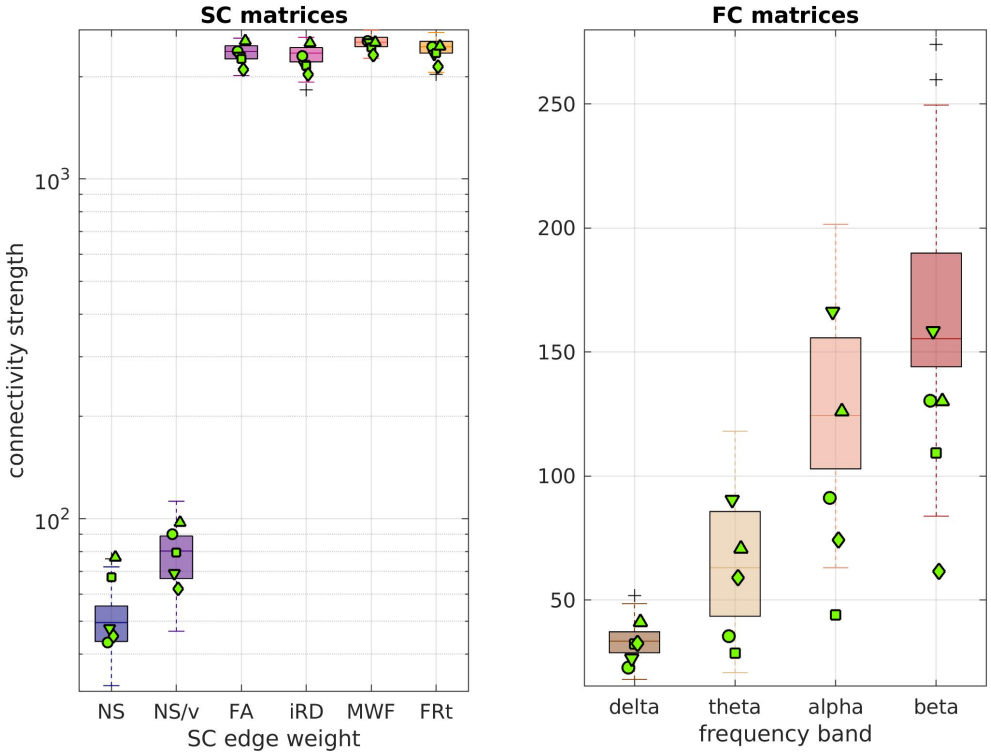

Figure 6: Distributions of the connection strength of the healthy participants (boxplots) in comparison to the connection strength of the psychosis participants (green markers).

many standard deviations from the mean of the distribution over the 101 healthy participants each connection is, for both the SC and the FC matrices. Table 3 shows how many SC connections were over 2.56 SDs away from the healthy-participant mean (therefore being part of the 1% tail of the distribution) for each psychosis participant, while Table 4 shows the same for the FC connections.

3.1 Prediction of FC with the GMHA-AE model

Maintaining the participant link between SC and FC

The GMHA-AE model was good at predicting the oFC (left panel of Fig. 7) with the mean of the correlations being above 0.8 for the alpha and beta frequency bands and above 0.4 for the delta and theta bands. The only exception was the prediction of the oFC with the NS-based SC matrices for the delta and theta band, for which the correlation coefficients between oFC and pFC were very low.

Breaking the participant link between SC and FC

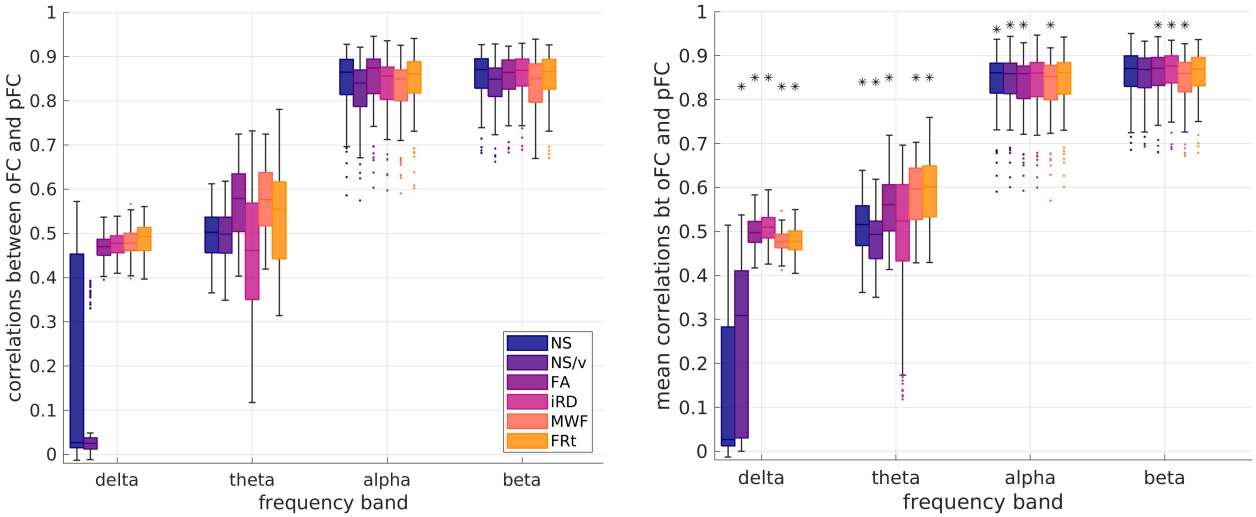

Figure 7: Left panel: Distributions (over the 126 participants) of the correlation coefficients between oFC and pFC derived with the GMHA-AE model, when no permutations of the SC matrices have been done. Right panel: Distributions (over the 126 participants) of the mean values (over permutations) of the oFC-pFC correlations derived with the GMHA-AE model. The asterisks indicate the cases for which there is a statistically significant difference after FDR multiple comparison correction between the distribution without shuffling to the distribution of the means when shuffling the healthy participants.

	delta	theta	alpha	beta
NS - NS/vol	2×10^{-4}	0.12	$< 10^{-10}$	$< 10^{-10}$
NS - FA	$< 10^{-10}$	$< 10^{-10}$	10^{-4}	5×10^{-5}
NS - invRD	$< 10^{-10}$	3×10^{-4}	6×10^{-5}	**0.71**
NS - MWF	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$	3×10^{-9}
NS - FRtot	$< 10^{-10}$	4×10^{-9}	**0.02**	3×10^{-6}
NS/vol - FA	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$
NS/vol - invRD	$< 10^{-10}$	4×10^{-4}	$< 10^{-10}$	$< 10^{-10}$
NS/vol - MWF	$< 10^{-10}$	$< 10^{-10}$	7×10^{-5}	**0.50**
NS/vol - FRtot	$< 10^{-10}$	4×10^{-9}	10^{-10}	$< 10^{-10}$
FA - invRD	0.004	$< 10^{-10}$	$< 10^{-10}$	6×10^{-4}
FA - MWF	10^{-4}	**0.15**	$< 10^{-10}$	10^{-5}
FA - FRtot	6×10^{-8}	**0.07**	$< 10^{-10}$	**0.47**
invRD - MWF	2×10^{-4}	$< 10^{-10}$	$< 10^{-10}$	10^{-9}
invRD - FRtot	10^{-9}	4×10^{-6}	**0.02**	0.003
MWF - FRtot	0.004	0.002	10^{-7}	10^{-5}

Table 5: p-values for the t-test between the correlation distributions for oFC and pFC for the 6 different SC edge weights for each frequency band, for prediction with the autoencoder model when all SC connections are kept. Bold-faced p-values are **not statistically significant** after FDR correction.

The pFC calculated via the GMHA-AE model after shuffling the SC matrices of the healthy participants exhibited a similar level of correlation with the oFC as when the SC matrices of the participants had not been shuffled (mean values over the 1000 permutations of the healthy participants shown on right panel of Fig. 7). Even though paired t-tests between distributions relating to the same edge weight / frequency band pairs resulted in several of the distributions being statistically significantly different (denoted with asterisks on the right panel of Fig. 7), there was no appreciable reduction in the prediction accuracy of the GMHA-AE model when the participants' SC matrices were shuffled.

Age dependence

For the pFC calculated via the GMHA-AE model, we found no statistically significant correlations between participant age and the oFC-pFC correlation coefficients after correcting for multiple comparisons (Fig. 8). This indicates that the predictive ability of the GMHA-AE model is stable across ages and not altered with participant age, at least for adults in the age range of 18 - 50 years.

