



University of São Paulo

TAMIRES CORRÊA MARÇAL

Comprehensive Study of Cortical Thickness and Thinning in the
Lifespan Combining MRI, Laminal Architecture, and Machine
Learning

Ribeirão Preto, São Paulo - Brazil

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Dissertation presented to the Neurology
Program (Neuroscience) of the School of
Medicine of Ribeirão Preto at USP.

Advisor: Prof. PhD. Carlos Garrido Salmon

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Espessamento Cortical, Citoarquitetura, Aprendizado de Máquina, Ressonância Magnética, Envelhecimento Saudável, Poda Neural, Neuroplasticidade.

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Abstract

Title: Comprehensive Study of Cortical Thickness and Thinning in the Lifespan
Combining MRI, Laminar Architecture, and Machine Learning

Cortical thinning is associated with pruning, neuroplasticity, and cognitive decline throughout the different phases of the lifespan. While age is a crucial factor in predicting thinning, it does not account for all its variability. To advance our comprehension of this process, we utilize Magnetic Resonance Imaging data, a Multivariate Dataset, and Machine Learning techniques. Our objective is to predict cortical thickness and thinning by analyzing a diverse set of temporal and spatial variables, including age, cortical type, lobes, brain structures, curvature, and cytoarchitectonic information. To achieve that we utilized anatomical MRI of 871 participants without a history of neurological diseases to estimate cortical thinning trajectories throughout the lifespan. We also used cytoarchitecture profiles that were estimated based on the BigBrain database. To assess the optimal method for modeling cortical thickness, we developed models based on both vertex-level and brain-structure-level. We found that the brain-structures model outperformed the vertex-level approach in predicting thickness, being able to explain 87% of its variability. To predict thinning, we began by calculating human annual cortical thinning, following which we utilized a boosting algorithm to predict thinning using three different models. A temporal model (age as only variable) achieved an r-squared of 0.79, a spatial model (all variables except age) had a score of 0.58, and temporal-spatial reached 0.84. Through the use of Shapley additive explanations in the temporal-spatial model, we see the contribution and interactions of each variable to cortical thinning. Age

was the feature that most contributed to the cortical thinning, followed by layer I thickness, cortical thickness at 10y.o. and layer IV thickness. Our examination suggests that regions that experience more thinning during development tend to undergo less thinning during aging, and this correlation is linked to Layer I thickness.

Keywords: Cortical Thinning, Cytoarchitecture, Machine Learning, Magnetic Resonance Imaging (MRI), Healthy Aging, Pruning, Neuroplasticity

Resumo

Título: Estudo abrangente da espessura e afinamento cortical ao longo da vida, combinando Ressonância Magnética (MRI), Arquitetura Laminar e Aprendizado de Máquina

O afinamento cortical está associado à poda neural, neuroplasticidade e declínio cognitivo ao longo das diferentes fases da vida. Embora a idade seja um fator crucial na previsão do afinamento, ela não explica toda a sua variabilidade. O intuito deste estudo é avançar a compreensão desse processo, utilizando dados de Ressonância Magnética, dados multivariados e técnicas de Aprendizado de Máquina. Nosso objetivo é prever a espessura e o afinamento cortical por meio da análise de um conjunto diversificado de variáveis temporais e espaciais, incluindo idade, tipo cortical, lóbulos, estruturas cerebrais, curvatura e informações citoarquitetônicas. Para isso, utilizamos imagens de Ressonância Magnética anatômica de 871 participantes sem histórico de doenças neurológicas para estimar as trajetórias de afinamento cortical ao longo da

vida. Também utilizamos perfis citoarquitetônicos estimados com base nos dados do BigBrain. Para avaliar o método ideal de modelagem da espessura cortical, desenvolvemos modelos baseados em nível de vértice e nível de estrutura cerebral. Descobrimos que o modelo de estruturas cerebrais superou a abordagem de nível de vértice na previsão da espessura, sendo capaz de explicar 87% de sua variabilidade. Para prever o afinamento, começamos calculando o afinamento cortical anual humano e, em seguida, utilizamos um algoritmo de *boosting* para prever o afinamento usando três modelos diferentes. Modelo temporal (idade como única variável) atingiu um r-quadrado de 0.79, modelo espacial (todas as variáveis, exceto idade) teve uma pontuação de 0.58, e modelo temporal-espacial atingiu 0.84. A idade foi a característica que mais contribuiu para o afinamento cortical, seguida pela espessura da camada I, espessura cortical aos 10 anos e espessura da camada IV. Nossa análise sugere que as regiões que experimentam mais afinamento durante o desenvolvimento tendem a sofrer menos afinamento durante o envelhecimento, e essa correlação está ligada à espessura da camada I.

Palavras-chaves: Espessamento Cortical, Citoarquitetura, Aprendizado de Máquina, Ressonância Magnética, Envelhecimento Saudável, Poda Neural, Neuroplasticidade.

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1. Introduction

The human brain is a complex and dynamic organ that undergoes remarkable transformations throughout an individual's life span. These transformations occur at various levels, encompassing cognitive, anatomical, and cellular processes. One of these brain transformations is cortical thinning, which is the reduction of cortical thickness that occurs after childhood as a person ages. Human cortical thickness varies throughout the lifespan and cortical areas [1-3]. Understanding the patterns and variations of cortical thinning in different cortical regions and stages of life is essential for gaining insight into the underlying mechanisms of brain development and aging.

The assessment of in vivo cortical thickness through neuroimaging techniques, specifically Magnetic Resonance Imaging (MRI), plays a significant role in elucidating the structural and functional aspects of the human brain. MRI is chosen primarily for its capacity to provide clear soft tissue contrast, predominantly through high-resolution 3D T1-weighted imaging, enabling precise delineation of cortical boundaries.

Cortical thickness, a fundamental parameter in the study of brain morphology, is defined as the distance between the gray-white matter boundary and the pial surface. This measurement requires the establishment of a computational mesh, dividing the cortical mantle into vertices for localized thickness estimations. Several available software tools, such as FreeSurfer, facilitate this intricate process. Nevertheless, it is essential to acknowledge that despite achieving millimeter-level spatial resolution through MRI, cortical thickness exists at a submillimeter scale due to the interpolation inherent in the mesh approximation. Furthermore, it is imperative to note that the current

spatial resolution does not enable the visualization of individual cortical layers, underscoring the reliance on inferential methods to reveal the functional implications of cortical thickness variations. This comprehensive approach to cortical thickness measurement via MRI contributes to a foundational understanding of brain structure while acknowledging the inherent methodological constraints.

1.1. Cortical Thinning in Healthy Development and Aging

Cortical Thickness and Thinning are relevant biomarkers of brain transformation. Cortical thickness refers to the measure of the gray matter's depth within the cerebral cortex, while thinning refers to the reduction in this cortical thickness over the lifespan. These measures serve as crucial indicators of brain health and are known to exhibit correlations with both cognitive abilities and cellular processes. Through the examination of these associations, we acquire elucidations regarding the fundamental mechanisms that underlie brain development, neuroplasticity, aging, and neurodegenerative disorders.

Cortical thinning has been associated with pruning [4-6], neuroplasticity [7-8], and cognitive decline [9]. Thinning has been demonstrated to be not associated with a decrease in the number of neurons [10], but rather it is connected with dendritic shrinking, growth, and several architectural aspects of the cortex [11-13]. Cortical thickness changes correlate with cognition changes and neuroplasticity, which can be measured by executive performance, education, intelligence, physical exercises and musical tasks [14-19]. However, it is not well known how cortex architecture and

cognitive aspects connect in a way that comprehends the decrease of neuroplasticity in development and the cognitive decline in aging. Understanding the neurobiological correlates underlying cortical thickness variations throughout development, mid-life and aging might help explain why thinning and thickening are more likely to occur in certain brain networks.

The investigation of the cellular underpinnings of cortical thickness has emerged as a captivating avenue of scholarly inquiry, offering insights into the intricate cellular processes that contribute to the growth and maintenance of cortical neurons, encompassing phenomena such as dendritic arborization, synaptogenesis, and myelination. Studies have unveiled compelling associations between cortical thickness and cellular markers, thus indicating that perturbations in these processes may exert a substantial influence on cortical thickness and subsequently impact cognitive functioning. Elucidating these intricate connections illuminates the underlying biological mechanisms that orchestrate brain development and plasticity.

Moreover, cortical thinning has been established as a crucial domain with profound cognitive and functional implications. Longitudinal investigations have consistently demonstrated that cortical thinning is a natural consequence of aging, exhibiting regional variability in its rate of occurrence [20]. This cortical thinning has been closely linked to cognitive decline and an elevated susceptibility to neurodegenerative pathologies, including Alzheimer's disease [21]. Thorough investigations of the cortex lifespan trajectories offer a unique vantage point for unraveling the intricate interplay between brain structure and function throughout different life stages. By comprehending these transformations, researchers can pave the way for targeted interventions and

therapies aimed at preserving brain health and optimizing cognitive function across the entire span of life.

