

Geometrical Deep Learning: A Feasible Methodology for Brain Age Prediction

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Abstract. The dynamic nature of the human brain through aging brings forth structural and functional changes that contribute to cognitive decline and increase the risk of neurodegenerative disorders. Predicting brain age, particularly through deviations from chronological age, can serve as a significant indicator of pathological aging. In this study, we integrate geometrical deep learning with neuroimaging data to predict brain age. We construct Graph Convolutional Networks by using resting-state magnetoencephalography data and structural connectivity measures derived from diffusion-weighted magnetic resonance imaging. These networks incorporate cortical morphometry and spectral features as node annotations to capture the multivariate patterns of age-related brain changes. Our findings highlight the effectiveness of Graph Convolutional Networks in leveraging functional and structural brain connectivity to predict brain age. This approach underscores the potential of graph-based deep learning methods in advancing our understanding of brain aging and its implications for neurodegenerative conditions.

Keywords. Aging, brain age prediction, functional connectivity, graph convolutional network, gray matter morphometry, MEG, MRI, power spectral density, structural connectivity.

1 Introduction

The human brain undergoes dynamic changes throughout life, with aging in adulthood leading to structural and functional changes that

contribute to gradual cognitive decline [87]. While these age-related changes are not inherently pathological, the likelihood of developing neurodegenerative disorders increases with age [1, 61]. Emerging research suggests that certain neurodegenerative conditions may stem from processes associated with accelerated brain aging [41].

In this context, preventive medicine can greatly benefit from individualized quantification of atypical aging, as significant deviations between predicted and chronological age may indicate pathological aging [51]. Understanding and identifying biomarkers that define healthy aging is crucial for detecting early-stage neurodegeneration and predicting age-related cognitive decline. One promising approach involves leveraging neuroimaging and electrophysiological data to capture multivariate patterns of age-related brain changes and formulating high-dimensional regression boundaries to accurately predict the age of healthy individuals. Machine learning (ML) models, trained on neurotypical subjects, can then be applied to clinical samples to reveal aberrant age-related changes, providing a population-level tool for assessing brain aging.

This approach has been validated under different neuropathologies, such as Alzheimer's [28, 32, 33, 31], traumatic brain injury [12], schizophrenia

[47, 91], HIV [49, 13], epilepsy [63], and Down's syndrome [11]. Additionally, predicting brain age has extended beyond neurological disorders, showing positive impacts of meditation [57], diet [62], increased education, and physical exercise [73, 80] on brain age.

The aforementioned studies have predominantly focused on estimating brain age by analyzing gray matter morphometry or spectral features from various brain regions of interest (ROIs). However, it is essential to recognize that the brain operates as a complex network of interconnected neural circuits, facilitated by white matter tracts that directly link different brain regions [2], and functionally supported by the coordinated activity between these distinct brain regions [67]. Both structural and functional connectivity within this neural network undergo significant age-related changes during healthy aging [16] and exhibit distinct patterns in various neural diseases [60, 52, 55]. Surprisingly, these properties have often been overlooked as potential features for predicting brain age.

To explore the significance of brain topology and integrate it with functional and structural information into age prediction models, we employed a Graph Convolutional Network (GCN) architecture on graphs generated from resting-state magnetoencephalography (MEG) data and structural connectivity measures derived from diffusion-weighted Magnetic Resonance Imaging (dMRI). Within this framework, each node was annotated with both gray matter morphometry (GMM) and spectral features.

2 Related Work

Numerous studies have delved into the intricate dynamics of age-related changes in the human brain, recognizing the crucial role of these alterations in cognitive decline and the onset of neurodegenerative disorders. These investigations underscore the potential of individualized quantification of atypical aging as a means for the early detection of pathological conditions.

In this section, our focus shifts exclusively to works published between 2018 and 2023 that leverage the Cam-CAN dataset detailed in Section

3.1, either independently or in conjunction with another database. These studies predominantly concentrate on estimating brain age based on morphometric or spectral data from different brain regions of interest (ROIs), extracted from structural magnetic resonance imaging (T1-weighted MRI) and M/EEG data, with the former being the most prevalent and exhibiting the best performance. However, most overlook the underlying topology of the brain, neglecting critical information related to the neighborhood, connectivity, or distribution of power and frequencies among ROIs.

For instance, Support Vector Machines (SVM) have been used on vectorized gray matter volume images, achieving a regression performance of $R=0.91$ with a $MAE=5.46$ years [50]. If not vectorized, the 3D gray matter volumes can be used to train 3D Convolutional Neural Networks [25, 23, 45], obtaining correlation values as high as $R=0.97$ and $MAE=4.06$ years. These results were obtained using multiple datasets, including Cam-CAN. These studies demonstrate the effectiveness of CNN in capturing age-related morphological changes in the brain. GMM features, such as volume, surface area, cortical thickness, mean curvature, Gaussian curvature, folding index, and intrinsic curvature, extracted from parcellated gray matter volumes, have been used to train linear and non-linear models such as Ridge regression [59] and XGBoost[17], reporting results of $R=0.889$ with $MAE= 6.79$, and $R=0.9$ with $MAE = 6.66$.

Additionally, 2D CNNs [54], SVM [49, 33], transfer learning models[5] such as AlexNet, VGGNet5, and ResNet5, elastic net Regression [4], siamese networks [86], and linear regression models [60] have been employed to capture the spatial topology of functional or structural connectomes, either by using the connectome as a 2D image or by extracting features using graph theory modeling.

Nevertheless, these models are designed for Euclidean spaces and may yield misleading conclusions when applied to graphs, since they are inherent inhabitants of non-Euclidean spaces. Furthermore, these approaches cannot incorporate node embeddings in the graph as part of the feature space.

While these studies validate the effectiveness of their chosen techniques, none has dedicated itself to methodologies that integrate electrophysiological, morphological, and connectomical data into a framework that best aligns with the brain's architecture.

In contrast, the present work achieves this integration through the use of Graph Convolutional Networks (GCN).

3 Materials and Methods

This section describes the feature extraction techniques and Deep Learning algorithm employed to tackle the challenge of age prediction, accompanied by a detailed description of the dataset.