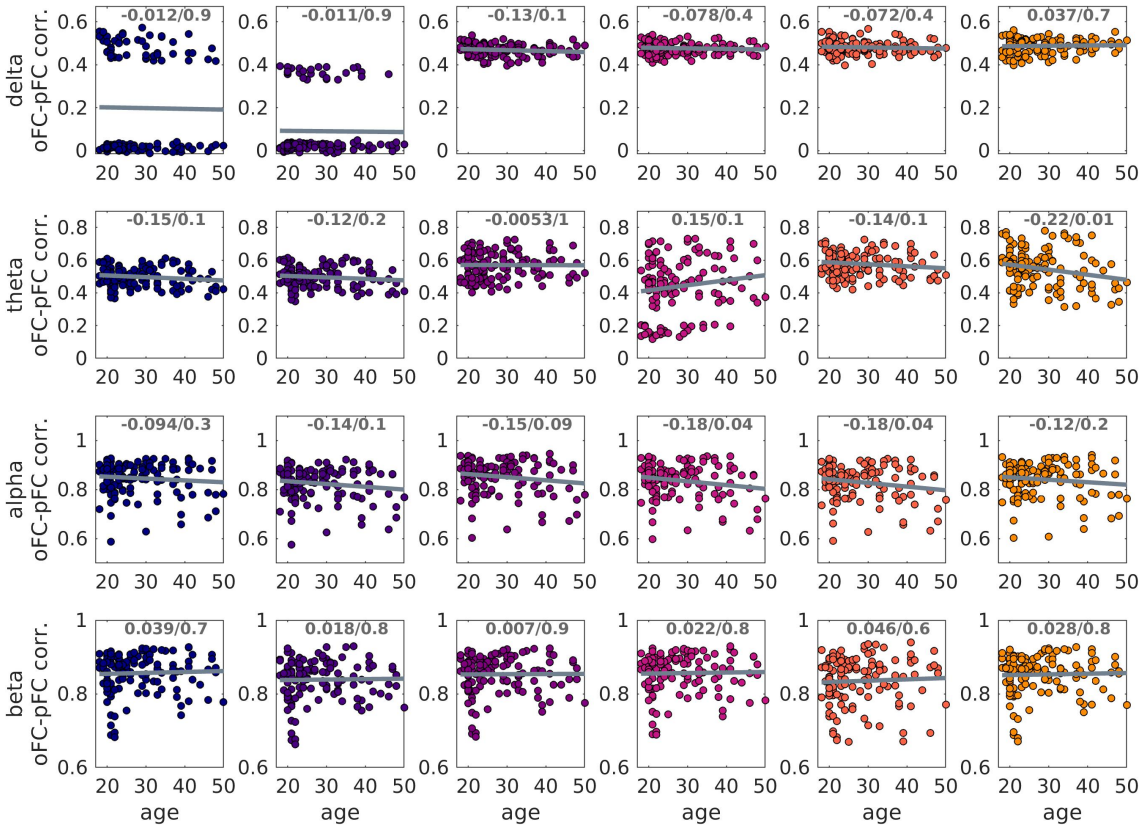

Figure 8: Scatter plots of the oFC-pFC correlation coefficients versus age. The six column refer to the six SC edge weights, from left to right: NS, NS/vol, FA, iRD, MWF and FRtot. The best-fit line is shown. The correlation coefficients and p-values are also shown at the top of each plot. None of the p-values were statistically significant after FDR correction for multiple comparisons.

Psychosis

When the GMHA-AE model that had been trained on the healthy participants was used to calculate the pFC of the psychosis participants, the correlations between oFC and pFC were lower for all

frequency bands and all SC edge weights compared to the healthy participants (Fig. 9). The p-values of the Mann-Whitney U test comparing the distributions of the healthy participants to those with psychosis were all less than 2×10^{-4} and survived FDR correction for multiple comparisons, with the exception of the NS/delta and FA/theta pairs (p = 0.48 and 0.10 respectively).

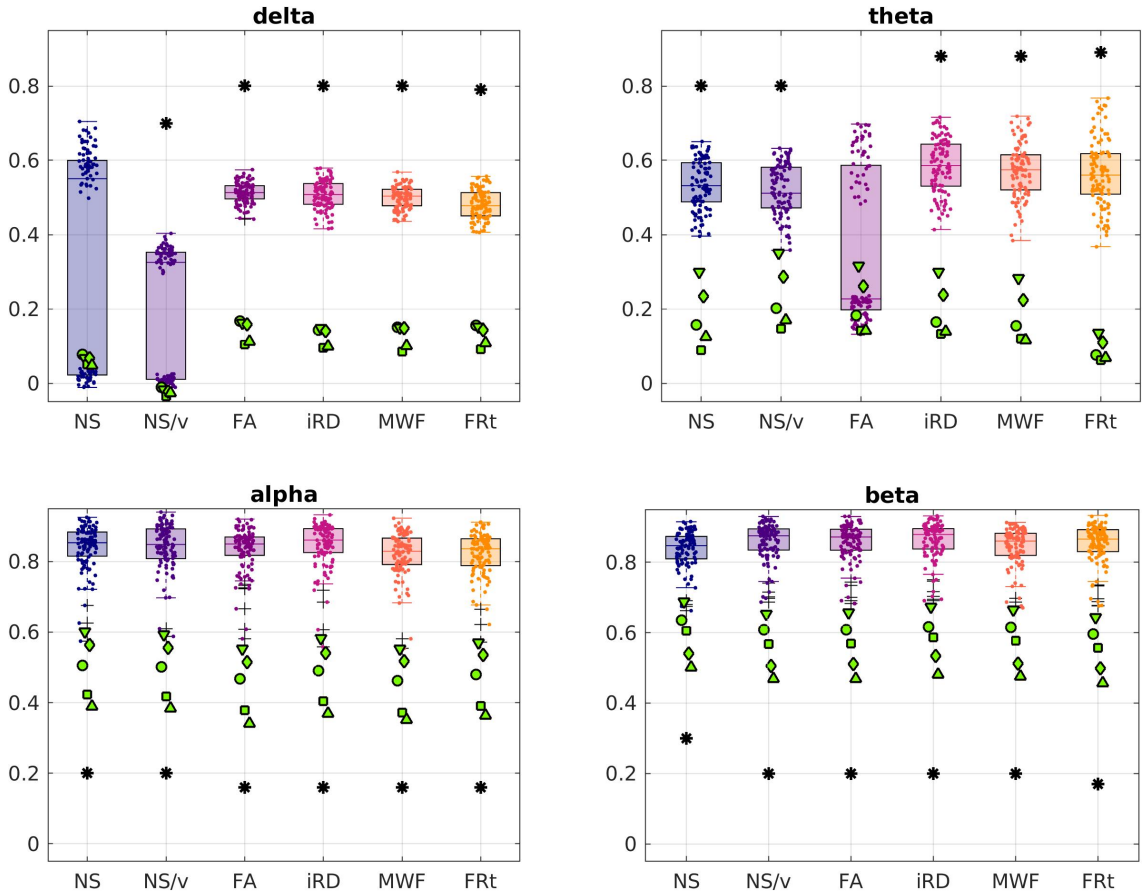

Figure 9: The oFC-pFC correlations of the psychosis participants (green markers) are overlaid on the corresponding correlation distributions of the healthy participants, for the case in which the FC is predicted with the GMHA-AE model. Each marker shape indicates a different psychosis participant. Asterisks indicate the cases in which there are statistically significant differences (after multiple comparison correction) between the distributions for the healthy participants and those with psychosis.

3.2 Prediction of FC with the analytical model

Maintaining the participant link between SC and FC

When the analytical model that combines the SPL and SI algorithms was used to predict the healthy participants' FC, the correlations between the oFC and pFC depended on the frequency band of the observed FC and on the edge weight used in the SC matrices, as shown on the left panel of Fig. 10. The higher frequency bands resulted in higher correlations between observed and predicted FC, indicating that a combination of the SPL and SI algorithms is better at predicting FC in higher rather than lower frequencies. Additionally, the structural metrics that are related to NS (NS and NS/vol) were worse at predicting FC in all 4 frequency bands considered as opposed to the other 4 structural metrics.

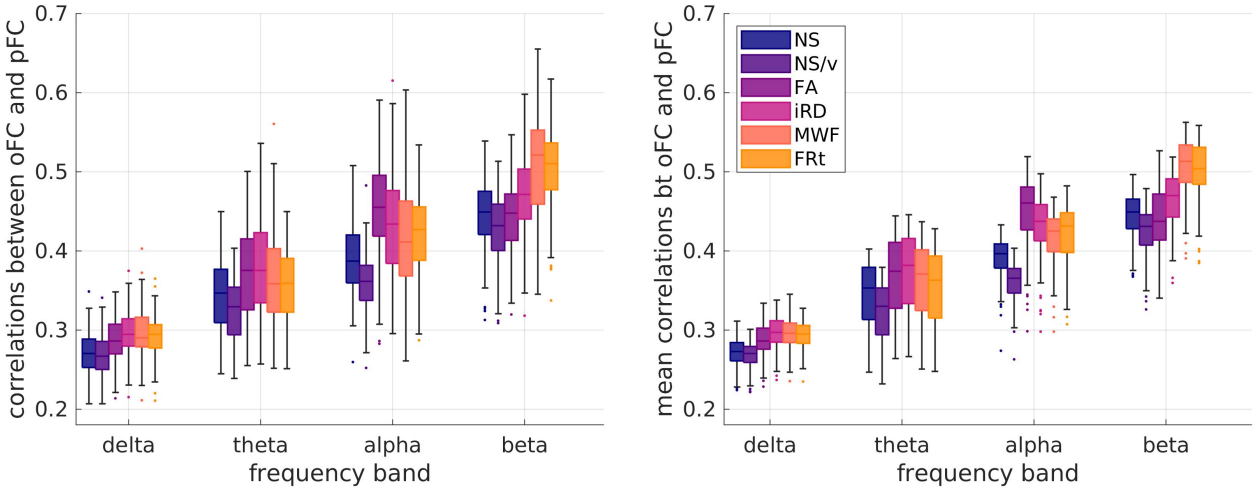

Figure 10: Left panel: Distributions (over the 126 participants) of the correlation coefficients between oFC and pFC derived with the analytical model when no permutations of the SC matrices have been done. Right panel: Distributions (over the 126 participants) of the mean values (over permutations) of the oFC-pFC correlations derived with the analytical model.