Further looking into the brain trajectory milestones, pruning and cognitive decline are unveiled as strong markers of the beginning and end of human lifespan. Pruning is a crucial developmental phase in the maturation of the nervous system, characterized by a reduction in synaptic connections, a decrease in cortical thickness, and heightened neuroplasticity potential [22-24]. This process is marked by cortical thinning, which is instrumental in refining neural circuitry and optimizing neural efficiency. Pruning plays a fundamental role in shaping the connectivity and functionality of the brain by eliminating unnecessary or redundant synaptic connections, allowing for more efficient information processing and integration.

In contrast, cognitive decline observed in healthy aging represents a distinct phase accompanied by impairments in both physiological and cognitive functions. This age-related decline is associated with a decrease in cortical thickness, diminished neuroplasticity potential, and a heightened vulnerability to neurodegenerative diseases [20-21, 25]. Similar to pruning during development, cortical thinning is a notable characteristic of cognitive decline in healthy aging. However, unlike developmental pruning, this thinning is often indicative of compromised cognitive abilities and increased susceptibility to neurodegeneration [9].

Understanding the differential manifestations of cortical thinning in pruning and cognitive decline is of paramount importance. Pruning during development reflects a process of neural refinement and optimization, driven by synaptic elimination and

cortical thinning. In contrast, cortical thinning observed during cognitive decline in healthy aging is correlated to decline in cognitive function and the exacerbation of neurodegenerative diseases. Further exploration of the underlying mechanisms and factors influencing cortical thinning in both processes is necessary for elucidating the neural basis of development and aging and may aid in the development of interventions to mitigate cognitive decline in older adults.

1.2. Cortical Microscopical Properties

In this study, we focus our analysis in the cerebral cortex, which is a complex and intricate structure that plays a pivotal role in our cognitive abilities, sensory perception, and motor control. Defined as the outermost layer of the brain, the cortex is characterized by its convoluted appearance, consisting of a vast network of interconnected neurons. Studying the cortex is valuable due to its role in high-functioning cognitive processes, offering insights into lifelong changes in the brain, such as how neuroplasticity evolves over time.

At a microscopic level, the cortical cytoarchitecture refers to the cellular organization and arrangement within the six distinct layers of the cerebral cortex. Each layer possesses unique structural and functional characteristics that contribute to the overall complexity and functionality of the cortex. These layers are composed of different types of neurons, glial cells, and intricate connections that facilitate information processing. The cytoarchitecture of the cortex forms the foundation upon which various

cognitive processes are built, making it a critical area of investigation in neuroscience research.

Figure 1: Cortical Laminar Architecture and Connectivity.

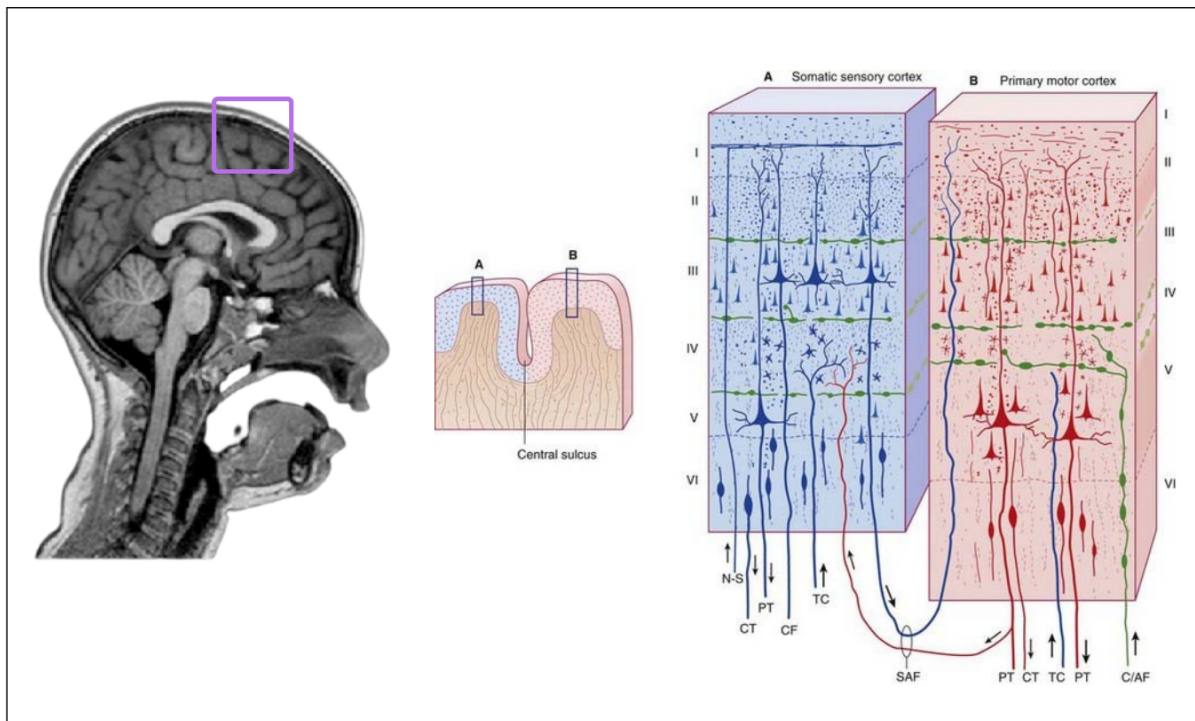


Figure 1: (a) Somatosensory cortex: N-S, non-specific; CT, corticothalamic fiber passing from fusiform neuron to ventral posterior nucleus of thalamus; PT, pyramidal tract fiber running from large pyramidal neuron to a sensory relay nucleus; TC, thalamocortical afferent from ventral posterior nucleus of thalamus; SAF, short association fiber passing to the motor cortex. (b) Primary motor cortex: SAF, short association fiber collateral passing to somatosensory cortex; PT, pyramidal tract fiber running to motor nucleus in brainstem or spinal cord; CT, corticothalamic fiber passing to ventral lateral nucleus of thalamus; TC, thalamocortical afferent from ventral lateral nucleus of thalamus; PT as above; C/AF, cholinergic or aminergic fiber. Adapted from "Clinical Neuroanatomy and Neuroscience" by Drs. M. J. T. FitzGerald Gregory Gruener and Estomih Mtui [26].

Layer I, also known as the molecular layer, contains few neuronal cell bodies and consists mainly of dendritic and axonal projections - corticocortical connections and subcortical projections. Layer II, the external granular layer, primarily houses small pyramidal neurons and interneurons involved in local processing. Layer III, the external pyramidal layer, is home to most medium-sized pyramidal neurons and is the principal source of corticocortical efferents. Layer IV, the internal granular layer, receives sensory inputs, is characterized by densely packed granule cells and is the main target of thalamocortical afferents. Layer V, the internal pyramidal layer, harbors large pyramidal neurons that project to subcortical structures, enabling motor control and execution. Lastly, Layer VI, the multiform layer, contains diverse neuronal types and provides feedback connections to other cortical regions and subcortical structures.

The layers have different thicknesses, which vary according to their cortical regions. They also play different functions associated with its microstructure. Layers III and V are predominantly responsible for sending information output (i.e., efferent pathways), while layers II and IV are primarily for receiving information inputs (i.e., afferent pathways). Layer I predominantly connects corticocortical structures. The cortical layers exhibit distinct characteristics across different functional areas of the cortex. In the motor cortex, there is a notable prominence of layer V, which is primarily responsible for sending motor commands and executing motor functions. Conversely, in sensory cortex regions, layer IV tends to be more prominent, as it is primarily associated with receiving sensory input and processing sensory information. However, in the associative cortex, there is no clear predominance of any specific cortical layer. This lack of predominance suggests a balanced integration of both input and output functions,

allowing for the complex integration and processing of information that is typically associated with higher-order cognitive functions. Each cortical layer's unique microstructural characteristics and connectivity patterns contribute to the intricate neural network responsible for the cognitive processes. As we age, alterations in cognitive functions occur. Exploring the relationship between cortical layer composition and cognitive changes across the lifespan represents a novel venture. It involves investigating how different atrophy rates in cortical structures, possibly influenced by the distinctive properties of cortical layers, contribute to variations in cognitive abilities.

1.3. Research Aim

Our objective is to enhance our understanding of cortical thinning by incorporating MRI, Cytoarchitecture, and Machine Learning techniques. We aim to explore this phenomenon across different scales, considering its implications for neuroplasticity during both developmental stages and healthy aging. By gaining a comprehensive comprehension of the neurobiological correlates associated with changes in cortical thickness, we can identify specific brain networks where thinning and thickening are more likely to occur. Such knowledge could establish the groundwork for targeted interventions and therapies, fostering brain health and optimizing cognitive function throughout an individual's lifespan.