The proposed algorithms were implemented in Python 3.9 on the Ubuntu 20.04 distribution. Specifically, the deep learning model was constructed utilizing PyTorch version 2.0.1.

3.1 Dataset

We conducted the analysis using data sourced from the open-access Cambridge Center for Aging Neuroscience (Cam-CAN) repository (refer to [71, 75], for detailed information on the dataset and acquisition protocols).

The dataset is accessible through the link in the footnote¹.

Specifically, our investigation utilized neuroimaging and electrophysiological data from a cohort of 652 healthy subjects.

After exclusions, which involved subjects lacking both MRI and MEG data, unsatisfactory preprocessing results, or failure to extract the cortical surface for source reconstruction, our final dataset comprised 606 subjects (male/female = 305/301, mean age = 54.9 ± 18.18 , age range 18–88 years).

¹<http://www.mrc-cbu.cam.ac.uk/datasets/camcan/>

3.1.1 Magnetoencephalography

MEG measures magnetic fields associated with electrical currents resulting from neuronal activity [9]. The electrical currents generating these magnetic fields are composite signals from multiple neuronal sources, formed by the temporal and spatial summation of transmembrane ionic currents [72].

These currents lead to postsynaptic potentials, causing sinks or active sinks depending on whether the synapse is excitatory or inhibitory. The resulting compensatory extracellular currents can be modeled as a dipolar system, influenced by the local tissue's electrical properties.

Activation of a cortical region involves the spatiotemporal coactivation of numerous neuronal bodies, forming large current dipoles with their associated magnetic fields. These signals can be recorded using an array of external sensors as shown in the leftmost panel in Figure 1.

However, electrodes capture a linear mixture of all nearby dipoles, complicating source localization and requiring interpretation of brain topography. Forward and inverse modeling assist in this interpretation by disentangling time series from overlapping sources. The forward problem, which describes how active sources generate sensor patterns, can be computed using source and volume conductor models. Assuming the useful frequency spectral range for electrophysiological signals is below 1 kHz, Maxwell's quasi-static approximations describe the source physics.

The Biot-Savart equation [35] relates the current flow $J(\mathbf{r}')$ to the magnetic field $B(\mathbf{r})$:

$$B(\mathbf{r}) = \frac{\mu_0}{4\pi} \int J(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dv'. \quad (1)$$

The current density in the head includes primary currents $J^P(\mathbf{r}')$, related to neuronal activity, and volume currents $J^V(\mathbf{r}')$, resulting from the electric field's influence on extracellular charge carriers. This can be expressed as:

$$\begin{aligned} J(\mathbf{r}') &= J^P(\mathbf{r}') + J^V(\mathbf{r}') = \\ &= J^P(\mathbf{r}') + \sigma(\mathbf{r}')E(\mathbf{r}') = \\ &= J^P(\mathbf{r}') - \sigma(\mathbf{r}')\nabla V(\mathbf{r}'), \end{aligned} \quad (2)$$

with $E(\mathbf{r}') = -\nabla V(\mathbf{r}')$ due to quasi-static properties, and $\sigma(\mathbf{r}')$ representing the head's average conductivity. The primary current distribution can be approximated by an equivalent current dipole $J^P(\mathbf{r}') = \mathbf{q}\delta(\mathbf{r}' - \mathbf{r}_q)$, where $\delta(\mathbf{r})$ is the Dirac delta function, and $\mathbf{q}$ is the moment.

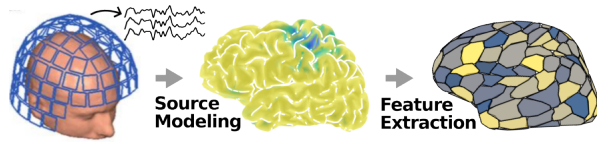


Fig. 1. Process of source modeling and feature extraction in MEG data. The image shows the acquisition of brain signals using a MEG helmet, followed by source modeling to identify active regions in the brain and feature extraction from the parcellated source model for further analysis

This leads to an expression for the magnetic field as a sum of contributions from primary and volume currents:

$$B(\mathbf{r}) = B_0(\mathbf{r}) + \frac{\mu_0}{4\pi} \sum_{ij} (\sigma_i - \sigma_j) \int_{S_{ij}} V(\mathbf{r}') \frac{\mathbf{r} - \mathbf{r}'}{\|\mathbf{r} - \mathbf{r}'\|^3} \times dS'_{ij}. \quad (3)$$

Solving the forward problem provides the sensor patterns with a primary current distribution. This requires numerical solutions using anatomical information from high-resolution MRI brain images for realistic head shapes [18, 90]. Various automated and semiautomated methods, such as spherical and overlapping-sphere head modeling, boundary element method (BEM), finite element method (FEM), and finite difference method, exist for surface extraction and defining the brain's geometry and properties.

Once the forward problem is solved, the inverse problem can be tackled to estimate the sources generating the time series recorded by the electrodes, as illustrated in the central panel of Figure 1. Inverse modeling techniques include dipole fitting procedures, distributed dipole models, and spatial filtering methods. Among these, spatial filtering, particularly beamforming, is a commonly used method [38]. Inspired by radar

and sonar data analysis, Beamforming enhances the spatial specificity of source localization by assuming each distinct source has a unique sum of vector weightings, making them independent of each other [79]. This technique provides clearer insights into the brain's functional architecture.

Resting-state magnetoencephalography (MEG) data were captured utilizing a 306-channel Elekta Neuromag Vectorview system, comprising 102 magnetometers and 204 planar gradiometers. The recordings took place in a well-lit magnetically shielded room, with a sampling rate of 1 kHz and an analog highpass filter set at 0.03 Hz. Throughout the resting-state scan, participants were instructed to maintain stillness, stay awake, and keep their eyes closed for approximately 9 minutes. Continuous estimation of head position within the MEG helmet was conducted using four Head-Position Indicator (HPI) coils, enabling offline correction of any head movement. Additionally, two pairs of bipolar electrodes were employed to capture vertical and horizontal electrooculogram (VEOG, HEOG) signals, facilitating the monitoring of blinks and eye movements. Furthermore, one pair of bipolar electrodes recorded the electrocardiogram (ECG) signal to monitor pulse-related artifacts.