	delta	theta	alpha	beta
NS - NS/vol	8×10^{-3}	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$
NS - FA	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$	**0.73**
NS - invRD	$< 10^{-10}$	$< 10^{-10}$	10^{-8}	3×10^{-6}
NS - MWF	$< 10^{-10}$	5×10^{-6}	6×10^{-6}	$< 10^{-10}$
NS - FRtot	$< 10^{-10}$	4×10^{-3}	10^{-7}	$< 10^{-10}$
NS/vol - FA	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$	3×10^{-3}
NS/vol - invRD	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$
NS/vol - MWF	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$
NS/vol - FRtot	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$
FA - invRD	$< 10^{-10}$	3×10^{-3}	10^{-8}	$< 10^{-10}$
FA - MWF	3×10^{-4}	**0.18**	4×10^{-7}	$< 10^{-10}$
FA - FRtot	8×10^{-4}	$< 10^{-10}$	$< 10^{-10}$	$< 10^{-10}$
invRD - MWF	**0.90**	3×10^{-3}	**0.06**	$< 10^{-10}$
invRD - FRtot	**0.05**	3×10^{-2}	10^{-3}	$< 10^{-10}$
MWF - FRtot	**0.08**	6×10^{-3}	**0.77**	**0.09**

Table 6: p-values for the t-test between the correlation distributions between oFC and pFC for the 6 different SC edge weights for each frequency band, for prediction with the SPL-SI model when all SC connections are kept. Bold-faced p-values are the ones that are **not statistically significant** after FDR correction.

	delta	theta	alpha	beta
NS	**0.0002**	0.60	0.18	0.22
NS/vol	**0.0002**	0.54	0.52	0.26
FA	**0.0014**	0.60	**0.0027**	**0.0035**
iRD	**0.0027**	0.49	**0.014**	**0.0046**
MWF	**0.0002**	0.86	0.14	0.0307
FRtot	**0.0002**	0.86	0.10	**0.0091**

Table 7: p-values for the Mann-Whitney U test comparing the correlation distributions for the healthy participants and the psychosis participants, when FC is predicted via the analytical model. p-values in bold-face font survive FDR multiple comparison correction.

The paired t-test between the correlation distributions for each pair of SC edge weights showed that the distributions are statistically significantly different after FDR correction for multiple comparisons with very few exceptions, as indicated in Table 6. The NS-based SCs were generally worse at predicting the oFC than the other 4 edge weights (Fig. 10).

Breaking the participant link between SC and FC

When the SC matrices of the participants were shuffled, so that the SC matrix used in the analytical model to predict the FC no longer corresponded to the same participant, small differences were observed in the correlation coefficients between oFC and pFC (Fig. 10).

The t-test between the correlation coefficients of oFC-pFC and the mean values of the distributions of the same coefficients when the SC matrices of the participants had been shuffled resulted in none of the p-values being under 0.05. Therefore there were no statistically significant differences between the distributions.

Age dependence

We found statistically significant correlations (after FDR multiple comparison correction) between the participant age and the oFC-pFC correlation coefficients derived with the analytical model for the iRD and MWF SCs (all frequency bands), for the FA SC matrices (theta, alpha and beta frequency bands), and the FRtot SC matrices (alpha and beta frequency bands) as shown in Fig. 11. The correlations were negative, indicating a weakening of the predictive power of the analytical model as participants age.

Psychosis

A Mann-Whitney U test between homologous distributions of oFC-pFC correlaions showed that the psychosis participants exhibited statistically significant differences in the correlations between oFC and pFC for the delta band (all edge weights), the alpha band (for the FA-weighted SC matrices) and the beta band (for SC matrices weighted with FA, MWF and FRtot). The correlations for the psychosis partiipants were higher in the delta band and lower in the alpha and beta bands (Fig. 12). This indicates that the SPL-SI model is a better representation of the communication mechanisms between brain areas in psychosis participants than it is in healthy participants in the delta band, while the opposite is true in the alpha and beta bands.

Table 7 gives the p-values for the Mann-Whitney U test between the healthy participant and the psychosis participants distributions of the correlations, for each frequency band and edge weight.

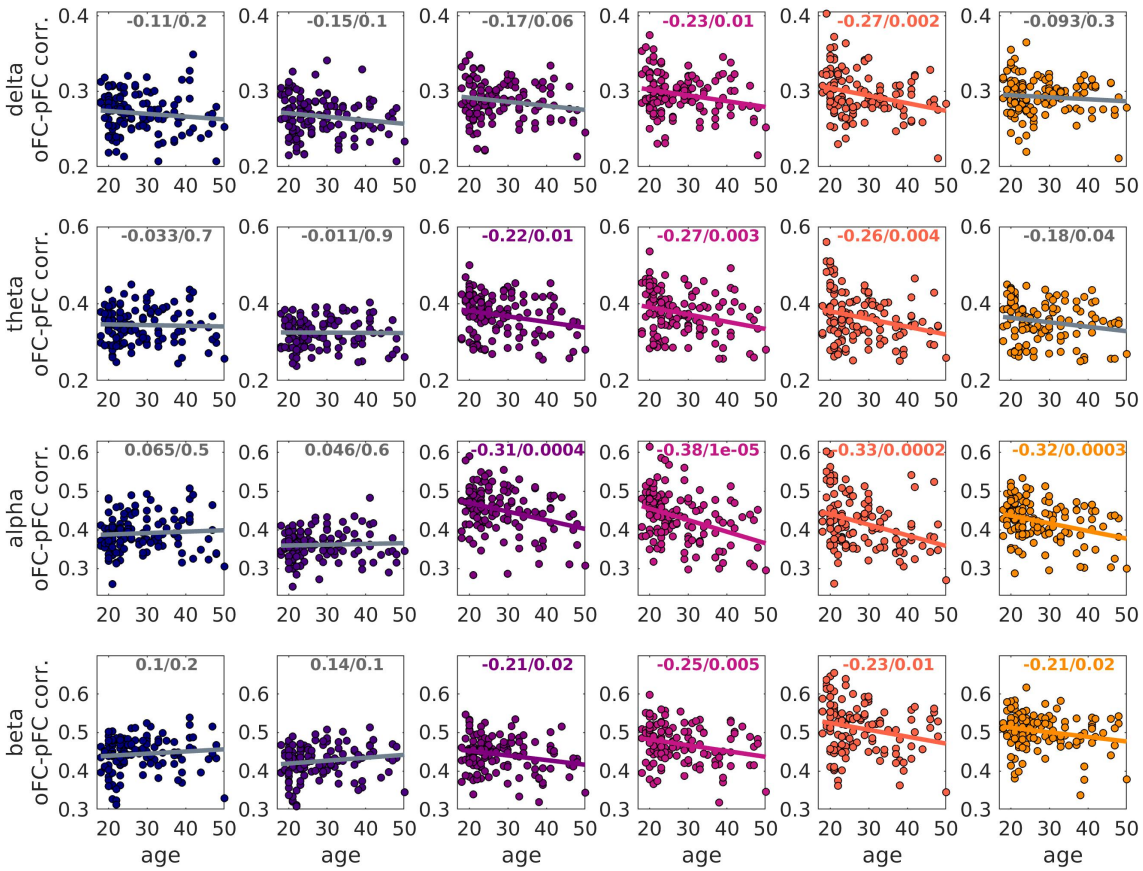

Figure 11: Scatter plots of the oFC-pFC correlation coefficients versus age, when the FC is predicted via the analytical model. The six column refer to the six SC edge weights, from left to right: NS, NS/vol, FA, iRD, MWF and FRtot. The best-fit line is shown. The correlation coefficients and p-values are also shown at the top of each plot. Colored font / line indicate that the related p-value survived FDR multiple comparison correction, while grey indicates that it did not.

	delta	theta	alpha	beta
NS	3×10^{-6}	0.0005	0.0031	0.0013
NS/vol	2×10^{-5}	0.0037	0.0029	0.0013
FA	0.0002	0.0006	0.0040	0.0001
iRD	0.0002	0.0006	0.0037	0.0004
MWF	10^{-6}	0.0003	0.068	0.0089
FRtot	0.0001	0.0004	0.014	0.0039

Table 8: p-values for the paired t-tests that compare the correlation distributions for the psychosis participants between the GMHA-AE and the analytical model. All p-values remain statistically significant after multiple-comparison correction, except for the one for the alpha band/MWF combination.