In this study, we aim to predict cortical thickness and thinning by examining a diverse set of temporal and spatial variables, including age, cortical type, lobes, brain structures, curvature, and cytoarchitectonic information. Previous research has

individually shown correlations between thickness and thinning with age [27], cytoarchitectonic composition [11-12], and curvature [28]. However, to the best of our knowledge, previous studies have only been able to explain up to 59% of the variance in cortical thickness [27], predominantly through univariate analyses. Our approach, in contrast, is inherently multivariate, as we focus on exploring how these various features interact and jointly contribute to the complexities of thinning and thickness variations.

We utilized Magnetic Resonance Imaging (MRI) scans of 871 participants to estimate cortical thinning variation throughout the lifespan and cortical regions. We implemented regression models based on the cortical thickness and thinning of all participants and used a multiscale [29] approach to investigate the role of different variables, including spatial and temporal features, curvature, and cytoarchitectonic profile, in predicting cortical thinning. To assess the optimal method for modeling cortical thickness, we developed models based on both vertex-level and brain-structure-level. We also used the Light Gradient Boosting Machine (LightGBM) method and SHapley Additive exPlanations (SHAP) technique to model and explain the contribution of each feature to individual model output, respectively [30-31]. By implementing the merge of different scale databases and using appropriate mathematical methods, we aim to showcase a modeling framework that focuses on the integration of data from different fields of neuroscience.

2. Methods

2.1. Neuroimaging Data

We used brain MRIs from the Nathan Kline Institute, made available through the International Neuroimaging Data-Sharing Initiative [32], to obtain a geometrical characterization of the individuals' cerebral cortices. The images were 3D T1-weighted (3DT1w) acquired in Magnetic Resonance 3T scanners using MP-RAGE acquisition.

2.2. Neuroimaging Processing

Neuroimaging representation of the cortical surface is a composition of vertices - values in a regular grid in three-dimensional space. To start working with this cortical data, we did anatomic segmentation to identify the cortex and then extracted the geometric information of each node in the cortex from each 3D-T1w image. For these tasks, we selected FreeSurfer, a well-known neuroimaging tool. It reconstructs the cortex surface using approximately 300,000 nodes and estimates the thickness and other geometrical properties of the cortex. We executed this pipeline on neuroimages from over 871 participants (8-83 y.o.). Also, we used two atlases for a cortical parcellation: Desikan–Killiany–Tourville (DKT) and Von Economo.

The DKT parcels the brain in 95 structures and is the default of neuroimaging processing. The traditional Von Economo parcels the brain in 107 structures, and it is the foundation of a public database providing thickness information for each cortical layer. Each atlas assigned each cortical vertex to one of its areas, and this information became a categorical feature in the modeling step along with the geometric information.

The image processing pipeline underwent parallel execution within a computer cluster, comprising three key methods: "mri_convert," "recon-all," and "mris_ca_label." The first method, "mri_convert," was employed to convert data from the .nii format to .mgz. The second method, "recon-all," performed mesh reconstruction and geometric characterization of the brain. The third method, "mris_ca_label," facilitated a novel segmentation procedure not incorporated in the default functionality of FreeSurfer. To accomplish this parallel processing, we harnessed the computational resources of the NeuroMat cluster, utilizing eight nodes each equipped with a memory capacity ranging from 128 GB to 192 GB. Furthermore, the cluster workload management was administered through SLURM, ensuring efficient task distribution and execution.

Furthermore, we created Python functions to monitor the neuroimage processing pipeline. The monitoring returned a database with all participant data that had been processed. There are two formats of return: vertex-wise and brain-structure-wise. The first format is the data without alteration and the second is the data with an aggregation according to Von Economo Atlas structures. We also gather information about the participants, the duration of each image processing, and any processing errors.

For data exclusion criteria, we did a quality assessment to eliminate data from neuroimages with artifacts. We looked at the distribution of geometric variables of the cortical structures of all images. We eliminated images with more than five cortical structures with values greater than four standard deviations. We calibrated the quality thresholds looking for a neuroimage sample and identifying image artifacts. In the quality assessment, the exclusion criteria eliminated 2.8% of the sample.

2.3. Cytoarchitecture Information

The cytoarchitectonic information was based on a whole-brain quantitative 3D laminar atlas called BigBrain by Wagstyl and colleagues [33]. It was created using a convolutional neural network to autonomously partition the cortical layers in both hemispheres using a 3D histology atlas of the human brain at 20-micrometer isotropic resolution, of a 65-year-old male brain. With the percentage of each layer in each cortical structure of a brain, we calculate approximated values of layers thickness based on our dataset of cortical thickness, as established in equation 1. We acknowledge that, to the best of our current knowledge, there is no conclusive evidence regarding the stability of cortical laminar composition throughout the lifespan. Nevertheless, we have chosen to utilize this 3D atlas as it represents the most reliable estimation available at this time.

$$(1) \quad \text{Layer Percentage}_{i=65,j,l} \times \text{Cortical Thickness}_{i,j} = \text{Layer Thickness}_{i,j,l},$$

$i = \text{age}, j = \text{cortical structure}, l = \text{layer} .$

2.4. Cortical Thinning Derivation

To get a human average cortical thinning for each cortical structure and throughout the lifespan, we implemented cubic polynomial regression models based on the cortical thickness of all participants, using age as the only feature [34]. There were 76 models, one model for each cortical structure in the Economo Atlas. The models were then differentiated in the temporal axis to get thinning trajectories. To create these models in Python, we utilize the `polyfit` and `polyld` methods from the NumPy package. The differentiated values comprises an interval of 75 years, 10-85 y.o.. The lower limit arises not from a lack of precision in neuroimaging but rather from the challenges encountered in defining the white/gray boundary accurately on T1 images in early childhood. Additionally, there is considerable variability among individuals in this regard below a certain age [3].

2.5. Cortical Thickness Models

We also created models to test the relevance of feature sets in understanding cortical thickness. The feature sets combined the list: sex, age, curvature, sulci, area, cortical

structure atlas Economo, cortical structure atlas DKT, and an estimation of the percentage of each cortical layer. The cortical layers information was based on a whole-brain quantitative 3D laminar atlas called BigBrain by Wagstyl and colleagues [33]. We trained all models with an ensemble algorithm, the LGBM Regressor, and evaluated it with the R-square metric. 80% of the data were used in the training step and 20% in the test step. The participants were separated into two sets, one for each step - training and evaluation.

I evaluated four different data aggregation approaches by conducting a model variation analysis to assess their relevance. Specifically, I compared vertex-wise training and evaluation with brain-structure-wise training and evaluation. For this study, I developed four distinct model architectures using the equations provided below. Three different combinations of grouping the independent variables were used (Equations 2-4) and two methods of calculating the R-squared metric were employed (Equation 5-6). Where: y = cortical thickness (dependent variable), X = feature set (independent variables), i = vertex, j = cortical structure, k = participant, n = number of vertices in j -th structure for the k -th participant, f = regression model, and g = R-square metric. Symbol $\hat{}$ represents the mean value.

$$(2) \frac{\sum_{i=0}^n y_{i,j,k}}{n_{j,k}} = f_j\left(\frac{\sum_{i=0}^n X_{i,j,k}}{n_{j,k}}\right)$$

$$(3) \quad y_{i,j,k} = f(X_{i,j,k})$$

$$(4) \quad \frac{\sum_{i=0}^n y_{i,j,k}}{n_{j,k}} = f\left(\frac{\sum_{i=0}^n X_{i,j,k}}{n_{j,k}}\right)$$

$$(5) \quad r^2 = g(\hat{y}, y)$$

$$(6) \quad r^2 = g\left(\frac{\sum_{i=0}^n \hat{y}_{i,j,k}}{n_{j,k}}, \frac{\sum_{i=0}^n y_{i,j,k}}{n_{j,k}}\right)$$

Equation 2 together with equation 6 creates a model for each cortical structure to replicate Frangou et al. work [27]. This approach is a brain-structure-wise training and evaluation - the variables are the mean values of all vertices inside a brain structure. Because there is one model for each structure, features related to localization are not included in the model, all the following models include them to create a more comprehensive approach. Equation 3, together with equation 5, represents the vertex-wise training and evaluation. Equation 3, together with equation 6, is a vertex-wise training and brain-structure-wise evaluation, so the intra variations of a structure are relevant to the training but not to the evaluation. Equation 4 together with equation 6 represents brain-structure-wise training and evaluation.

2.6. Cortical Thinning Models

The cortical thinning model took another approach. It was a structure wise training and evaluation, and further dive in the multiscale modeling, a necessary perspective to be able to understand a phenomenon occurring at multiple spatial and temporal scales. It allows for the integration of data from different sources and levels of resolution, revealing emergent properties and mechanisms that explain function.

We examine whether there is a consistent pattern for a cortical structure that belongs to the same hemisphere or lobe. We investigate the role of cortical curvature, i.e., a spectrum from gyri to sulci, and the role of the cytoarchitectonic profile, i.e., the thickness of each cortical layer [Figure 2a]. We also estimated the cortical thickness of each structure at age 10 using the polynomial models to use as a reference point to the model. Together these variables compose the spatial features, and to encode the temporal component, we used age, expressed in years, from 10 to 85.