3.1.2 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a medical imaging technique that exploits hydrogen protons' magnetic moment and spins to generate contrast images depicting various tissues. Hydrogen protons possess a non-zero net spin, making them susceptible to influence by an external magnetic field B_{0z} . Under a constant field, protons align and precess around the axis defined by this field, with a frequency ω determined by the gyromagnetic constant γ according to the Larmor equation: $\omega = \gamma B_{0z}$. The collective magnetic moments of the protons within a volume V (voxel) define the magnetization vector $\vec{M} = \frac{1}{V} \sum_i \vec{\mu}_i$, where V must be small enough for B_{0z} to be constant, but large enough to contain a sufficient number of protons. Neglecting the interaction of the protons with the medium, the motion of the spins can be modeled by:

$$\frac{d\vec{M}}{dt} = \gamma \vec{M} \times B_{0z}. \quad (4)$$

In the presence of a radio frequency (RF) pulse perpendicular to B_0 and in resonance with the precession frequency, the magnetization vector deviates from the longitudinal axis towards the transverse plane at an angle $\Delta\theta = \gamma B_1 \tau$, where τ is the exposure time to B_1 . Once the pulse is removed, two independent events occur: transverse and longitudinal relaxation. The longitudinal relaxation, or spin-lattice relaxation, is characterized by the rate of change of the longitudinal magnetization vector, given by $\frac{dM_z}{dt} = \frac{1}{T_1}(M_0 - M_z)$, where M_0 and M_z represent the equilibrium and residual longitudinal magnetization vectors, respectively, and T_1 denotes the empirical time for the signal to return to $1 - e^{-1}$ of its maximum value. The solution to this equation illustrates the exponential time evolution of longitudinal relaxation as:

$$M_z(t) = M_z(0)e^{-t/T_1} + M_0(1 - e^{-t/T_1}). \quad (5)$$

Transverse relaxation, or spin-spin relaxation, describes the decay of the transverse magnetization vector $M_\perp$, where spins experience local fields that cause dephasing and reduce the net magnetization vector. The time constant T_2 characterizes the rate of this decay, described by $M_{xy}(t) = M_{xy}(0)e^{-t/T_2}$. This equation demonstrates that once a transverse component is present, it rapidly begins to diminish due to the dephasing of spins in different local fields, resulting in signal loss. The relaxation parameters T_1 and T_2 vary for different tissues, influencing the timing for optimal signal differentiation and echo time (TE) during MRI signal acquisition, which is crucial for generating high-resolution images to distinguish between brain tissues, as seen in the top-left panel of Figure 5.

In addition to T1 and T2-weighted sequences, Diffusion Weighted Imaging (DWI) is another crucial MRI sequence for visualizing brain tracts, providing critical insights into the brain's structural connectivity and integrity. Structural connectivity refers to the anatomical pathways and connections formed by white matter tracts in the

brain, indicating the physical wiring that enables communication between different regions. Using computational reconstruction methods grounded in dMRI facilitates the visualization and mapping of white matter pathways within the brain [58].

Diffusion-weighted MRI is a non-invasive technique sensitive to the microscopic motion (diffusion) of water molecules. In biological tissues, the diffusion process is influenced by membranes and macromolecules, which can hinder or restrict the molecular random walk [24, 82], revealing the underlying structure's geometry.

To measure anisotropy and reconstruct tracts, magnetic diffusion-sensitizing gradients are applied. If molecules experience minimal displacement, the gradients nullify, maximizing the signal. Conversely, displacement due to tissue absence increases precession inhomogeneities, reducing the signal. The Larmor equation describes the precession frequency of protons under a magnetic field:

$$\omega = \gamma B. \quad (6)$$

By applying gradients in various directions [44], a 3D spherical grid is formed, enabling High Angular Resolution Diffusion Imaging (HARDI). The strength and timing of these gradients are parametrized by the b-value:

$$b = \gamma^2 |\mathbf{G}|^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right). \quad (7)$$

The HARDI signal can be modeled using spherical harmonics (SH), analogous to Fourier transforms but on a sphere. This involves estimating coefficients describing the HARDI signal, which are used to generate the Orientation Distribution Function (ODF) through the Funk-Radon transform (FRT) [29]. The smooth estimation of the HARDI signal $S(\theta_i, \phi_i)$ can be formulated as:

$$S(\theta_i, \phi_i) = \sum_{l=0}^{\infty} \sum_{m=-l}^l C_l^m Y_l^m(\theta_i, \phi_i). \quad (8)$$

The ODF is then refined into the Fiber Orientation Distribution (FOD) using spherical deconvolution [76], described by:

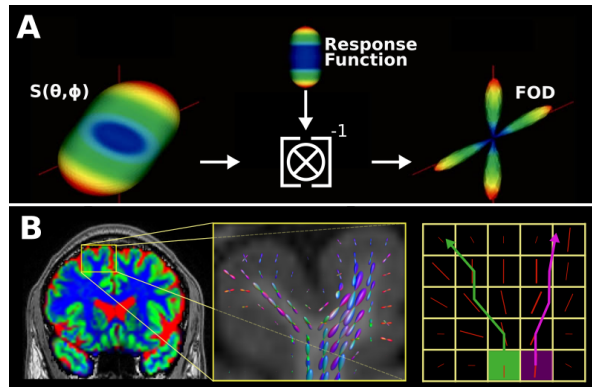


Fig. 2. A. Spherical deconvolution intuition to improve angular resolution of ODF reconstruction. Adapted from [20]. B. Left panel shows the volume fraction maps (CSF/GM/WM), mid panel the ODFs (left-right/front-back/up-down) and right the reconstructed tract starting from two different voxels. Adapted from [42]

$$S(\theta, \phi) = \sum_i f_i \hat{A}_i R(\theta). \quad (9)$$

An intuitive example of the constructed FODs for each voxel is represented in figure 2.A.

Left and central panels from Figure 2.B show a visual representation of the different tissues as a fractional map, and its FODs respectively.