3.3 Comparison of results of the two models for the psychosis participants

Fig. 13 shows the oFC-pFC correlations for the psychosis participants for the GMHA-AE and the analytical model. The distributions of the correlations are statistically significantly different for all FC frequency bands and SC edge weights, except for the alpha band/MWF combination. The p-values of the paired t-tests of those comparisons are shown in Table 8. Notably, the GMHA-AE model performs better than the analytical one for the alpha and beta frequency bands, while the opposite is true for the delta and theta bands.

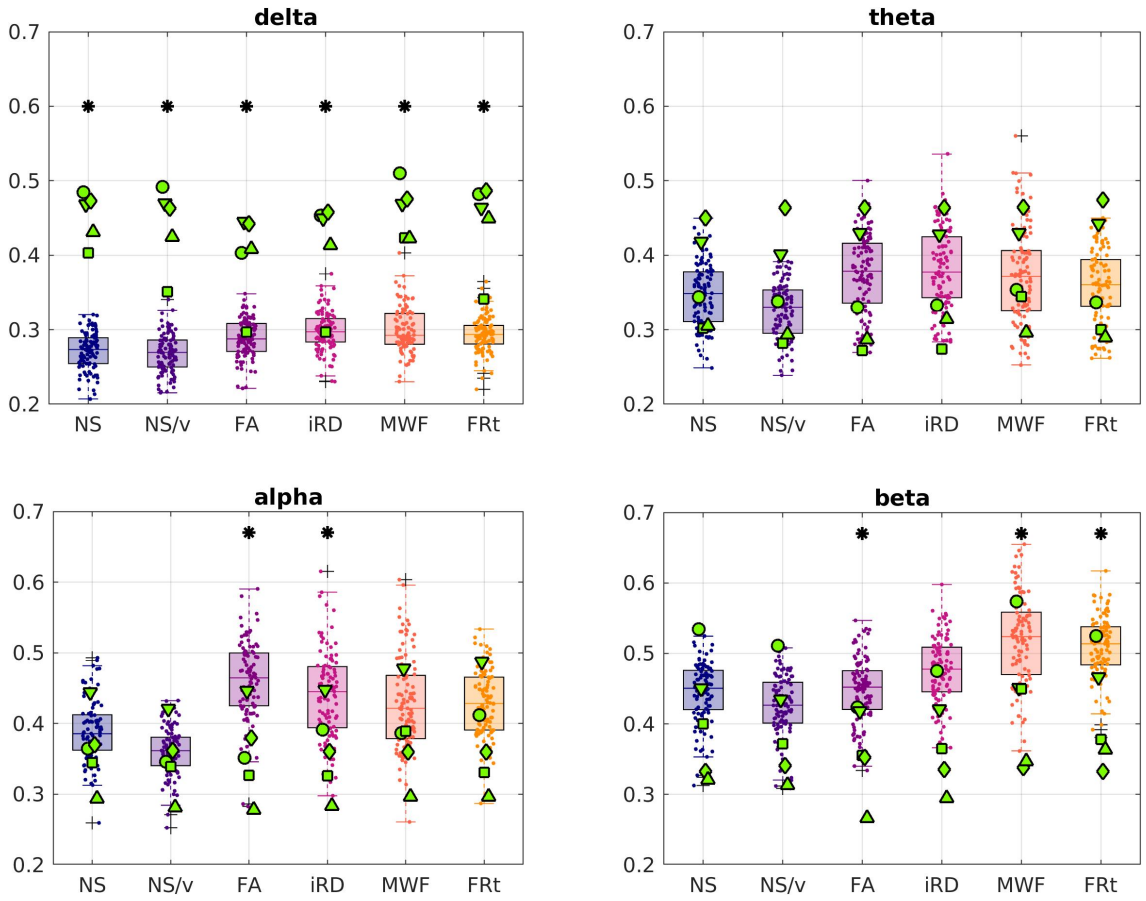

Figure 12: The oFC-pFC correlations of the psychosis participants (green markers) are overlaid on the equivalent correlation distributions of the healthy participants, when the analytical model is used to predict the FC. Each marker shape indicates a different psychosis participant. The asterisks indicate the frequency bands and edge weights for which the two distributions are statistically significantly different after multiple comparison correction.

4 Discussion

To the best of our knowledge, this is the first study to investigate the relationship between SC and electrophysiological resting-state FC with an attantion-based deep-learning model, in both health and in psychosis.

The GMHA-AE model resulted in pFC that better matches the oFC compared to the SPL-SI model, across the 4 frequency bands and edge weights, with the exception of the delta band/NS-based edge weights combination. Additionally, in the alpha and beta frequency bands the mean of the correlation distributions was above 0.8 across SC edge weights, which is higher than the 0.55 for the distributions of the individual-level correlations reported in the fMRI-based study described in [18] (in which the NS was used to assign SC strength between regions). This difference in performance could be due to either differences in our deep-learning model compared to that in [18], differences in the measures used to calculate FC, or the fact that they did not use information on the Euclidean distance between nodes of the networks, which has been shown to improve the FC prediction [10]. We note that an exact comparison between our MEG-based study to their fMRI-based one is not feasible due to the different aspects of FC that the two modalities measure. When comparing our results to those of [18], we do so using our results for the alpha and beta

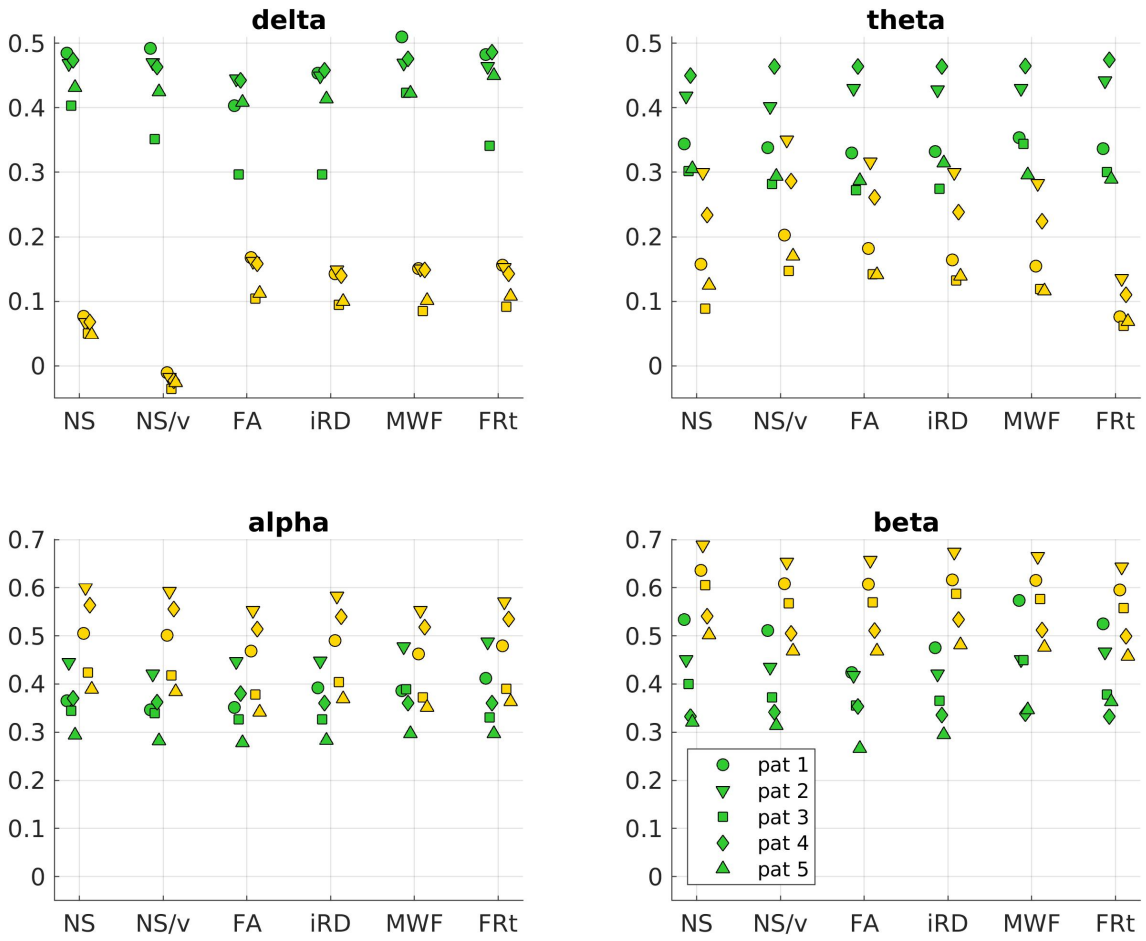

Figure 13: Correlations between oFC and pFC for the 5 psychosis participants for the GMHA-AE model (yellow markers) and the analytical model (green markers) across FC frequency bands and SC edge weights. Each marker shape denotes a different psychosis participant.

bands because those have been shown to give functional connectivity that is the most comparable to fMRI-measured functional connectivity [12]. However, in accordance with the conclusion reached in [18] about fMRI-measured FC, our results imply that FC measured via electrophysiological recordings is tightly linked to SC derived via tractography, and that relationship is present at individual-participant level. Therefore, existing models of communication between brain areas can be improved to incorporate sources of that interdependence [1] that could increase the correlations.