We modeled the thinning rates using the Light Gradient Boosting Machine (LightGBM) framework, a fast, distributed, high-performance gradient boosting framework based on decision tree algorithms [30]. The implementation in Python was done using the LGBMRegressor class with the default parameters. This framework can handle multicollinearity and variable's interaction, which are needed because of our dataset characteristics. The maximum tree leaves for base learners was set to 31, default. No limit was set to tree depth for base learners. Boosting learning rate was set to 0.1. The number of boosted trees to fit, i.e., the number of estimators was set to 100. The minimum loss reduction required to make a further partition on a leaf node of the

tree was set to 0. The minimum sum of instance weight (Hessian) needed in a child (leaf) was set to $1e-3$. The minimum number of data needed in a child (leaf) was set to 20.

Aiming to investigate whether the patterns of brain atrophy are consistent and if we can predict the thinning of one specific brain region based on its distinctive features, we implemented a cross-validation approach. 38 models were trained- each one was trained with 37 structures and tested on 1 [35-37]. In which were evaluated whether the thinning of an unknown structure can be predicted by a model trained on all cortical structures, leaving one out. Therefore, the data of the same structure, but in different years of life, were not in the training and the test set simultaneously [figure 2c]. This reduces the risk of data leakage and overfitting because all time points of a structure are either in the training or the test. This strategy replicates the modeling for each cortical structure separately, increases the generalizability of the results, and maintains an experimental design with replicability and randomization.

To evaluate the performance, we use an r-square of each model and an r-square average, which does not include structures that the models could not explain. The criterion for this exclusion was r-square less than 0 (predictions worse than a constant function that always predicts the mean of the data).

Figure 2: Machine Learning Framework for Multiscale Modeling.

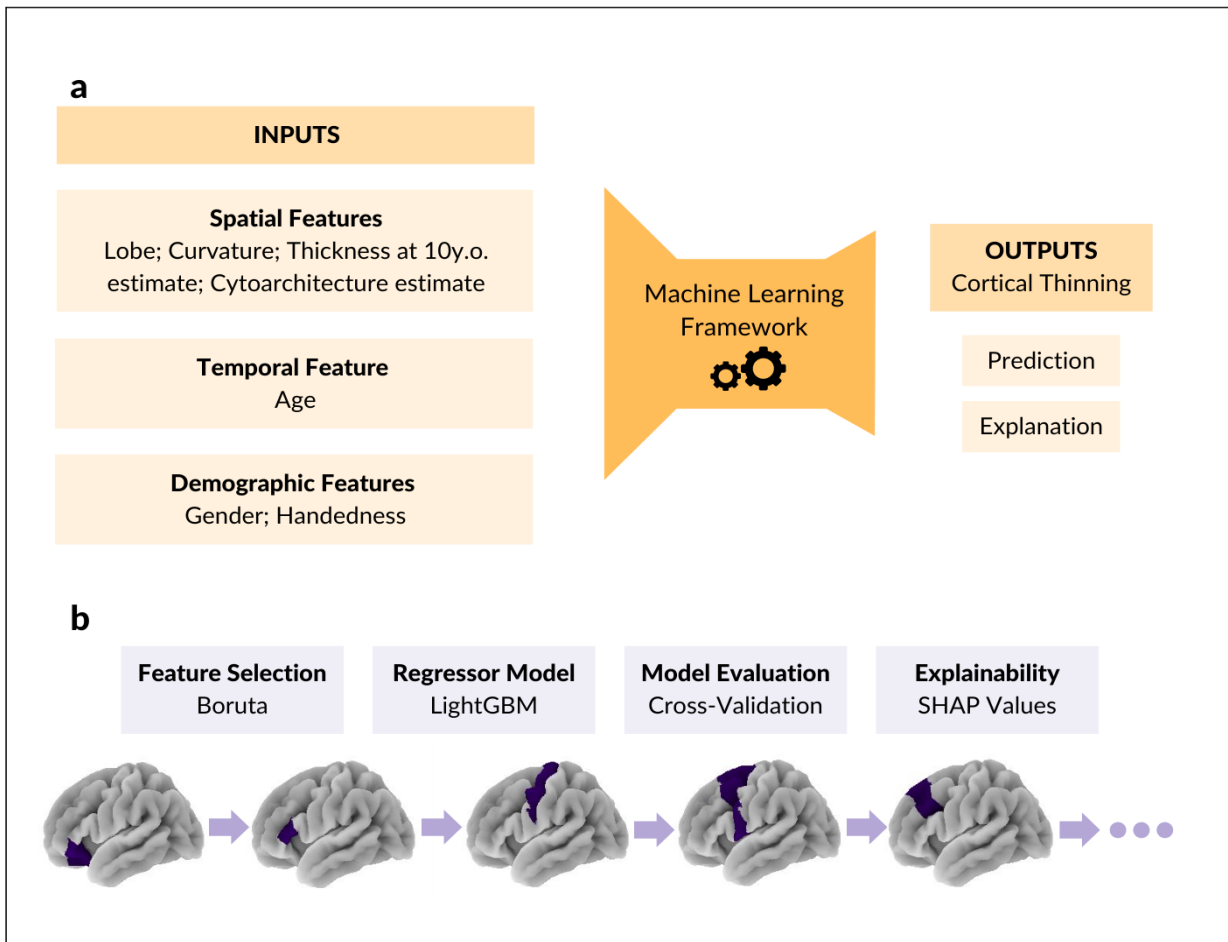


Figure 2: Machine Learning Framework: (a) Spatial and temporal features input in regression model to predict and explain cortical thinning variation throughout the cortex and the lifespan. The model uses LightGBM and SHAP frameworks. (b) Main steps of the machine learning framework. (c) Cross-validation approach by cortical structures. We trained 38 models - each one was trained with 37 (gray) structures and tested with 1 (purple).

2.7. Feature Selection - Boruta

Boruta is a feature selection algorithm that helps to identify the most important features from a dataset while filtering out irrelevant ones. In this work, Boruta was used to analyze if thinning is influenced by temporal, spatial, or demographic features testing the relevance of each feature. To do that, it answers which features contribute to a generic random forest model of thinning, it is based on shadow features and bootstrap [38]. The implementation in Python is done using BorutaPy package and Sklearn Random Forest Regressor package.

Boruta was chosen for its ability to deal with multicollinearity that is present in our dataset and also be able to account for features interactions, it returns the 'all-relevant' set of attributes, not the 'minimal-optimal' set (which should not contain correlated variables). The number of estimators was determined automatically based on the size of the dataset. The threshold for comparison between shadow and real features, the percentile, was set to 100. In the higher percentile, the less false positives will be picked as relevant, but also some relevant features will be left out. Alpha was 0.01, the level at which the corrected p-values will get rejected. The number of maximum iterations to perform was the default, 100.

2.8. Model Explainability - SHAP

Understanding why a model generates a certain prediction is just as important as the prediction's performance. Also, due to the large size of the current datasets, the

maximum accuracy is frequently attained by complex models that are hard to interpret, such as ensemble models that we use, creating a conflict between accuracy and interpretability. To address that, we calculated the SHAP (SHapleyAdditive exPlanations), a technique that utilizes game theory to determine the contribution of each feature to individual model output [31,39]. Shapley regression values give feature importance for models in the presence of multicollinearity, which is needed to handle our dataset. It shows the interactions between variables and gives a comprehensive knowledge of the nature of the interactions when calculating the explanation of each individual model output. In our case, having models that include both temporal and spatial variables allows for a more sophisticated analysis of the interactions and roles of variables across multiple domains.

Through three major contributions, SHAP improves the interpretability of tree-based models. (1) A polynomial-time approach for calculating optimum explanations based on game theory. (2) A novel style of explanation that directly assesses the impacts of local feature interaction. (3) A set of tools for comprehending global model structure that is built on merging several local explanations for each prediction. SHAP tools allow us to: identify high-magnitude but low-frequency nonlinear contributions to thinning, highlight distinct variable subgroups with shared contributions and identify nonlinear interaction effects among each variable.

3. Results

3.1. Cortical Thickness Characterization

As expected, average cortical thickness was from 1.8mm until 3.4mm. Each structure had a different amount of vertices in the cortical mesh varying from 0.1×10^7 to 1.6×10^7 . Structures average thickness decreased from development to mid-life to aging [figure 3a], on the other hand standard deviation had no recognizable pattern trend in the three life stages [figure 3b]. Some structures had small variation between individuals and some had bigger variation.

3.2. Predictive Thickness Model

The models with higher scores were the ones with age, curvature, sulci, area, and cytoarchitecture percentage of each cortical layer by cortical structure. Cortical structure atlas Economo and cortical structure atlas DKT showed no relevance when applied together with BigBrain features, but alone they influenced 77%. Sex had no influence.