Now that we have the $F(\theta, \phi)$ for each voxel, white matter tracts can be reconstructed using probabilistic tractography methods, which explicitly model uncertainty and allow for the generation of multiple pathways as a probability map. Once fiber-orientation probability density functions (PDFs) have been generated for each voxel in the brain (see Estimation of Fiber Orientation PDFs for Probabilistic Tractography in [43]), it is possible to simulate the likely range of outputs of a deterministic tracking process using various approaches such as Monte Carlo techniques, running a randomly selected sample from each PDF [64], it is also possible to invoke the diffusion process itself as a propagator for the tractography process as a random walk [46], or attempt to identify routes through the brain by front propagation methods [7], providing a comprehensive map of brain connectivity.

For all sequences, the raw data from MRI scans are stored in a conceptual domain known as *k-space* before being transformed into an image. An inverse Fourier transform is applied to the data in *k-space*, converting the frequency information into the spatial domain to produce the final MRI image. All Magnetic Resonance Imaging (MRI) datasets were collected at a single site (MRC-CBSU) using a 3T Siemens TIM Trio scanner with a 32-channel head coil. For the T1-weighted MRI, the imaging parameters of the MPRAGE sequence were: TR = 2250 ms, TE = 2.99 ms, Flip angle = 9°, Field of View = 256 × 240 × 192 mm³, and voxel size = 1 mm isotropic.

For the multi-shell dMRI (b=0,1000,2000), the imaging parameters of the Twice-refocused SE sequence were: TR = 9100 ms, TE = 104 ms, Field of View = 192 × 192 mm², and voxel size = 2 mm isotropic.

3.2 MEG Data Preprocessing and Feature Extraction

MEG preprocessing procedures closely followed the methodology outlined in [14], adhering to established good-practice guidelines [34]. Data analysis was performed with Brainstorm [74] in MATLAB 2020b (Mathworks, Inc., Massachusetts, USA), which is documented and freely available for download online under the GNU General Public License².

At the sensor level, a notch filter bank was applied to eliminate the line noise artifact (60 Hz) and its first three harmonics. Slow-wave and DC-offset artifacts were removed using a high-pass FIR filter with a 0.3 Hz cutoff. Signal-Space Projections (SSPs) [78] were derived to effectively remove cardiac and ocular artifacts. This involved defining signal projectors based on electrocardiogram and electrooculogram recordings around identified artifact occurrences. SSPs were also applied to attenuate low-frequency (1–7 Hz) and high-frequency noisy components (40–400 Hz) related to saccades and muscle activity, respectively.

Next, distinct brain source models were generated for all narrowband versions of the

²neuroimage.usc.edu/brainstorm

MEG sensor data. Individual T1-weighted MRI data were automatically segmented and labeled with FreeSurfer [15].

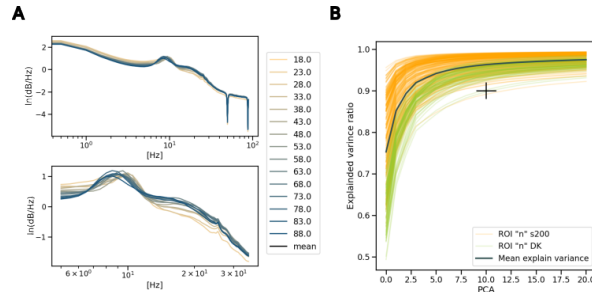


Fig. 3. A. Mean Global PSD: The global PSD was computed by averaging the PSD within each parcellated brain region. The mean global PSD represents the average across subjects, grouped in intervals of 5 years. B. PCA per ROI. Each curve represents the explained variance for each ROI within the DK, s200 atlases, as function of the number of principal components. The solid black curve is the mean explained variance

Co-registration with MEG sensor locations was established using digitized head points collected during each MEG session. MEG forward head models were created for each participant using the overlapping spheres approach [40], and cortical source models were developed with linearly constrained minimum-variance (LCMV) beamforming [89]. Data covariance regularization was performed, and to mitigate the impact of variable source depth, the estimated source variance was normalized by the noise covariance matrix. Elementary MEG source orientations were constrained to be normal to the surface at 15,000 cortical locations. Noise statistics for source modeling were estimated from two-minute empty-room recordings collected as close in time as possible to each participant's MEG session.

Finally, the source time series were organized into 68 and 200 cortical ROIs based on the Desikan-Killiany (DK) and Schaefer-200 (s200) atlases, respectively, which constituted the nodes of the graphs. An example of the parcellated cortex using the s200 map is depicted in Figure 1. To streamline the time series within each ROI, dimension reduction was performed using the first principal component computed through principal

component analysis (PCA) [85]. To standardize the duration of recordings across subjects, the time series were uniformly cropped to 300 seconds, excluding the first 30 seconds, which are often contaminated by preprocessing artifacts.

3.2.1 Power Spectral Density

After estimating the time series for each ROI, the power spectral density (PSD) was computed using the Welch method, which involves: (1) Dividing the data into overlapping segments; (2) Calculating the periodogram for each segment via the Discrete Fourier Transform (DFT); (3) Averaging these estimates [83].

For each segment of length L , a modified periodogram is computed using a window $W(j)$, forming sequences $X_k(j)W(j)$. The Fourier transforms $A_k(n)$ of these sequences are obtained:

$$A_k(n) = \frac{1}{L} \sum_{j=0}^{L-1} X_k(j)W(j)e^{-i\frac{2\pi kn}{L}}. \quad (10)$$

The periodograms are:

$$I_k(f_n) = \frac{L}{U} |A_k(n)|^2, \quad (11)$$

where:

$$f_n = \frac{n}{L}, U = \frac{1}{L} \sum_{j=0}^{L-1} W^2(j).$$

The spectral estimate is the average:

$$\hat{P}(f_n) = \frac{1}{K} \sum_{k=1}^K I_k(f_n). \quad (12)$$

A two-seconds window with 50% overlap was used, encoding frequencies between 0 and 500 Hz at 0.5 Hz resolution. Figure 3.A shows global spectral power distribution, emphasizing theta, alpha, and beta bands (5-35 Hz) with age-related changes.