Both the GMHA-AE and the analytical model were better at predicting the FC in the alpha and beta frequency bands in comparison to the delta and theta bands. This result is in agreement with the results presented in [17], which examined a cohort of 90 healthy participants and investigated four microstructural measures as edge weights for the SC matrices (NS, FA, iRD, MWF). That study, however, exhibited lower oFC-pFC correlations across functional frequency bands and SC edge weights, a fact that could be attributed to differences in the tractography algorithm used, as well as the quality of the diffusion-MRI and mcDESPOT data acquired (the MRI data for this study were collected on a Connectom scanner that has high diffusion gradients as opposed to the MRI scanner used for the data collected in [17], while the MEG data were collected in the same system as the MEG data presented in this work).

The structural measure that was used as edge weight in the SC matrices impacted how well the oFC was predicted, mainly for the SPL-SI analytical model. Edge weights that are related to myelin or axonal characteristics (MWF, FA, iRD and FRtot) resulted in better FC prediction than those related to NS when the analytical model was used, with the differences in the respective distributions being highly statistically significant. This indicates that, if the SPL-SI analytical algorithm is representative of communication between brain areas, resting-state FC is supported by myelin and axonal characteristics more than it is by the relative number of axonal projections between brain areas. When the GMHA-AE model was used, SC matrices with edge weights related to myelin and axonal measures gave better prediction for the delta and theta frequency bands (except when theta-band FC was predicted using the iRD-weighted SC matrices). That model gave a much more stable performance across SC edge weights for the alpha and beta bands, even though the distributions were statistically significantly different. This likely points to an ability of the GMHA-AE model to capture patterns in the SC matrices that pertain to communication between brain areas, regardless of the edge weights used.

The oFC-pFC correlation coefficients derived via the analytical SPL-SI model correlated negatively with healthy participant age for the non-NS weighted SC matrices (surviving FDR correction for multiple comparisons). The correlations were strongest for the alpha frequency band, and for the iRD- and MWF-weighted SC matrices. This indicates that the SPL-SI model is a better model of communication between brain areas for younger healthy participants than for older ones. It also points to the fact that alternative analytical models should be explored for describing communication between brain areas at different times across the life span. This result is in agreement with the results of [19], which reported decreases of the SC-FC relationship with age for fMRI-based FC. We also note that a similar trend was observed for a cohort of adolescent participants [20]. The fact that there is no correlation between participant age and oFC-pFC correlation coefficients when pFC is derived via the GMHA-AE model indicates that the model is more robust when it comes to detecting such relationships than the analytical model, and can capture intricate relationships even as those change over time.

We now discuss the results that pertain to the psychosis participants. Firstly, the GMHA-AE model that was trained on the healthy participant data, and which gave high prediction accuracy for those participants, did poorly at predicting the oFC of the psychosis participants, with the differences between the distributions of healthy participants and psychosis participants being highly statistically significant after FDR correction for multiple comparisons. Despite the fact that the GMHA-AE model does not provide any direct information about the communication mechanisms that underlie the SC-FC relationship, this finding clearly points to the fact that the features that the GMHA-AE model captures in the healthy-participant SC and FC matrices, and which result to it predicting oFC very well, are likely not present or reduced in the SC and/or FC connectomes of the psychosis participants.

In contrast to the poorer performance of the GMHA-AE model for the psychosis participants across frequency bands, the analytical model gave much better predictions for the FC of psychosis participants than that of healthy participants for the delta band, across SC edge weights. As the p-values for the differences between the healthy versus the psychosis participant distributions of the correlation coefficients indicate (Table 7), the difference is highly statistically significant. This indicates that the SPL-SI algorithm employed in our analytical model is a better representation of the communication mechanisms that are responsible for the evocation of delta band resting-state FC in psychosis than it is for healthy participants. When looking at the beta frequency band, however, the

prediction accuracy of the same analytical model was lower for psychosis participants compared to healthy participants for the FA-, MWF- and FRtot-weighted SC matrices; the same trend was present for the iRD-weighted SC matrices (p = 0.0307) but that p-value did not survive multiple comparison correction. No statistically significant differences were observed in the correlation distributions between healthy participants and psychosis participants for the theta and alpha bands, with the exception of the {alpha band / FA} and {alpha band / iRD} combinations, where a reduction in the prediction accuracy was observed. These results are in agreement with the results reported in [21], where healthy participants exhibited larger correlation between the average functional connectivity (measured via fMRI) and white-matter integrity in comparison to schizophrenia patients.

The performance of the two models on the psychosis participants depends strongly on the FC frequency band. Specifically, the analytical model performs much better in the delta and theta frequency bands, while the GMHA-AE model performs better in the alpha and beta bands. Keeping in mind that the GMHA-AE model was trained on healthy participants, this implies that the healthy-participant communication mechanisms are worse for describing the SC-FC relationship in psychosis participants compared to the simpler analytical model based on the SPL-SI algorithms. For the alpha and beta frequency bands, on the other hand, the complex communication patterns that the GMHA-AE model captures from the healthy participants are better at describing the SC-FC relationship than the analytical model. Finally, above and beyond any FC-specific or SC-specific alterations in psychosis [94], our work confirms that those alterations extend to the relationship between SC and FC.

Our study has a few limitations that need to be taken into account. Firstly, as mentioned earlier, the GMHA-AE deep-learning model does not provide insight into the communication mechanisms between brain areas. This lack of insight is, however, compensated by the fact that the model can capture complex relationships that analytical algorithms of brain communication cannot fully incorporate. Secondly, even though the healthy participant sample we used was large (126 participants) the number of psychosis participants was low (5). This is an issue with many similar studies - in particular some psychosis participants who volunteered for our study were not eligible to be scanned in our state-of-the-art, high-gradient Connectom MRI scanner, resulting in a smaller sample than a study using more conventional scanners would have. However, the statistical tests we used when comparing healthy to psychosis participants are appropriate to use when there is such a difference in the two samples, and therefore the differences we detected between healthy and psychosis participants are robust. The high statistical significance of our results indicates the need for followup studies of larger cohorts.

5 Conclusion

In this work, we proposed a brain SC-FC mapping framework based on the Graph Multi-Head Attention AutoEncoder, which can predict a participant's FC based on that participant's SC with great accuracy. By employing an autoencoder, our GMHA-AE model is capable of efficiently handling the distributed and heterogeneous patterns of the brain and of learning complex relationships between brain structure and function by utilizing attention mechanisms. We compared the GMHA-AE performance to that of an analytical model. We also used both models to investigate the SC-FC relationship in psychosis participants and compare it to that of healthy participants, and identified crucial differences in that relationship between the two groups. In the future, the use of deep-learning models could be explored to quantify the SC-FC relationship for younger age

groups, for task-based electrophysiological recordings, as well as for neurological disorders other than psychosis.

6 Author contributions

QC: Data analysis, writing of the manuscript. HT, VH: Data collection, data curation, data analysis. PLL: Analysis pipeline development. CBM: Data collection, data analysis. KDS: Data analysis. DKJ: Study design. EM: Data collection, data analysis, study design, writing of the manuscript.

A Appendix

Based on the effectiveness of graph networks for representing brain topological structures, the encoder and decoder in this study are both selected to use graph network structures.

Encoder Structure

The graph attention mechanism is employed as the encoder layer to generate effective high-dimensional latent feature representations. By adding multiple layers of graph attention mechanisms to the encoder structure, the model's depth and learning capability are enhanced. Additionally, the representation learning of graph structure nodes produces richer node embeddings. To determine the relation between nodes and their neighbors, we use a self-attention mechanism that shares parameters between nodes. The input required by the encoder is the symmetrical adjacency matrix of the structural connectivity $A \in \mathbb{R}^{n \times n}$ and the set of node features $x = \{x_1, x_2, \ldots, x_n\}$, where $n = 82$ represents the number of nodes, i.e., the number of cortical regions partitioned in the DK brain atlas. The initial feature of node i is $h_i^0 = x_i \in \mathbb{R}^{1 \times d}$. In the l-th layer of the encoder, the attention coefficient between node i and its neighbor node j is calculated as follows:

$$a_{ij}^l = \frac{\exp\left(\mathrm{LeakyReLU}\left(\alpha^{l\top}\left[\mathbf{W}^l h_i^{l-1} || \mathbf{W}^l h_j^{l-1}\right]\right)\right)}{\sum_{k \in \mathcal{N}_i} \exp\left(\mathrm{LeakyReLU}\left(\alpha^{l\top}\left[\mathbf{W}^l h_i^{l-1} || \mathbf{W}^l h_k^{l-1}\right]\right)\right)} \tag{1}$$

where $(\mathcal{N}_i)$ is a set of nodes connected to node *i* according to the adjacency matrix A, α denotes a learnable weight vector, $||$ represents the concatenation operation, $\mathbf{W}$ is a learnable linear transformation weight matrix, and $\mathrm{LeakyReLU}$ is the activation function. Further, the output representation of node i in the l-th layer of the encoder is as follows:

$$h_i^l = \sigma\left(\frac{1}{K}\sum_{k=1}^{K}\sum_{j \in \mathcal{N}_i} a_{ij}^l \mathbf{W}^l h_j^{l-1}\right) \tag{2}$$

After passing through L encoder layers, the output of the last layer is regarded as the final node embedding, i.e., $h_i = h_i^L, \forall i \in \{1, 2, \ldots, n\}$.