Figure 4 shows the performance of each model architecture. The vertex-wise training and evaluation (b) had the worst metric, of 37%. It was the biggest dataset, vertex-wise dataset were approximately 270 millions data points, compared to the brain-structure-wise dataset that were approximately 30 thousands data points. The best metrics were brain-structure-wise training and evaluation (a) and vertex-wise training and brain-structure-wise evaluation (d), with 87%. Brain-structure-wise training and evaluation with one model for each brain structure (c) were in the middle with 84%.

Figure 3: Cortical Thickness Variability Across Age Groups and Brain Regions.

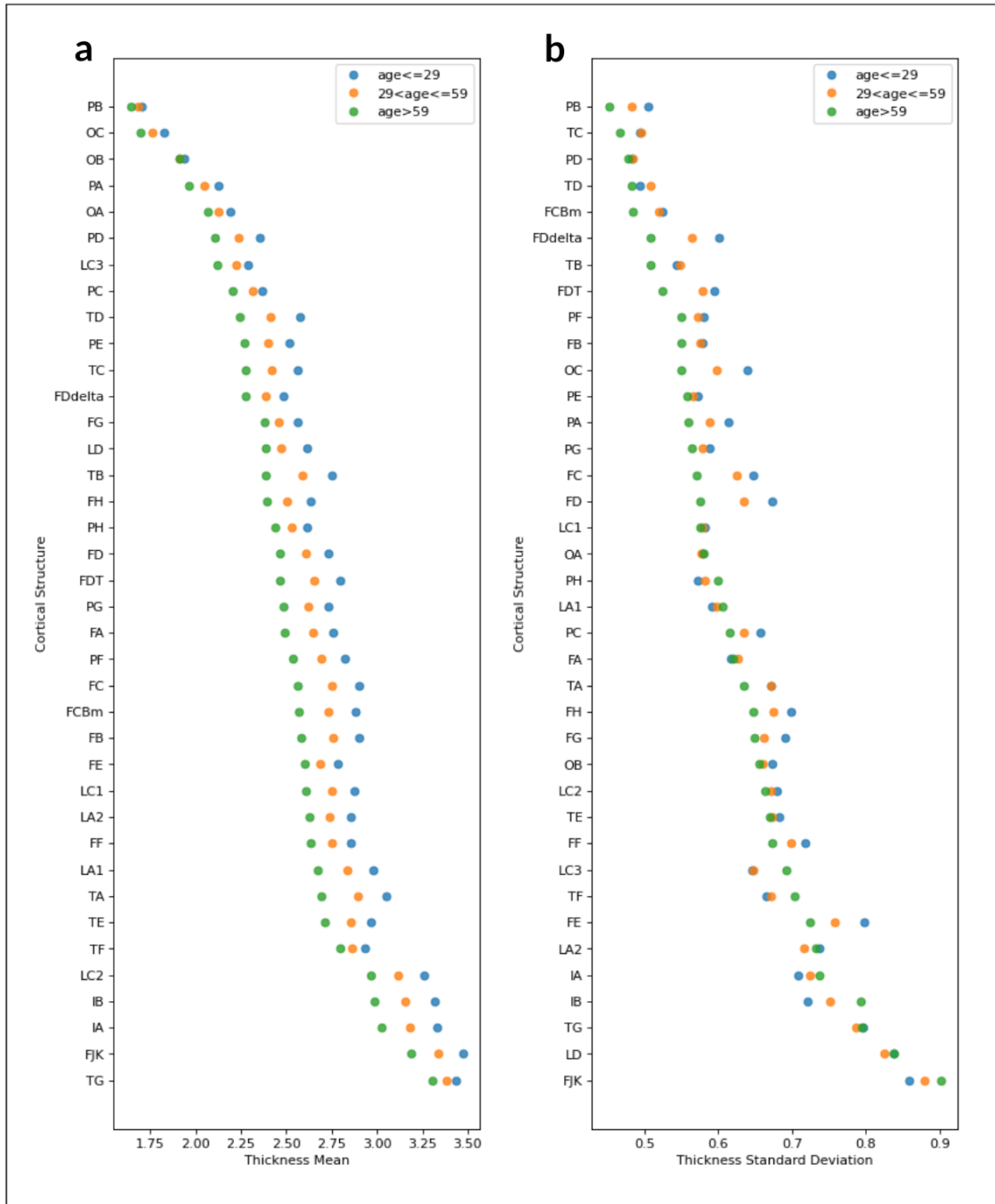


Figure 3: (a) Average and (b) Standard Deviation of Cortical Structures' Thickness, Segregated by Age Stages: 10-29, 30-59, 60-83.

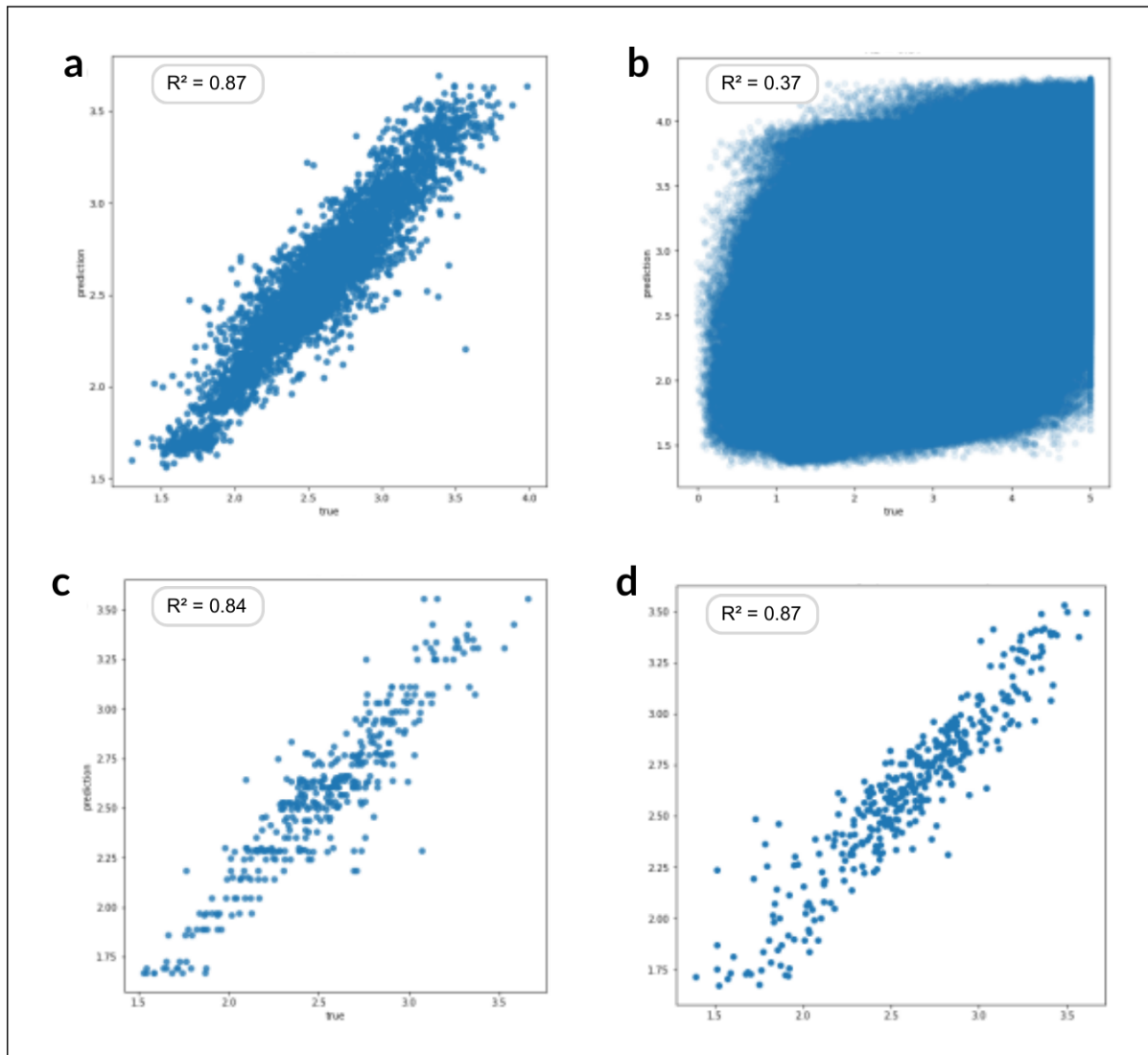
Figure 4: Performance Assessment of Cortical Thickness Models

Figure 4: Prediction results of 4 models. The x-axis is the true value of the cortical thickness and the y-axis is the predicted value for each model: (a) brain-structure-wise training and evaluation, (b) vertex-wise training and evaluation (c) brain-structure-wise training and evaluation with one model for each brain structure, and (d) vertex-wise training and brain-structure-wise evaluation.

Figure 5: Model Explainability in Cortical Thickness Predictions.