Due to the imbalance between the number of participants and the number of spectral features (ROIs x PSD), there is a risk of data sparsity, which can make it difficult for the model to identify

meaningful patterns. Therefore, PCA was selected for dimensionality reduction. Figure 3.B illustrates the explained variance for the first 20 components for each ROI within each atlas. The cross indicates that the first 10 components are sufficient to explain at least 90% of the variance for all ROIs, leading to a 99% reduction in the search space.

These 10 principal components were then concatenated with the structural features generated in Section 3.3.1 to create the annotations for the graphs described in sections 3.2.2 and 3.3.2.

3.2.2 Functional Connectivity

Functional connectivity involves examining the statistical relationships and temporal dependencies among distinct brain regions or neuronal populations [26]. In neuroimaging, it measures the extent to which activities in different brain areas correlate or synchronize over time.

The observed co-activation patterns between brain regions indicate the brain's functional network organization [88]. High synchronization implies that spatially separated regions of interest (ROIs) participate in similar neural processes, while low connectivity suggests reduced coordination among these regions. Aberrant connectivity can indicate various neurological and psychiatric conditions. To calculate the degree of synchronization, the amplitude envelope correlation (AEC) [6] was used.

The AEC uses amplitude envelopes to derive Pearson correlation coefficients between all pairs of ROIs. First, the Hilbert transform [10] decomposed the time series into the time-frequency domain for envelope computation. The Hilbert transform $\mathcal{H}[x(t)]$ of a signal $x(t)$ is expressed as:

$$\mathcal{H}[x(t)] = \frac{1}{\pi} \int_{-\infty}^{\infty} \frac{x(t-\tau)}{\tau} d\tau = a_{\tilde{x}}(t)e^{j\phi_{\tilde{x}}(t)}. \quad (13)$$

The result, denoted as $\tilde{x}(t)$, is an analytic signal—a complex time series associated with the original data time series, $x(t)$, where the modulus $a_{\tilde{x}}(t)$ and phase $\phi_{\tilde{x}}(t)$ of $\tilde{x}(t)$ correspond to the instantaneous amplitude (or envelope) and

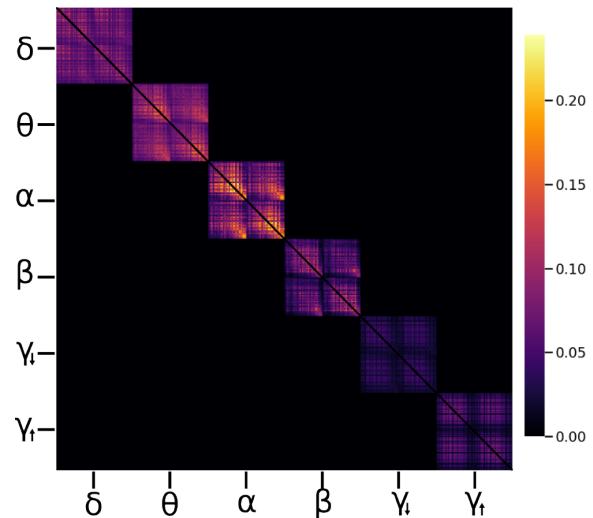


Fig. 4. Mean functional connectomes computed using the orthogonalized AEC for each of the six canonical bands (delta, theta, alpha, beta, low-gamma, and high-gamma) from the 606 subjects. This heatmap, built by diagonalizing the mean connectomes for each band, is for visualization purposes. Each connectome was used individually

instantaneous phase of the original time series $x(t)$, respectively.

To derive power envelopes for correlation analysis, a crucial step involves orthogonalizing the two signals that may be correlated [39]. This ensures that the signals do not share trivial co-variability in power from measuring the same sources, while preserving co-variation related to different sources.

The orthogonalized AEC was used to compute the individual functional connectivity matrices, or functional connectomes, derived for each typical frequency band of electrophysiology to determine whether certain brain rhythm ranges better explain age differentiation, as shown in Figure 4. MEG signals were bandpass filtered into delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–50 Hz), and high gamma (50–150 Hz) frequency bands.

Given that the AEC returns the pairwise correlation value, the resulting connectome is a fully connected graph $\mathcal{G} = \{\mathcal{V}, \mathcal{E}, \mathbf{A}\}$, with entries in the adjacency matrix $\mathbf{A}(i, j)$ representing

the strength or number of connections between ROIs, containing non-relevant connections (low correlation values). To generate a sparse graph, the connectomes were thresholded using Kruskal's Minimum Spanning Tree (MST) algorithm [48]. Finally, the diagonals of each connectome (autocorrelation) were set to zero.

Calculating the Pearson correlation for all pairwise regions has a computational complexity of $O(n^2)$. Given that six different narrowband frequencies were used for 606 subjects, the functional connectome was computed only using the DK atlas. Each of these connectomes yields a 68×68 symmetric connectome matrix.

3.3 MRI Data Preprocessing and Feature Extraction

The preprocessing of the raw NIFTI data in Brain Imaging Data Structure (BIDS) format from the Cam-CAN repository was executed utilizing the official singularity container images. The processing of anatomical MRI data was conducted using the FreeSurfer 6.0 recon-all pipeline [15]. FreeSurfer is specialized in preprocessing MRI data and includes a series of steps for thoroughly processing T1-weighted (T1w) anatomical images. Briefly, the preprocessing involves motion correction to enhance the signal-to-noise ratio, addressing intensity non-uniformities (INU) in the T1w images to ensure consistency, removal of non-brain tissues through skull-stripping, tissue segmentation to delineate different anatomical structures, and surface reconstruction for detailed cortical analyses. Finally, spatial normalization aligns T1w images to a standard space using the MNI-152 template, facilitating cross-subject comparisons.

Once the surface was reconstructed, the cortex was parcellated into 68 and 200 Regions of Interest (ROIs) based on the Desikan-Killiany (DK) [21] and Schaefer-200 (s200) [69] atlases, respectively.

Preprocessing of dMRI data was conducted using QSIprep 0.17.0 [8]. The dMRI preprocessing steps included denoising, Gibbs-ringing artifact removal, bias field correction, intensity normalization, head-motion estimation and

correction for eddy currents, as well as registration and normalization to a standard space.