Decoder Structure

Contrary to the "compression" in the encoder, the decoder's role is to reconstruct the high-dimensional representations into the size of the functional connectivity matrix. We use a decoder with the same number of layers as the encoder, where each decoder layer reverses the process of its

corresponding encoder layer, i.e., each decoder layer reconstructs the representation of the nodes by utilizing the representations of their neighboring nodes (according to their relevance). In the l-th decoder layer, the attention coefficient between node i and its neighbor node j is calculated as follows:

$$\hat{a}_{ij}^{l} = \frac{\exp\left(\text{LeakyReLU}\left(\hat{\alpha}^{l\top}\left[\hat{\mathbf{W}}^{l}\hat{h}_{i}^{l}||\hat{\mathbf{W}}^{l}\hat{h}_{j}^{l}\right]\right)\right)}{\sum_{k\in\mathcal{N}_i}\exp\left(\text{LeakyReLU}\left(\hat{\alpha}^{l\top}\left[\hat{\mathbf{W}}^{l}\hat{h}_{i}^{l}||\hat{\mathbf{W}}^{l}\hat{h}_{k}^{l}\right]\right)\right)} \tag{3}$$

Similar to Equation 1, $\hat{\mathbf{W}}$ and $\hat{\alpha}$ are learnable weight matrices.

Taking the output of the encoder as the input to the decoder, i.e., $\hat{h}_i^L = h_i^L, \forall i \in \{1, 2, \ldots, N\}$, the representation of node i in the $(l-1)$-th layer of the decoder is reconstructed as follows:

$$\hat{h}_i^{l-1} = \sigma\left(\frac{1}{K}\sum_{k=1}^{K}\sum_{j\in\mathcal{N}_i}\hat{a}_{ij}^{l}\hat{\mathbf{W}}^{l}\hat{h}_{j}^{l}\right) \tag{4}$$

After passing through the same L layers of the decoder, the set of outputs of all nodes in the last layer is regarded as the reconstructed functional connectivity matrix, i.e., $\hat{y} = \{\hat{h}_1^0, \hat{h}_2^0, \ldots, \hat{h}_n^0\}$.

Objective Function

To achieve more accurate predictions of functional connectivity from the structural connectivity matrices, the objective function of the neural network is designed to meet two requirements: 1) minimizing the prediction error between the oFC and the model-predicted pFC, which is achieved by calculating the mean squared error between oFC and pFC. 2) introducing a regularization term to ensure that the correlation (inter-pFC) between different individuals in the pFC is comparable to the correlation (inter-oFC) between different individuals in the oFC. This ensures that the neural network learns the mapping from SC to oFC while retaining individual differences, rather than predicting a population-average representation of functional connectivity for all individuals. Based on these two requirements, the objective function for the proposed overall structure is:

$$J = L(\theta) + \lambda(|\gamma - \phi(\theta)|) \tag{5}$$

where θ represents the parameters of the neural network to be learned, $L(\cdot)$ is the loss function, and λ is a regularization constant used in the regularization function $|\gamma - \phi(\cdot)|$, similar to the L1 norm. The mean squared error is used as the loss function, as shown below:

$$L = \frac{1}{n}\sum_{i=1}^{n}(y^i - \hat{y}^i)^2 \tag{6}$$

where n is the number of samples in a training batch, i represents a sample, y is the actual label (oFC), and $\hat{y}$ is the predicted output (pFC). The mean squared error ensures that the spatial correlation between SC and FC is approximately preserved during training.

The objective of the overall autoencoder structure is to predict the actual FC while also maintaining the inter-oFC differences between individuals. Therefore, a regularization term is added to the objective function, and the Pearson correlation coefficient r is introduced into the regularization function $|\gamma - \phi(\theta)|$:

$$r(a,b) = \frac{\sum(a-\bar{a})(b-\bar{b})}{\sqrt{\sum_{n-1}(a-\bar{a})^2}\sqrt{\sum(b-\bar{b})^2}} \tag{7}$$

$$\gamma = \frac{2}{n(n-1)} \sum_{i=1}^{n} \sum_{j=i+1}^{n} r\left(y^i, y^j\right) \tag{8}$$

$$\phi = \frac{2}{n(n-1)} \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} r\left(\hat{y}^i, \hat{y}^j\right) \tag{9}$$

In the above equations, γ represents the inter-oFC correlation of the training dataset, which remains unchanged during training. It is noteworthy that γ varies for different datasets. In this case, ϕ represents the inter-pFC correlation, which is expected to be less than or equal to the inter-oFC correlation. Thus, the regularization function $\lambda(|\gamma - \phi(\theta)|$ ensures that the inter-individual differences in the pFC are comparable to the inter-individual differences in the oFC.

Acknowledgments

The WAND data were acquired at the UK National Facility for In Vivo MR Imaging of Human Tissue Microstructure funded by the EPSRC (grant EP/M029778/1), and The Wolfson Foundation, and supported by a Wellcome Trust Investigator Award (096646/Z/11/Z) and a Wellcome Trust Strategic Award (104943/Z/14/Z). We acknowledge contributions of Svetla Manolova, Elena Stylianopoulou, Emma Morgan, Gavin Perry, Alexander Shaw, Mark Drakesmith and Holly Rossiter to the data collection.

References

[1] L E Suárez, R D Markello, R F Betzel, and B Misic. Linking structure and function in macroscale brain networks. *Trends Cogn Sci.*, 24:302–315, 4 2020.

[2] C. J. Honey, O. Sporns, L. Cammoun, X. Gigandet, J. P. Thiran, R. Meuli, and P. Hagmann. Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*, 106:2035–2040, 2 2009.

[3] Bratislav Mišić, Richard F. Betzel, Marcel A. de Reus, Martijn P. van den Heuvel, Marc G. Berman, Anthony R. McIntosh, and Olaf Sporns. Network-level structure-function relationships in human neocortex. *Cerebral Cortex*, 26:3285–3296, 7 2016.

[4] P Tewarie, B Prasse, J Meier, F A N Santos, L Douw, M M Schoonheim, C J Stam, P Van Mieghem, and A Hillebrand. Mapping functional brain networks from the structural connectome: Relating the series expansion and eigenmode approaches. *NeuroImage*, 216:116805, 2020.

[5] J Cabral, M Kringelbach, and G Deco. Functional connectivity dynamically evolves on multiple time-scales over a static structural connectome: Models and mechanisms. *NeuroImage*, 160:84–96, 2017.

[6] G Deco, V Jirsa, and A McIntosh. Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nature Reviews Neuroscience*, 12(1):43, 2011.

[7] G Deco, A R McIntosh, K Shen, R M Hutchison, R S Menon, S Everling, P Hagmann, and V K Jirsa. Identification of optimal structural connectivity using functional connectivity and neural modeling. *Journal of Neuroscience*, 34(23):7910–7916, 2014.

[8] G Deco, J Cabral, M Woolrich, A Stevner, T van Hartevelt, and M Kringelbach. Single or multiple frequency generators in on-going brain activity: A mechanistic whole-brain model of empirical meg data. *NeuroImage*, 152:538–550, 2017.

[9] C Honey, R Kötter, M Breakspear, and O Sporns. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *PNAS*, 104(24):10240–10245, 2007.

[10] Joaquín Goñi, Martijn P. van den Heuvel, Andrea Avena-Koenigsberger, Nieves Velez de Mendizabal, Richard F. Betzel, Alessandra Griffa, Patric Hagmann, Bernat Corominas-Murtra, Jean-Philippe Thiran, and Olaf Sporns. Resting-brain functional connectivity predicted by analytic measures of network communication. *Proceedings of the National Academy of Sciences*, 111:833–838, 1 2014.

[11] Joana Cabral, Henry Luckhoo, Mark Woolrich, Morten Joensson, Hamid Mohseni, Adam Baker, Morten L. Kringelbach, and Gustavo Deco. Exploring mechanisms of spontaneous functional connectivity in meg: How delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. *NeuroImage*, 90:423–435, 4 2014.

[12] Pilar Garces, Ernesto Pereda, Juan A. Hernandezâ-Tamames, Francisco Del-Pozo, Fernando Maestu, and Jose Ãngel Pineda-Pardo. Multimodal description of whole brain connectivity: A comparison of resting state meg, fmri, and dwi. *Human Brain Mapping*, 37:20–34, 1 2016.

[13] P. Tewarie, A. Hillebrand, E. van Dellen, M.M. Schoonheim, F. Barkhof, C.H. Polman, C. Beaulieu, G. Gong, B.W. van Dijk, and C.J. Stam. Structural degree predicts functional network connectivity: A multimodal resting-state fmri and meg study. *NeuroImage*, 97:296–307, 8 2014.

[14] Prejaas Tewarie, Romesh Abeysuriya, Aine Byrne, George C. O'Neill, Stamatios N. Sotiropoulos, Matthew J. Brookes, and Stephen Coombes. How do spatially distinct frequency specific meg networks emerge from one underlying structural connectome? the role of the structural eigenmodes. *NeuroImage*, 186:211–220, 2 2019.