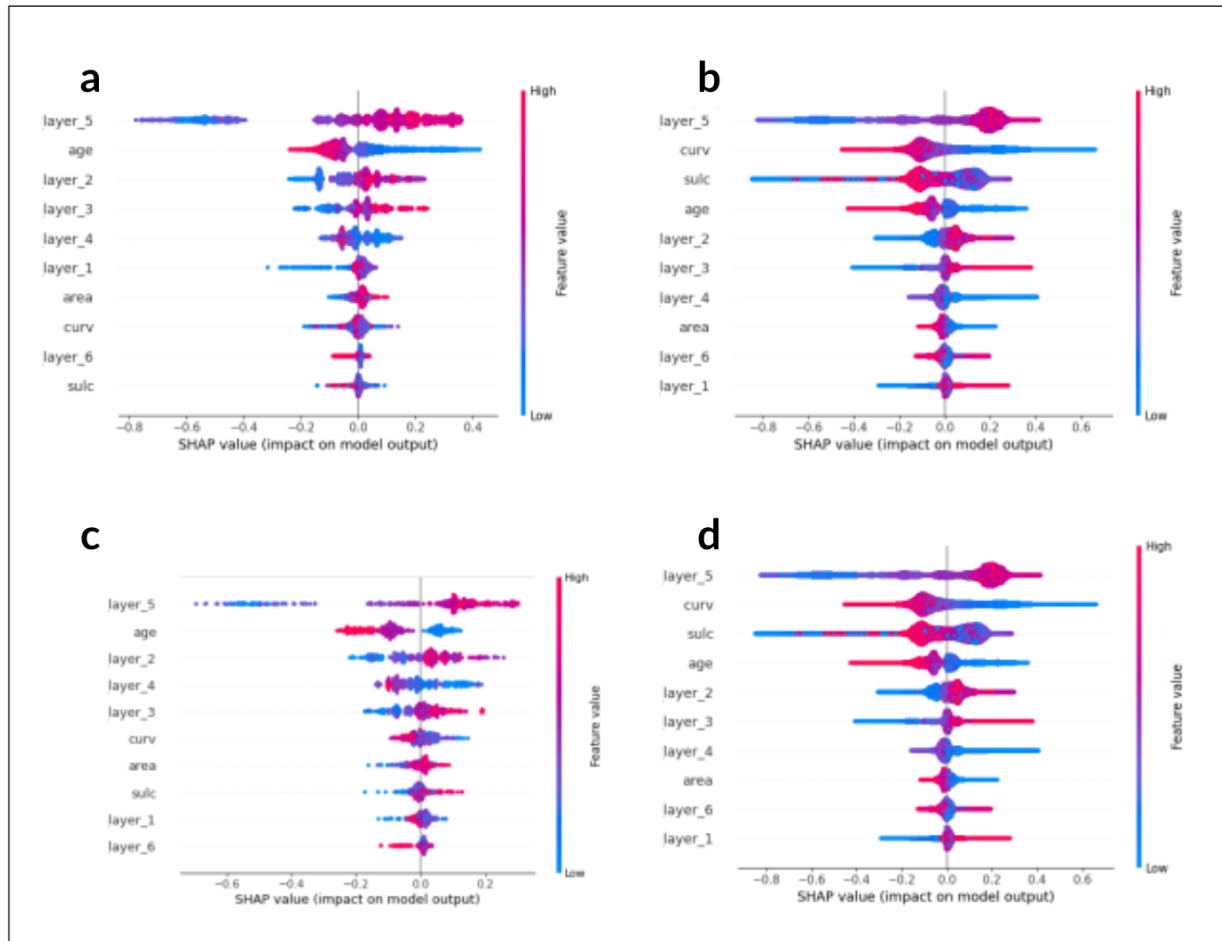


Figure 5: Shap Values of 4 models. The x-axis stands for SHAP value, and the y-axis has all the features. Each point on the chart is one SHAP value for a prediction and feature. Red color means higher value of a feature. Blue means lower value of a feature. The models are the (A) brain-structure-wise training and evaluation, (B) vertex-wise training and evaluation, (C) brain-structure-wise training and evaluation with one model for each brain structure, and (D) vertex-wise training and brain-structure-wise evaluation.

3.3. Variables Roles in Thickness: Model Explainability

Figure 5 shows the feature importance in each model using Shap Values. Layer V is the most noteworthy feature in all models. Age is the second feature in models A and C, and the fourth feature in models B and D. Some features have a monotonic relation with thickness prediction. We can see it by blue on one side, purple in the middle, and red on the other side. Layer V showed a positive monotonic relation, and age showed a negative one.

3.4. Cortical Thinning Characterization

Shifting our focus to the thinning aspect, the average thinning trajectory shown as a parabola has symmetry between 20 and 85 years, with a minimum thinning average of 54 years and a maximum thinning between 10 and 20 years. This general behavior was observed in different structures [figure 6c]. No region showed a constant value of cortical thinning during life. As expected, the phases of development and aging showed the strongest thinning. Depending on the cortical structure and life stage, thinning can vary greatly, with differences of up to an order of magnitude. Thinning in development was associated with pruning [22-24], and thinning in age was associated with cognitive decline [20-21,25]. However, not all structures thin throughout the years, 10% of them showed a discrete increase of thickness in development, mid-life, or aging; and 1.4% of them show a more significant increase, going over 2.0 $\mu\text{m}/\text{year}$. The entorhinal cortex was the structure with the most prominent thickening in both hemispheres in development and mid-life.

Figure 6: Cortical Thinning Across the Lifespan and Brain Region.

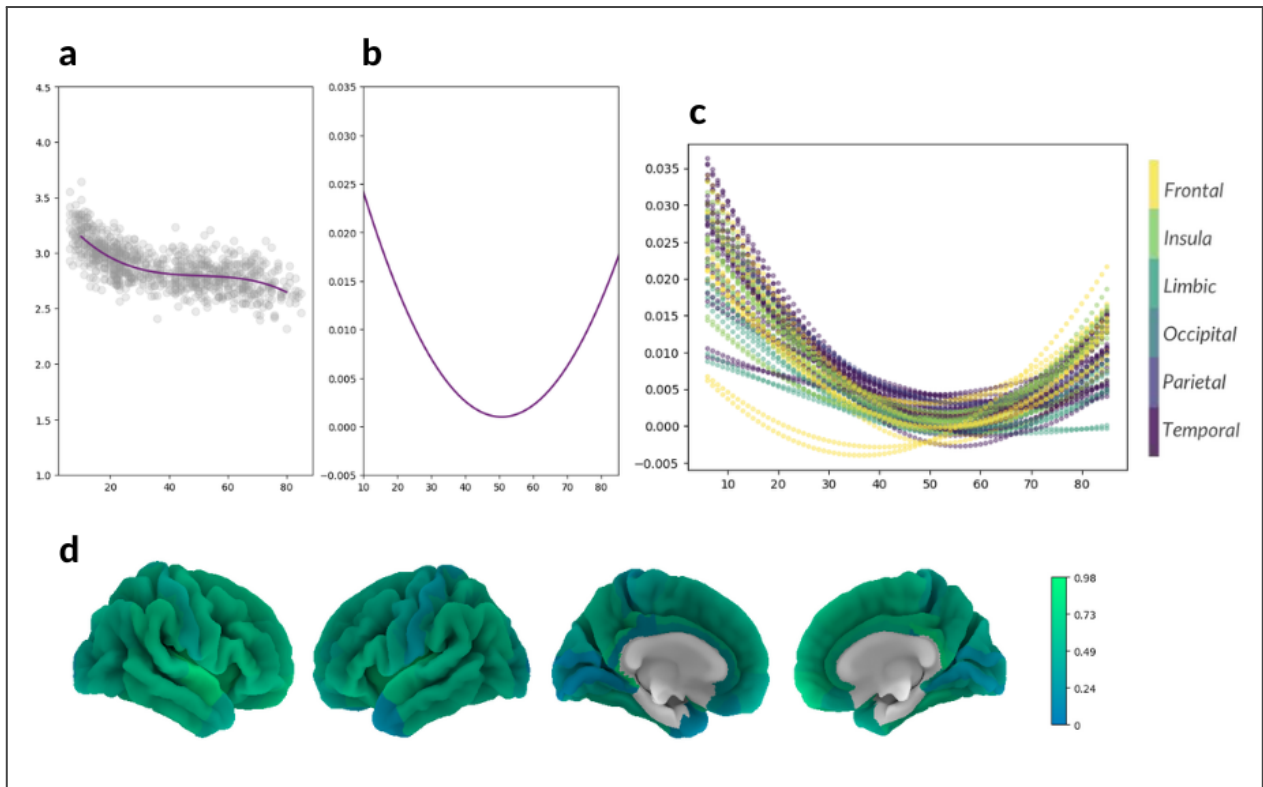


Figure 6: (a) Example of cortical thickness (mm) versus age (years) for a cortical structure (Intercalated Supratemporal area) of 871 subjects and polynomial fit (solid line) of this variation. (b) Thinning (mm/year) derived from the polynomial fit of the same cortical structure. (c) Thinning (mm/year) of all cortical structures color-coded by lobe. (d) Total average thinning (mm) in the lifespan (10-85 years) for each cortical structure.