For the reconstruction of the structural connectivity matrices, we employed the `mrtrix_multishell_msmt_ACT-hsvs` pipeline. Tissue fiber response functions were estimated using the Dhollander algorithm [22], and fiber orientation distributions (FODs) were estimated using the multi-shell multi-tissue constrained spherical deconvolution (MSMT-CSD) algorithm. Probability tractography was implemented using the iFOD2 probabilistic tracking method. Anatomically-constrained tractography (ACT) was applied, incorporating T1-weighted segmentation constraints. The T1w segmentation used FreeSurfer outputs from the anatomical processing steps, enabling the hybrid surface volume segmentation (HSVS) method. Streamline weights were calculated using the SIFT2 algorithm, ensuring a refined representation of white matter connections.

3.3.1 Gray Matter Morphometry

Once the T1-weighted image has been reconstructed, gray matter can be segmented to extract morphological measurements. Gray matter segmentation relies on image processing algorithms to define the inner/outer boundaries of the cortex at the gray/white matter (white matter surface) and gray matter/cerebrospinal fluid interfaces (pial surface) represented by the red and yellow curves in the top left panel of Figure 5 and the embedded volumes in the bottom panel.

Post-preprocessing, FreeSurfer (see Section 3.3) derives the gray matter morphometry (GMM) values for each ROI encompassing: Surface area [84], cortical thickness [53], gray matter volume [84], mean and gaussian curvature [65], intrinsic curvature index [65], folding index [70], and number of vertices.

All of these features were computed to be used as node attributes in the connectomes generated by the tractography (Section 3.3.2) and functional connectivity for the DK and s200 atlases, respectively. The GMM, were concatenated with the spectral features generated

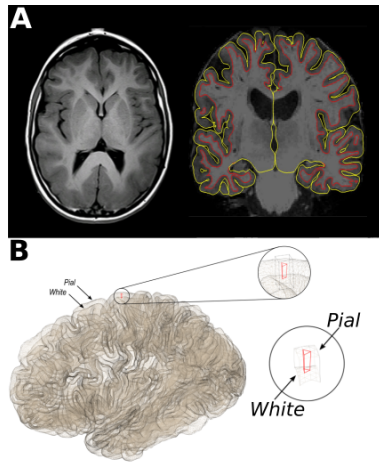


Fig. 5. T1-weighted image and surface segmentation. A) Transverse view MRI image before non-brain tissue removal. In the right panel, a coronal view of a skull-stripped MRI image depicts segmented gray matter between the white matter surface (red) and the pial surface (yellow) (adapted from [56]). B) Surface representation of the cortex, delineated internally by the white matter and externally by the pial surface. Additionally, the red triangular prism represents the proposed solution for measuring cortical volume (adapted from [84])

in Section 3.2.1 to generate the annotations for the graphs described in Sections 3.2.2 and 3.3.2.

3.3.2 Structural Connectivity

Once the fiber tracts are generated, as explained in 3.1.2, a reconstruction of the tracts similar to that in figure 6 is obtained. The structural connectivity matrix, or structural connectome, is computed to represent the structural connections between different ROIs. Here, the whole brain connectome was computed using the s200 atlas. The functional connectome $\mathcal{G} = \{\mathcal{V}, \mathcal{E}, \mathbf{A}\}$, with entries on the adjacency matrix $\mathbf{A}(i, j)$, represents the number of connections between ROIs.

To generate a sparse graph, the connectomes were thresholded using Kruskal's Minimum Spanning Tree (MST) algorithm [48] keeping 15% of the connections. Finally, the diagonal of each one of the connectomes (autocorrelation) was set to zero. Figure 7 shows the mean

normalized connectome and standard deviation for the 606 subjects.

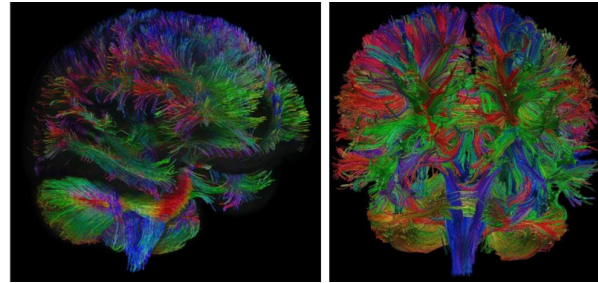


Fig. 6. Example whole-brain fibre-tracking results from human healthy subject (left-right/front-back/up-down)

3.4 Graph Convolutional Network

Classic convolutional neural network (CNN) models designed for grid-like data, such as images, have demonstrated considerable success in medical assistive diagnosis models [19, 77, 27]. The efficacy of these models relies on inherent properties of grid-like data, specifically: (1) a fixed number of neighboring pixels for each pixel and (2) a naturally determined spatial order when scanning images, i.e., from left to right and top to bottom. However, in arbitrary graph data, unlike images, neither the number of neighboring units nor their spatial order is fixed.

In this context, our focus is on Graph Convolutional Network (GCN) models applied to undirected connected graphs $\mathcal{G} = \{\mathcal{V}, \mathcal{E}, \mathbf{A}\}$. The functional and structural connectomes used in our study give rise to such graphs, consisting of a set of nodes $\mathcal{V}$ with $|\mathcal{V}| = n$, a set of edges $\mathcal{E}$ with $|\mathcal{E}| = m$, and an adjacency matrix $\mathbf{A}$. If there is an edge between node i and node j , the entry $\mathbf{A}(i, j)$ denotes the weight of the edge; otherwise, $\mathbf{A}(i, j) = 0$:

$$A_k(n) = \frac{1}{L} \sum_{j=0}^{L-1} X_k(j) W(j) e^{-i \frac{2\pi k j}{L}}. \quad (14)$$

Node attributes are represented as $\mathbf{X} \in \mathbb{R}^{n \times d}$, where d is the length of the attributes for each node n . In our case, these attributes include the concatenated PCA(PSD) and GMM features for