[15] Jose Angel Pineda-Pardo, Ricardo Bruna, Mark Woolrich, Alberto Marcos, Anna C. Nobre, Fernando Maestu, and Diego Vidaurre. Guiding functional connectivity estimation by structural connectivity in meg: an application to discrimination of conditions of mild cognitive impairment. *NeuroImage*, 101:765–777, 11 2014.

[16] J. Meier, P. Tewarie, A. Hillebrand, L. Douw, B van Dijk, S Stufflebeam, and P. V. Mieghem. A mapping between structural and functional brain networks. *Brain Connectivity*, 6(4):298–311, 2016.

[17] E Messaritaki, S Foley, S Schiavi, L Magazzini, B Routley, D K Jones, and K D Singh. Predicting meg resting-state functional connectivity from microstructural information. *Network Neuroscience*, 5, 2021.

[18] T Sarwar, Y Tian, B.T.T. Yeo, K. Ramamohanarao, and A. Zalesky. Structure-function coupling in the human connectome: A machine learning approach. *NeuroImage*, 226:117609, 2021.

[19] F Zamani Esfahlani, J Faskowitz, J Slack, B Mišić, and R. F. Betzel. Local structure-function relationships in human brain networks across the lifespan. *Nature Communications*, 13:2053, 2022.

[20] G L Baum, Z Cui, D R Roalf, C Rastko, R F Betzel, B Larsen, M Cieslak, P A Cook, C H Xia, T M Moore, K Ruparel, D J Oathes, A F Alexander-Bloch, R T Shinohara, A Raznahan, R E Gur, R C Gur, D S Bassett, and T D Satterthwaite. Development of structure-function coupling in human brain networks during youth. *PNAS*, 117(1):771–778, 2020.

[21] L Cocchi, I H Harding, A Lord, C Pantelis, M Yucel, and A Zalesky. Disruption of structure-function coupling in schizophrenia connectome. *NeuroImage: Clinical*, 9:4:779–787, 2014.

[22] Caio Seguin, Y Tian, and A Zalesky. Network communication models improve the behavioral and functional predictive utility of the human structural connectome. *Network Neuroscience*, 4:980–1006, 2020.

[23] K Koller, S Umesh Rudrapatna, M Chamberland, E P Raven, G D Parker, C M W Tax, M Drakesmith, F Fasano, D Owen, G Hughes, C Charron, C J Evans, and D K Jones. Micra: Microstructural image compilation with repeated acquisitions. *NeuroImage*, 225:117406, 2021.

[24] Sean C. L. Deoni, Lucy Matthews, and Shannon H. Kolind. One component? two components? three? the effect of including a nonexchanging "free" water component in multicomponent driven equilibrium single pulse observation of t1 and t2. *Magnetic Resonance in Medicine*, 70:147–154, 7 2013.

[25] Anders M. Dale, Bruce Fischl, and Martin I. Sereno. Cortical surface-based analysis: I segmentation and surface reconstruction. *NeuroImage*, 9:179–194, 2 1999.

[26] Anders M. Dale and Martin I. Sereno. Improved localizadon of cortical activity by combining eeg and meg with mri cortical surface reconstruction: A linear approach. *Journal of Cognitive Neuroscience*, 5:162–176, 4 1993.

[27] B. Fischl, A. Liu, and A.M. Dale. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Transactions on Medical Imaging*, 20:70–80, 2001.

[28] Bruce Fischl, David H. Salat, Evelina Busa, Marilyn Albert, Megan Dieterich, Christian Haselgrove, Andre van der Kouwe, Ron Killiany, David Kennedy, Shuna Klaveness, Albert Montillo, Nikos Makris, Bruce Rosen, and Anders M. Dale. Whole brain segmentation. *Neuron*, 33:341–355, 1 2002.

[29] B. Fischl. Automatically parcellating the human cerebral cortex. *Cerebral Cortex*, 14:11–22, 1 2004.

[30] Bruce Fischl, David H. Salat, André J.W. van der Kouwe, Nikos Makris, Florent Ségonne, Brian T. Quinn, and Anders M. Dale. Sequence-independent segmentation of magnetic resonance images. *NeuroImage*, 23:S69–S84, 1 2004.

[31] Bruce Fischl, Martin I. Sereno, and Anders M. Dale. Cortical surface-based analysis. *NeuroImage*, 9:195–207, 2 1999.

[32] Bruce Fischl, M I Sereno, R B Tootell, and A M Dale. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping*, 8:272–284, 1999.

[33] Bruce Fischl and Anders M. Dale. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences*, 97:11050–11055, 9 2000.

[34] Xiao Han, Jorge Jovicich, David Salat, Andre van der Kouwe, Brian Quinn, Silvester Czanner, Evelina Busa, Jenni Pacheco, Marilyn Albert, Ronald Killiany, Paul Maguire, Diana Rosas, Nikos Makris, Anders Dale, Bradford Dickerson, and Bruce Fischl. Reliability of mri-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. *NeuroImage*, 32:180–94, 8 2006.

[35] Jorge Jovicich, Silvester Czanner, Douglas Greve, Elizabeth Haley, Andre van der Kouwe, Randy Gollub, David Kennedy, Franz Schmitt, Gregory Brown, James MacFall, Bruce Fischl, and Anders Dale. Reliability in multi-site structural mri studies: Effects of gradient non-linearity correction on phantom and human data. *NeuroImage*, 30:436–443, 4 2006.

[36] Martin Reuter, H. Diana Rosas, and Bruce Fischl. Highly accurate inverse consistent registration: A robust approach. *NeuroImage*, 53:1181–1196, 12 2010.

[37] Martin Reuter, Nicholas J. Schmansky, H. Diana Rosas, and Bruce Fischl. Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage*, 61:1402–1418, 7 2012.

[38] Rahul S. Desikan, Florent Ségonne, Bruce Fischl, Brian T. Quinn, Bradford C. Dickerson, Deborah Blacker, Randy L. Buckner, Anders M. Dale, R. Paul Maguire, Bradley T. Hyman, Marilyn S. Albert, and Ronald J. Killiany. An automated labeling system for subdividing the human cerebral cortex on mri scans into gyral based regions of interest. *NeuroImage*, 31:968–980, 7 2006.

[39] M Jenkinson, C F Beckmann, T E Behrens, M W Woolrich, and M A Smith. Fsl. *NeuroImage*, 62:782–790, 2012.

[40] J-D Tournier, R E Smith, D Raffelt, R Tabbara, Thijs Dhollander, M Pietsch, D Christiaens, B Jeurissen, C-H Yeh, and A Connelly. Mrtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *NeuroImage*, 202:116137, 2019.

[41] Jelle Veraart, Dmitry S Novikov, Daan Christiaens, Benjamin Ades-aron, Jan Sijbers, and Els Fieremans. Denoising of diffusion mri using random matrix theory. *NeuroImage*, 142:394–406, 2016.

[42] Jelle Veraart, Els Fieremans, and Dmitry S. Novikov. Diffusion mri noise mapping using random matrix theory. *Magnetic Resonance in Medicine*, 76:1582–1593, 11 2016.

[43] Viljami Sairanen, Alexander Leemans, and Chantal M W Tax. Fast and accurate slicewise outlier detetion (solid) with informed model estimation for diffusion mri data. *NeuroImage*, 181:331–346, 2018.

[44] Jesper L R Andersson, Stefan Skare, and John Ashburner. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *NeuroImage*, 20:870–888, 2003.

[45] S M Smith, M A Jenkinson, M W Woolrich, C F Beckmann, T E Behrens, H Johansen-Berg, P R Bannister, M De Luca, I Drobnjak, D E Flitney, R K Niazy, J Saunders, J Vickers, Y Zhang,

N De Stefano, J M Brady, and P M Matthews. Advances in functional and structural mr image analysis and implementation as fsl. *NeuroImage*, 23:S208–S219, 2004.

[46] Jesper L R Andersson and Stamatios N Sotiropoulos. An integrated approach to correction for off-resonance effects and subject movement in diffusion mr imaging. *NeuroImage*, 125:1063–1078, 2016.

[47] Elias Kellner, Bibek Dhital, Valerij G Kiselev, and Marco Reisert. Gibbs-ringing artifact removal based on local subvoxel-shifts. *Magnetic Resonance in Medicine*, 76:1574–1581, 2016.

[48] F Isensee, M Schell, I Pflueger, G Brugnara, D Bonekamp, U Neuberger, A Wick, H-P Schlemmer, S Heiland, W Wick, M Bendszus, K H Maier-Hein, and P Kickingereder. Automated brain extraction of multisequence mri using artificial neural networks. *Human Brain Mapping*, 40(71):4952–4964, 2019.

[49] B Avants, N Tustison, and G Song. Advanced normalization tools, ants 1.0. *Sourceforge*, 2009.

[50] M Jenkinson, P R Bannister, J M Brady, and S M Smith. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, 17:825–841, 2002.

[51] M Jenkinson and M A Smith. A global optimisation method for affine registration of brain images. *Medical Image Analysis*, 5:143–156, 2001.

[52] T C Wood. Quit: Quantitative imaging tools. *Journal of Open Source Software*, 3(26):656, 2018.