3.5. Predictive Thinning Model

The tree models created to compare the performance of different variables predicting thinning - only temporal features, only spatial features and a combination of both - showed that 13% of the structures are better predicted by the model of spatial features

only, 32% by the model of temporal features only, 42% by the model of the combination of temporal and spatial features, and 13% are not predicted by neither of them [Figure 7a]. For the average prediction: (1) the temporal model - age - explains 79% of thinning; (2) the spatial model - curvature, cytoarchitecture, and thickness at 10y.o. - explains 58% of thinning; (3) and, the model with both features sets together explains 84% of thinning. The combined model included temporal and spatial information; it was more stable, showing higher mean and lower standard deviation in model performance across all cortical structures [Figure 7b]. Gender and hemisphere were the only features rejected by Boruta test, which iteratively compares the importance of attributes with the importance of their shadows, which are created by shuffling original ones.

Five spread structures were not well fitted to the tested models; predictions were worse than the result of a constant function that would always predict the mean of the data. In no model was the thickness variation of these structures explained: (1) the parastriate area, in the Occipital lobe, which is part of the cuneus, lingual and lateral occipital Desikan-Kiliany structures; (2) the intermediate postcentral area, in the Parietal lobe, which is part of postcentral Desikan-Kiliany structure; (3) the precingulate agranular anterior limbic area, in the Cingulate cortex, which is part of the posteriorcingulate Desikan-Kiliany structure; (4) the temporopolar area, in the Temporal Lobe, which is part of the temporal pole, inferior temporal Desikan-Kiliany structures; and (5) the precentral gyrus, in the Frontal Lobe, which is part of precentral, superior frontal Desikan-Kiliany structures. The model with spatial features could not predict others four structures, and the model with a temporal feature only could not predict one more structure.

Figure 7: Performance Assessment of Cortical Thinning Models.

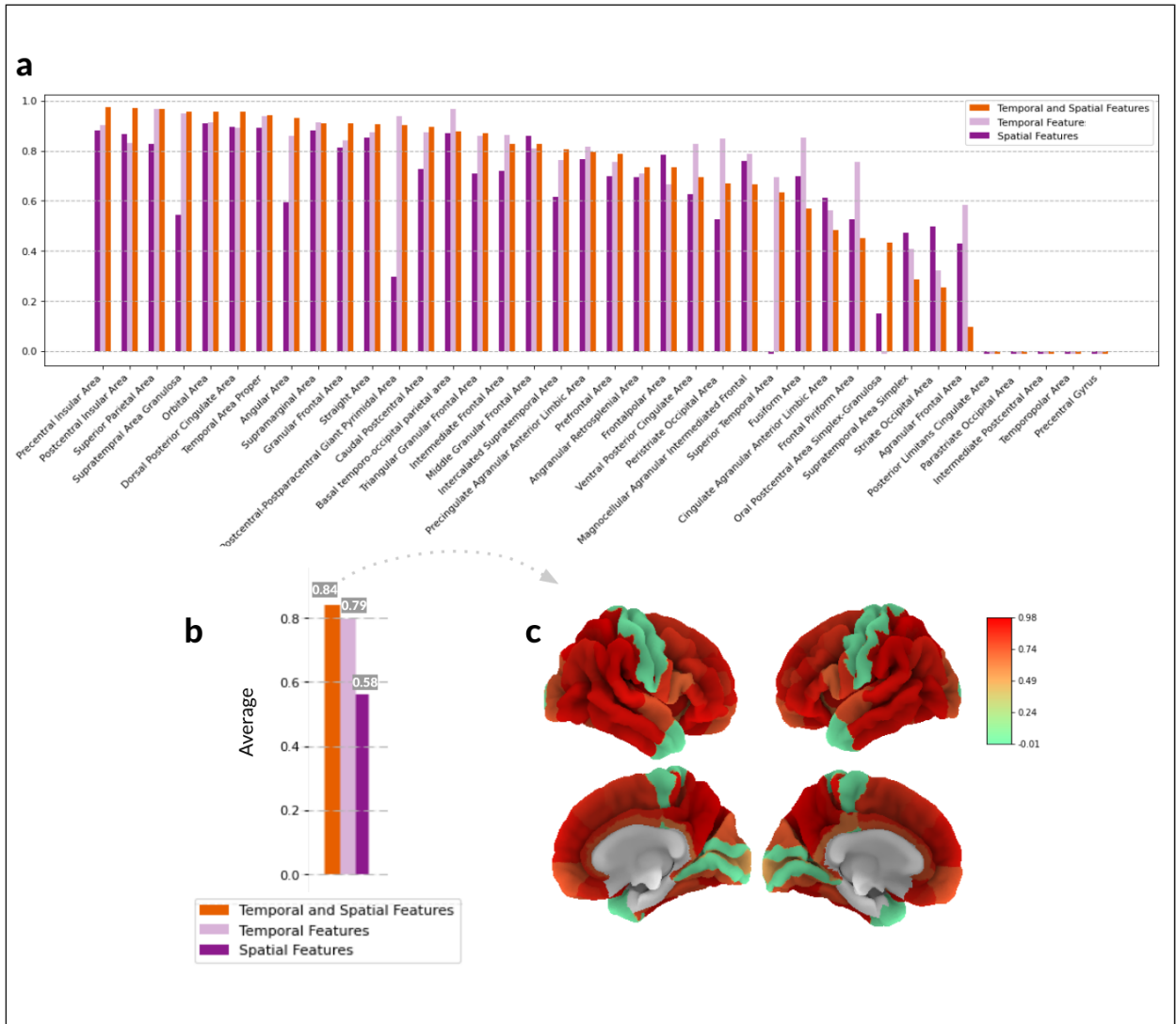


Figure 7: Performances of the three tested models using different features: only age as the temporal feature; only spatial features; and both, temporal and spatial features. (a) r-square of each structure in Atlas Economo in cross-validation processes. (b) Average r-square. (c) Cortical visualization of r-square values for the combined model (all structures with r-square <0 were coded as -0.01).

3.6. Variables Roles in Thinning: Model Explainability

Age was the variable that contributes most to explaining thinning, as expected, followed by layer I thickness, thickness at 10y.o., layer IV thickness, lobe, and curvature. Gender and hemisphere had virtually no contribution to the model [figure 8a-b]. Age presented a positive relation to thinning, layer I thickness, thickness at 10y.o. and layer IV thickness presents a negative relation. Cytoarchitectonic information (the sum of all six layers) contributed as much as 42% of what ages contribute to thinning.

3.6.1. Age

In accordance with the SHAP (SHapley Additive exPlanations) methodology, the assessment calculates the precise influence of each feature within an observation in terms of deviating the prediction from the model's baseline prediction. Notably, SHAP values equaling zero signify that the respective feature has exerted no discernible impact on altering the prediction from the baseline average. The average thinning was $8.0 \mu\text{m}/\text{yr}$, so positive SHAP values mean less thinning than average. The contributions of age to thinning showed a parabola with higher contributions before 30 years and after 75 years [figure 8c-d]. Age had a positive quadratic contribution. The highest thinning rate was at the beginning and end of the age dimension, varying the period of stable cortical thickness between cortical regions. The interaction between age and lobe showed a relationship between the two variables [figure 8c].

Figure 8: Model Explainability in Cortical Thinning Predictions.