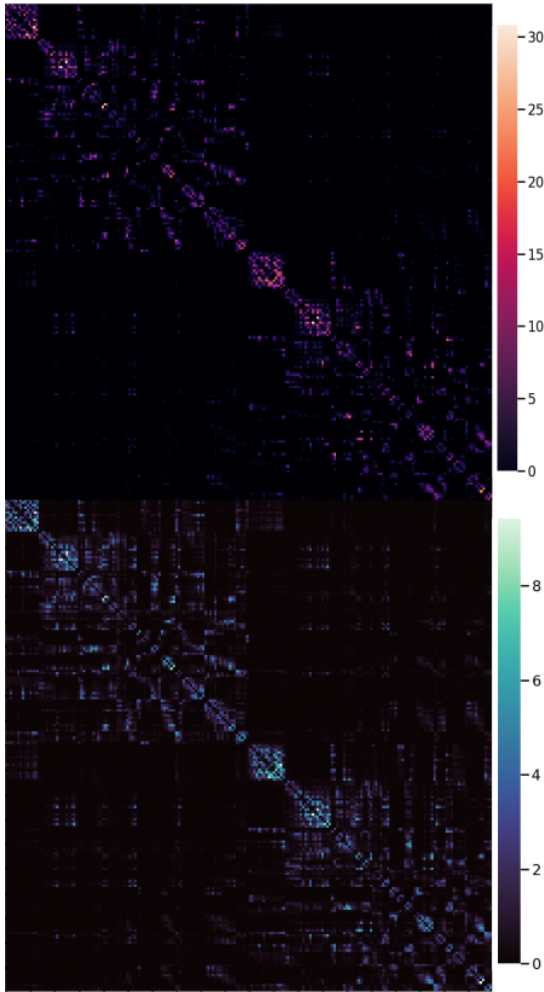


Fig. 7. Mean and Standard Deviation structural connectome computed from the 606 subjects

each ROI. The multi-layer GCN used, follows the layer-wise propagation rule:

$$\mathbf{H}^{(l+1)} = \sigma \left(\hat{\mathbf{D}}^{-\frac{1}{2}} \hat{\mathbf{A}} \hat{\mathbf{D}}^{-\frac{1}{2}} \mathbf{H}^l \mathbf{W}^l \right). \quad (15)$$

Here, $\hat{\mathbf{A}} = \mathbf{A} + \mathbf{I}_N$, equivalent to adding self-loops to the original graph. $\mathbf{I}_N$ is the identity matrix, $\hat{\mathbf{D}}_{ii} = \sum_j \hat{\mathbf{A}}_{ij}$ is used for neighborhood normalization, and $\mathbf{W}^l$ is a layer-specific trainable weight matrix. $\sigma(\cdot)$ denotes an activation function, such as $\text{ReLU}(\cdot) = \max(0, \cdot)$. $\mathbf{H}^l \in \mathbb{R}^{n \times d}$ is the matrix of activations in the l^{th} layer, with $\mathbf{H}^0 = \mathbf{X}$.

This layer-wise approach implies that in each layer, a node u updates its attributes by aggregating information only from nodes $\{\forall v \in \mathcal{N}\{u\}\}$. The addition of more layers allows the aggregation of more distant neighbors.

The output of the final layer can then be used to define the embeddings for each node, i.e:

$$\mathbf{z}_u = h_u^k, \forall u \in \mathcal{V}, \quad (16)$$

where k represents the last layer. However, caution is warranted as a very deep network may oversample the graph and, in the worst case, cover the entire graph.

Let's recall that the graphs in question represent individualized connectomes, and our objective is to forecast a property related to the entire graph - specifically, the biological age of the subjects. In contrast to learning a node-level embedding $\mathbf{z}_u$, we aim to acquire a graph-level embedding $\mathbf{z}_G$. This undertaking is commonly termed "graph pooling," as it involves aggregating node embeddings to derive an embedding that encapsulates the entire graph.

The pooling function f_p , which has to be ordering and permutation invariant, maps a set of node embeddings $\{\mathbf{z}_1, \dots, \mathbf{z}_{|V|}\}$ to an embedding $\mathbf{z}_G$. The global embedding can be used as an input for a multi-layer perceptron (MLP) to perform graph-level prediction or classification tasks. To compute the global embeddings, the node level embeddings were vectorized into a long array:

$$\mathbf{z}_G = [\mathbf{z}_1, \mathbf{z}_2, \dots, \mathbf{z}_N], \quad N = |V| \times C, \quad (17)$$

allowing for the full exploration of the search space by the MLP.

This approach is only possible due to the MST thresholding implemented, since it assures the preservation of all nodes.

Figure 8 illustrates the architecture used in the present work. We believe that there is significant value in preserving residual information within each layer and inspired by the architectural principles of residual networks [37], we propose concatenating the outputs from each convolutional layer and linearly combining them using a fully connected layer.

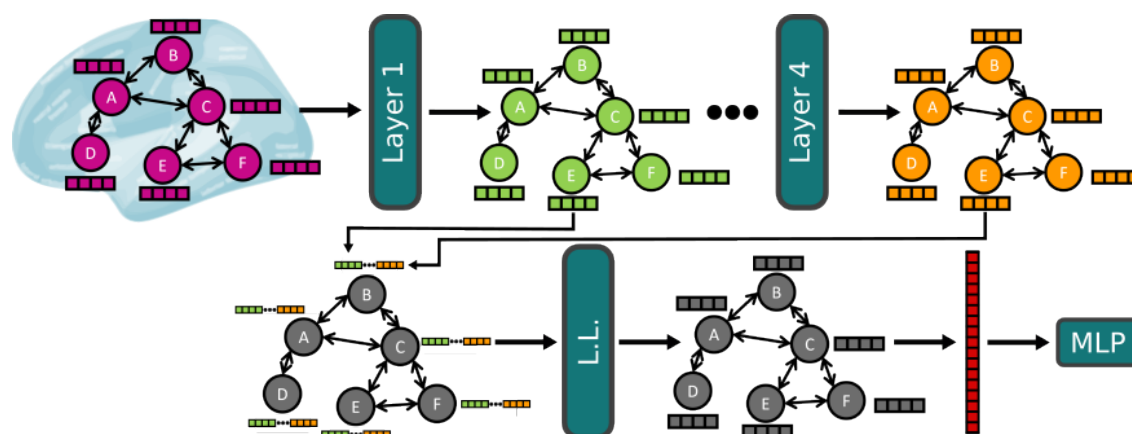


Fig. 8. Graph Convolutional Network architecture comprising 4 convolutional layers, with each layer's output concatenated to preserve residual information. These connected embeddings undergo dimensional reduction via a fully connected linear layer (L.L.). The resulting output is flattened and utilized as features for the Multi-Layer Perceptron (MLP)