[53] S C L Deoni, B K Rutt, and T M Peters. Rapid combined t1 and t2 mapping using gradient recalled acquisition in the steady state. *Magnetic Resonance in Medicine*, 49:515–526, 2003.

[54] Deoni S C L. High-resolution t1 mapping of the brain at 3t with driven equilibrium single pulse observation of t1 with high-speed incorporation of rf field inhomogeneities (despot1-hifi). *Journal of Magnetic Resonance Imaging*, 26(4):1106–1111, 2007.

[55] S C L Deoni, B K Rutt, T Arun, C Pierpaoli, and D K Jones. Gleaning multicomponent t1 and t2 information from steady-state imaging data. *Magnetic Resonance in Medicine*, 60:1372–1387, 2008.

[56] Thijs Dhollander, D Raffelt, and A Connelly. Unsupervised 3-tissue response function estimation from single-shell or multi-shell diffusion mr data without a co-registered t1 image. *ISMRM Workshop on Breaking the Barriers of Diffusion MRI*, 5, 2016.

[57] Thijs Dhollander, R Mito, D Raffelt, and A Connelly. Improved white matter response function estimation for 3-tissue constrained spherical deconvolution. *Proc Intl Soc Mag Reson Med*, page 555, 2019.

[58] B Jeurissen, J-D Tournier, Thijs Dhollander, A Connelly, and J Sijbers. Multi-tissue constrained spehrical deconvolution for improved analysis of multi-shell diffusion mri data. *NeuroImage*, 103:411–426, 2014.

[59] B Patenaude, S M Smith, D N Kennedy, and M A Jenkinson. A bayesian model of shape and appearance for subcortical brain segmentation. *NeuroImage*, 56:907–922, 2011.

[60] R E Smith, J-D Tournier, F Calamante, and A Connelly. Anatomically-constrained tractography: Improved diffusion mri streamlines tractography through effective use of anatomical information. *NeuroImage*, 62:1924–1938, 2012.

[61] S M Smith. Fast robust automated brain extraction. *Human Brain Mapping*, 17:143–155, 2002.

[62] Y Zhang, M Brady, and S Smith. Segmentation of brain mr images through a hidden markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, 20:45–57, 2001.

[63] M W Woolrich, S Jbabdi, B Patenaude, M Chappell, S Makni, T Behrens, C F Beckmann, M Jenkinson, and M A Smith. Bayesian analysis of neuroimaging data in fsl. *NeuroImage*, 45:S173–S186, 2009.

[64] J-D Tournier, F Calamante, and A Connelly. Improved probabilistic streamlines tractography by 2nd order integration over fibre orientation distributions. *Proceedings of the International Society for Magnetic Resonance in Medicine*, page 1670, 2010.

[65] R E Smith, J-D Tournier, F Calamante, and A Connelly. Sift2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. *NeuroImage*, 119:338–351, 2015.

[66] Anastasia Mirza-Davies, Sonya Foley, Xavier Caseras, Emily Baker, Peter Holmans, Valentina Escott-Price, Derek K. Jones, Judith R. Harrison, and Eirini Messaritaki. The impact of genetic risk for alzheimer's disease on the structural brain networks of young adults. *Frontiers in Neuroscience*, 16, 11 2022.

[67] Hannah J Clarke, Eirini Messaritaki, Stavros I Dimitriadis, and Claudia Metzler-Baddeley. Dementia risk factors modify hubs but leave other connectivity measures unchanged in asymptomatic individuals: a graph theoretical analysis. *Brain Connectivity*, 12:26–40, 2022.

[68] Eirini Messaritaki, Sonya Foley, Kali Barawi, Ulrich Ettinger, and Derek K. Jones. Increased structural connectivity in high schizotypy. *Network Neuroscience*, 7:213–233, 1 2023.

[69] M Drakesmith, R Harms, S U Rudrapatna, G D Parker, C J Evans, and D K Jones. Estimating axon conduction velocity in vivo from microstructural mri. *NeuroImage*, 203:116186, 2019.

[70] Eirini Messaritaki, Stavros I. Dimitriadis, and Derek K. Jones. Optimization of graph construction can significantly increase the power of structural brain network studies. *NeuroImage*, 199:495–511, 10 2019.

[71] Stavros I Dimitriadis, Eirini Messaritaki, and Derek K Jones. The impact of graph construction scheme and communite detection algorithm on the repeatability of community and hub identification in structural brain networks. *Human Brain Mapping*, 42:4261–4280, 2021.

[72] Beaulieu C. The biological basis of diffusion anisotropy. *Diffusion MRI*, pages 155 – 183, 2009.

[73] Y Chen, H An, H Zhu, T Stone, J K Smith, C Hall, E Bullitt, D Shen, and W Lin. White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented hiv+ patients. *NeuroImage*, 47:1154–1162, 2009.

[74] M D Cykowski, P T Fox, R J Ingham, J C Ingham, and D A Robin. A study of the reproducibility and etiology of diffusion anisotropy differences in developmental stuttering: a potential role for impaired myelination. *NeuroImage*, 52:1495–1504, 2010.

[75] Derek K Jones, T R Knosche, and R Turner. White matter integrity, fiber count and other fallacies: the do's and dont's of diffusion mri. *NeuroImage*, 73:239–254, 2013.

[76] Yaniv Assaf and Peter J. Basser. Composite hindered and restricted model of diffusion (charmed) mr imaging of the human brain. *NeuroImage*, 27(1):48–58, 2005.

[77] Jiri Vrba and Stephen E. Robinson. Signal processing in magnetoencephalography. *Methods*, 25:249–271, 10 2001.

[78] Loes Koelewijn, Thomas M Lancaster, David Linden, Diana C Dima, Bethany C Routley, Lorenzo Magazzini, Kali Barawi, Lisa Brindley, Rachael Adams, Katherine E Tansey, Aline Bompas, Andrea Tales, Antony Bayer, and Krish D Singh. Oscillatory hyperactivity and hyperconnectivity in young apoe-epsilon4 carriers and hypoconnectivity in alzheimer's disease. *eLife*, 8, 2019.

[79] Robert Oostenveld, Pascal Fries, Eric Maris, and Jan-Mathijs Schoffelen. Fieldtrip: Open source software for advanced analysis of meg, eeg, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, 2011:1–9, 2011.

[80] Guido Nolte. The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. *Physics in Medicine and Biology*, 48:3637–3652, 11 2003.

[81] Arjan Hillebrand, Gareth R. Barnes, Johannes L. Bosboom, Henk W. Berendse, and Cornelis J. Stam. Frequency-dependent functional connectivity within resting-state networks: An atlas-based meg beamformer solution. *NeuroImage*, 59:3909–3921, 2 2012.

[82] G.L. Colclough, M.J. Brookes, S.M. Smith, and M.W. Woolrich. A symmetric multivariate leakage correction for meg connectomes. *NeuroImage*, 117:439–448, 8 2015.

[83] G.L. Colclough, M.W. Woolrich, P.K. Tewarie, M.J. Brookes, A.J. Quinn, and S.M. Smith. How reliable are meg resting-state connectivity metrics? *NeuroImage*, 138:284–293, 9 2016.

[84] Megan Godfrey and Krish D. Singh. Measuring robust functional connectivity from resting-state meg using amplitude and entropy correlation across frequency bands and temporal scales. *NeuroImage*, 226:117551, 2 2021.

[85] D.E. Rumelhart, G.E. Hinton, and R.J Williams. "learning internal representations by error propagation". *Parallel Distributed Processing, Volume I: Foundations. MIT Press, Cambridge, MA*, 1986.

[86] Franco Scarselli, Marco Gori, Ah Chung Tsoi, Markus Hagenbuchner, and Gabriele Monfardini. The graph neural network model. *IEEE transactions on neural networks*, 20(1):61–80, 2008.

[87] M Rubinov and O Sporns. Complex network measures of brain connectivity: uses and interpretations. *NeuroImage*, 52:1059–1069, 2010.

[88] D V Jeste, O M Wolkowitz, and Palmer B W. Divergent trajectories of physical, cognitive, and psychosocial aging in schizophrenia. *Schizophrenia Bulletin*, 37:451–455, 2011.

[89] J R Glausier and D A Lewis. Dendritic spine pathology in schizophrenia. *Neuroscience*, 251:90–107, 2013.

[90] C E Moyer, M A Shelton, and R A Sweet. Dendritic spine alterations in schizophrenia. *Neuroscience Letters*, 601:46–53, 2015.

[91] N E M van Haren, H G Schnack, W Cahn, M P van den Heuvel, C Lepage, L Collins, H E Evans, A C adn Hulshoff Pol, and R S Kahn. Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry*, 68:871–880, 2011.

[92] Y Benjamini and D Yekutieli. The control of the false discovery rate in multiple testing under dependency. *The Annals of Statistics*, 29(4):1165–1188, 2001.

[93] D Groppe. *MATLAB Central File Exchange*, 2019.

[94] A J Mackintosh, R de Bock, Z Lim, V-N Trulley, A Schmidt, S Borgwardt, and C Andreou. Psychotic disorders, dopaminergic agents and eeg/meg resting-state functional connectivity: A systematic review. *Neuroscience and Biobehavioral Reviews*, 120:354–371, 2021.