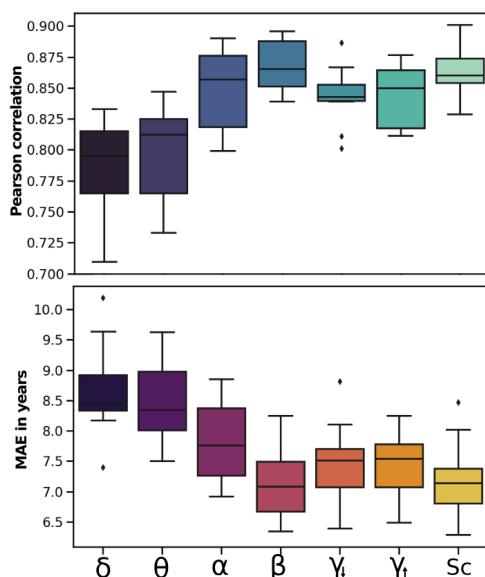


Fig. 9. Boxplots representing the performance of the Graph Convolutional Network (GCN) model evaluated over 10 training iterations. The y-axis shows the Pearson correlation and the Mean Absolute Error (MAE) in years (bottom panel), computed using the predicted and chronological age. The x-axis indicates the type of connectome used: delta, theta, alpha, beta, gamma low, gamma high functional connectomes, or the structural connectome. Each boxplot summarizes the model's performance, highlighting the variability and central tendency across different connectomes

4 Results

In this study, we employed Graph Convolutional Networks (GCNs) on graphs generated from functional and structural connectivity matrices, derived from resting-state MEG and dMRI to explore the significance of brain topology in predicting brain age. The graphs were annotated using concatenated PSD and GMM features extracted from each node (ROIs). The dataset consisted of 606 subjects from the Cambridge Center for Aging Neuroscience (Cam-CAN) repository.

The data was divided into three subsets: 62% for training, 8% for validation, and 30% for testing. The model was trained and tested 10 times using each graph.

The model's performance was evaluated using seven different graphs: six constructed from the AEC functional connectivity matrices computed across the canonical frequency bands (delta, theta, alpha, beta, low gamma, and high gamma), and a seventh based on the structural connectome derived from dMRI data. This comprehensive approach allowed us to assess both functional and structural aspects of brain connectivity.

Figure 9 presents a summary of our results. The boxplots show the Pearson correlation between the predicted and chronological age (top), as a

measurement of regression accuracy, and the mean absolute error (MAE) in years (bottom) for each graph.

The results indicate that the most informative graphs are those built from the alpha and beta functional connectomes, as well as the structural connectome. The best results obtained by each of these connectomes were $R=[.86, .89, .90]$ and $MAE=[7.4, 6.4, 6.3]$ years, respectively.

5 Conclusion

In this study, we demonstrated the effectiveness of using GCNs to predict brain age by integrating functional and structural connectivity data derived from resting-state MEG and dMRI. By evaluating the performance of the GCN on graphs constructed from the six canonical frequency bands (delta, theta, alpha, beta, gamma low, and gamma high) as well as a structural connectome, we highlighted the importance of incorporating both functional and structural information for accurate brain age prediction.

Our results demonstrated that the alpha and beta functional connectomes, along with the structural connectome, provided the most informative structures. These were closely followed by the gamma band, while the graphs constructed using the delta and theta bands were the least informative. These findings highlight the significance of specific frequency bands and structural connectivity in capturing the complex dynamics of brain morphology in aging.

The results are consistent with previous scientific publications: M/EEG PSD and connectomics have shown that lower frequency bands, such as delta and theta, exhibit increased activity in older adults, reflecting age-related changes in cognitive processes and brain function. However, these bands alone may not be the most effective predictors of brain age compared to higher frequency bands [36]. Research on the alpha band indicates that alpha power and coherence decrease with age, which is associated with cognitive decline and neural network reorganization, making alpha band characteristics highly informative for predicting brain age [68].

The beta activity also shows age-related changes, including shifts in power and frequency that correlate with cognitive and motor functions, though it might not be as strongly predictive of brain age as the alpha band [66, 81].

Gamma band activity is associated with higher cognitive functions and tends to decrease with age, with changes in gamma activity reflecting neural processing efficiency and network integrity, making it a valuable predictor for brain age [30]. Additionally, structural connectivity in the aging brain shows significant declines in white matter integrity, making it highly informative [3].

A key strength of GCNs, as demonstrated in this study, is their ability to effectively model non-Euclidean data structures inherent in brain networks. Traditional machine-learning approaches, often require vectorization or rely on Euclidean assumptions that may overlook critical topological information. As reviewed in section 2, SVMs have shown efficacy in vectorized gray matter volume images but fail to account for the spatial relationships within the brain's connectome.

Similarly, while 3D CNNs can capture age-related morphological changes with high accuracy, they do not inherently accommodate the graph-based nature of brain connectivity. The present work addresses this limitation by effectively modeling the brain's connectivity patterns, integrating both functional and structural information into a cohesive predictive framework, allowing for a more detailed and accurate representation of the brain's functional and structural networks.

The success of the GCN model in predicting brain age highlights the importance of preserving the spatial and topological integrity of the data. This demonstrates the potential of graph-based deep learning approaches in neuroimaging studies and represents an advancement in the field of computational neuroscience.

This approach not only offers a promising pathway for advancing research and improving our ability to monitor and understand the aging brain, but also provides a robust tool for early detection of atypical aging patterns, which could indicate neurodegenerative conditions.

Acknowledgments

The Instituto Politécnico Nacional funded this research through the project SIP20240187. We thank CONAHCyT for partial support of the present work. The data supporting reported results can be found at the link in the footnote³.

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³<https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/>

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Article received on 19/08/2024; accepted on 10/09/2026.

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