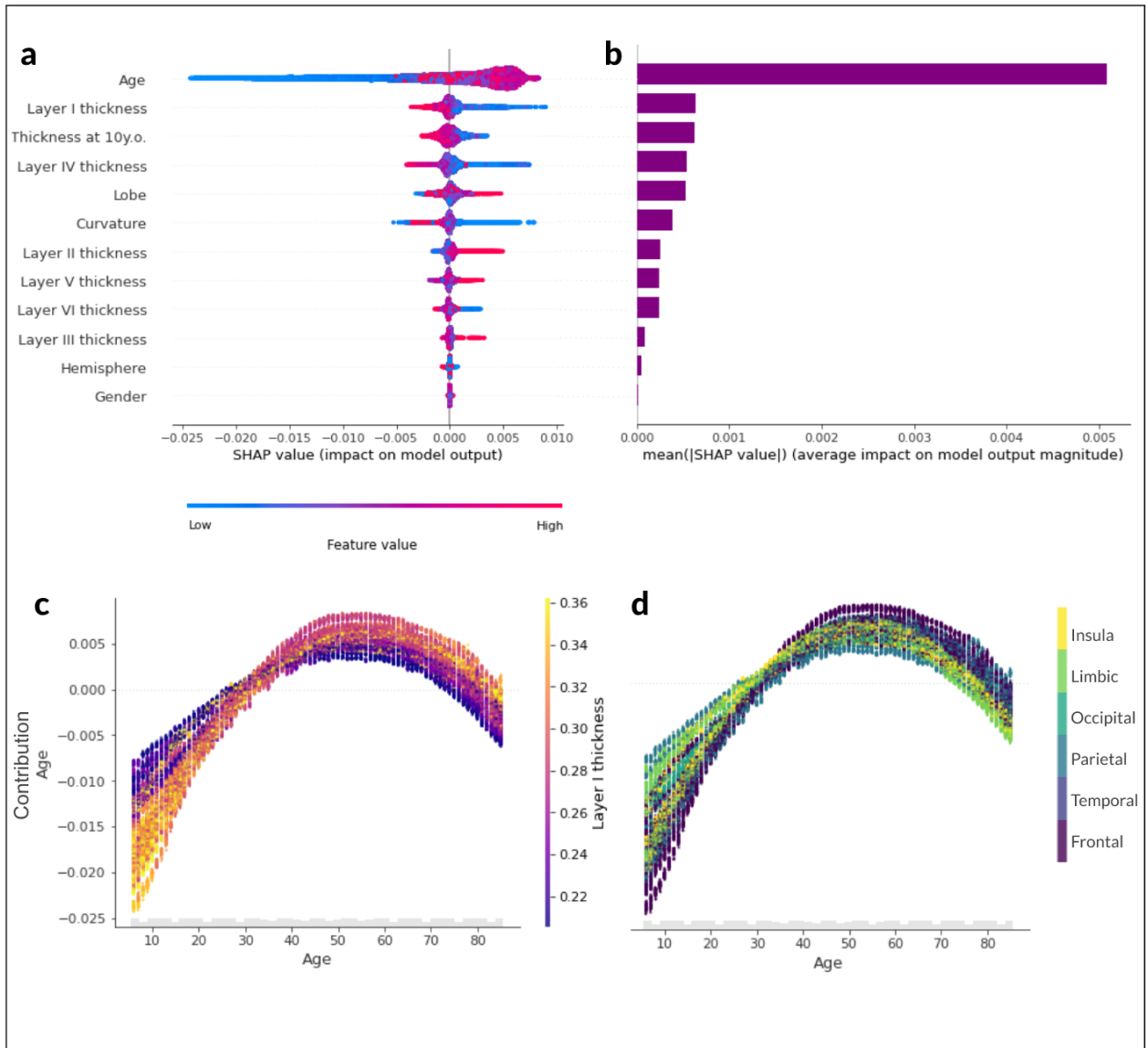


Figure 8: (a) Features contribution to the model ranking, color-coded by feature value and distributed by positive/negative impact in the thinning model. (b) Mean absolute contribution of each feature to the model ranking. (c-d) Age contribution to thinning throughout the lifespan color-coded by layer I thickness and by lobes (smaller contribution values indicate an increase in thinning levels).

Figure 9: Spatial Features' Roles to Cortical Thinning Across the Lifespan.

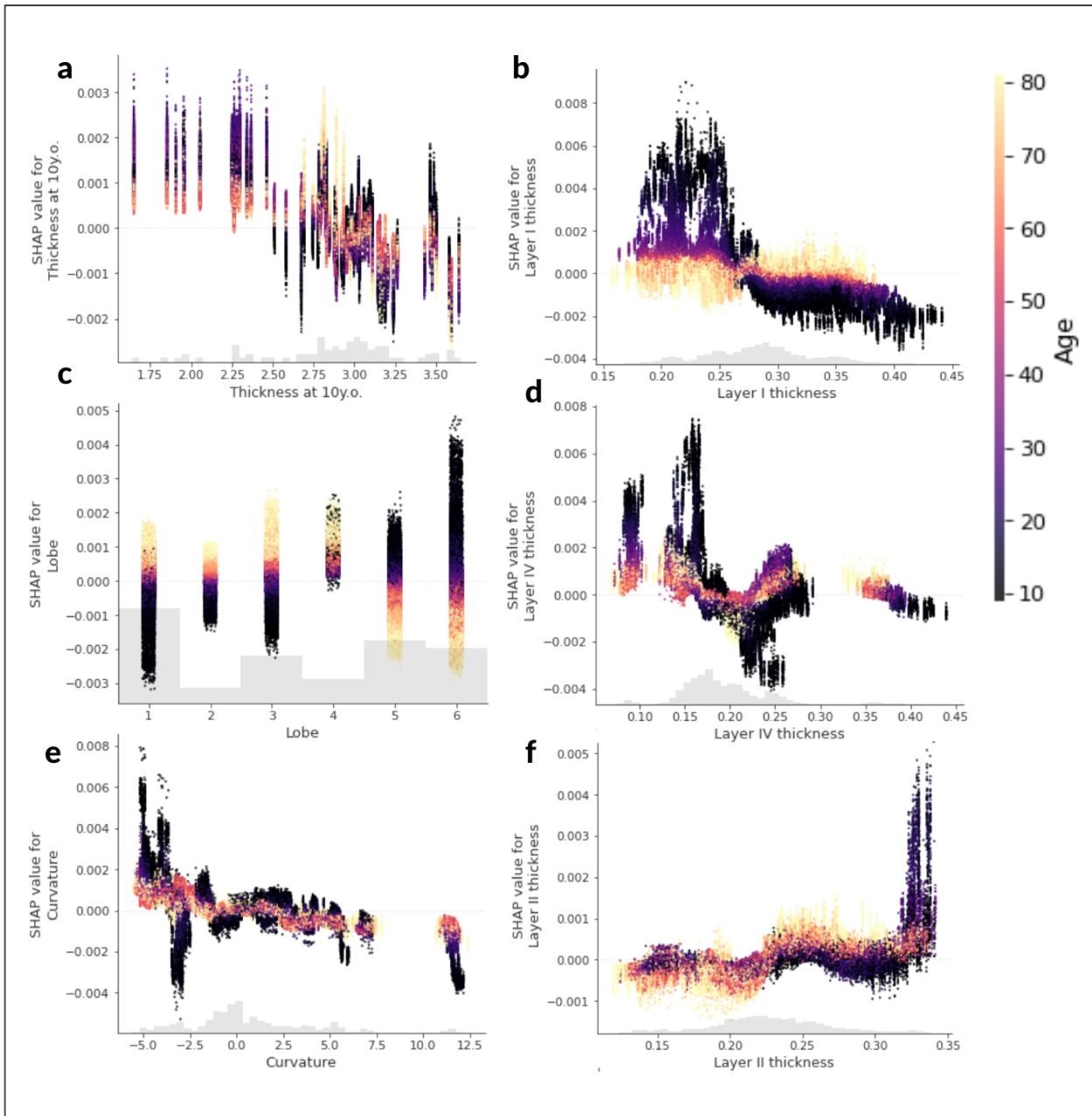


Figure 9: (a-f) Contribution of the six most relevant spatial features color-coded by age (smaller contribution values indicate an increase in thinning levels). (c) Lobes: 1-Insula, 2- Limbic, 3-Occipital, 4-Parietal, 5-Temporal and 6-Frontal.

3.6.2. Cytoarchitecture

Layer I thickness was the cytoarchitectonic variable with the biggest contribution to thinning. Its contribution was strongly conditional to life stages [figure 9b]. Bigger values of layer I thickness mean bigger values of thinning during the development but small values in aging. There is a sigmoidal relation to it isolating the age interaction, and the inflection point between the life stages - development, mid-life and aging - is on a thickness of 0.27mm. Layer IV is the second cytoarchitectonic variable with the biggest contribution to thinning, followed by layers II, V, VI and III. All interact with life stages but not as high as layer I.

3.6.3. Curvature, lobes and structures

Curvature is a morphological measurement that differentiates gyri and sulci, which exhibit, respectively, lower and higher curvature. Curvature contribution to thinning is proportional to its values. Regions with higher curvature, corresponding to sulci, exhibited increased rates of cortical thickness atrophy, whereas regions with lower curvature, corresponding to gyri, demonstrated lessened thinning [figure 8b]. The lobes contribution to thinning vary throughout the lifespan, but in mid-life, all lobes have approximately equal contribution [figure 9c]. The frontal lobe, insular cortex and cingulate cortex have similar behavior related to their interaction with age. Structures on them thin proportionally more in development than aging. The parietal and temporal lobes have the opposite behavior. Structures on them thin proportionally more in aging than in development. The occipital lobe has no distinguished contribution to thin from

development to aging. Our results demonstrate that multiscale spatial variables have different roles in development and healthy aging.

3.7. Thinning trends in development and aging

A further analysis was done to understand the association of each feature to thinning in different stages of life. The goal was to validate our previous findings using a different mathematical approach while still using the same data set. We separated the thinning rates into three-thirds of life: 10-30 years, 30-60 years, and >60 years [1]. For the purpose of this study, we classify the first group as the developmental phase, the second as mid-life, and the third as old-age. We analyzed the correlation of the variables with each age interval. Seeking to further describe the link between thinning in pruning and thinning in cognitive decline in healthy aging, we examined the normalized difference of thinning in the two life stages [40]. Normalization is needed to make them comparable because the thinning rates in development are one order of magnitude above the thinning rates in aging. Without it, it would not be possible to compare whether a structure thins proportionally more than others in aging than in development.

Figure 10: Thinning Differences among Age Groups and Their Link to Layer I

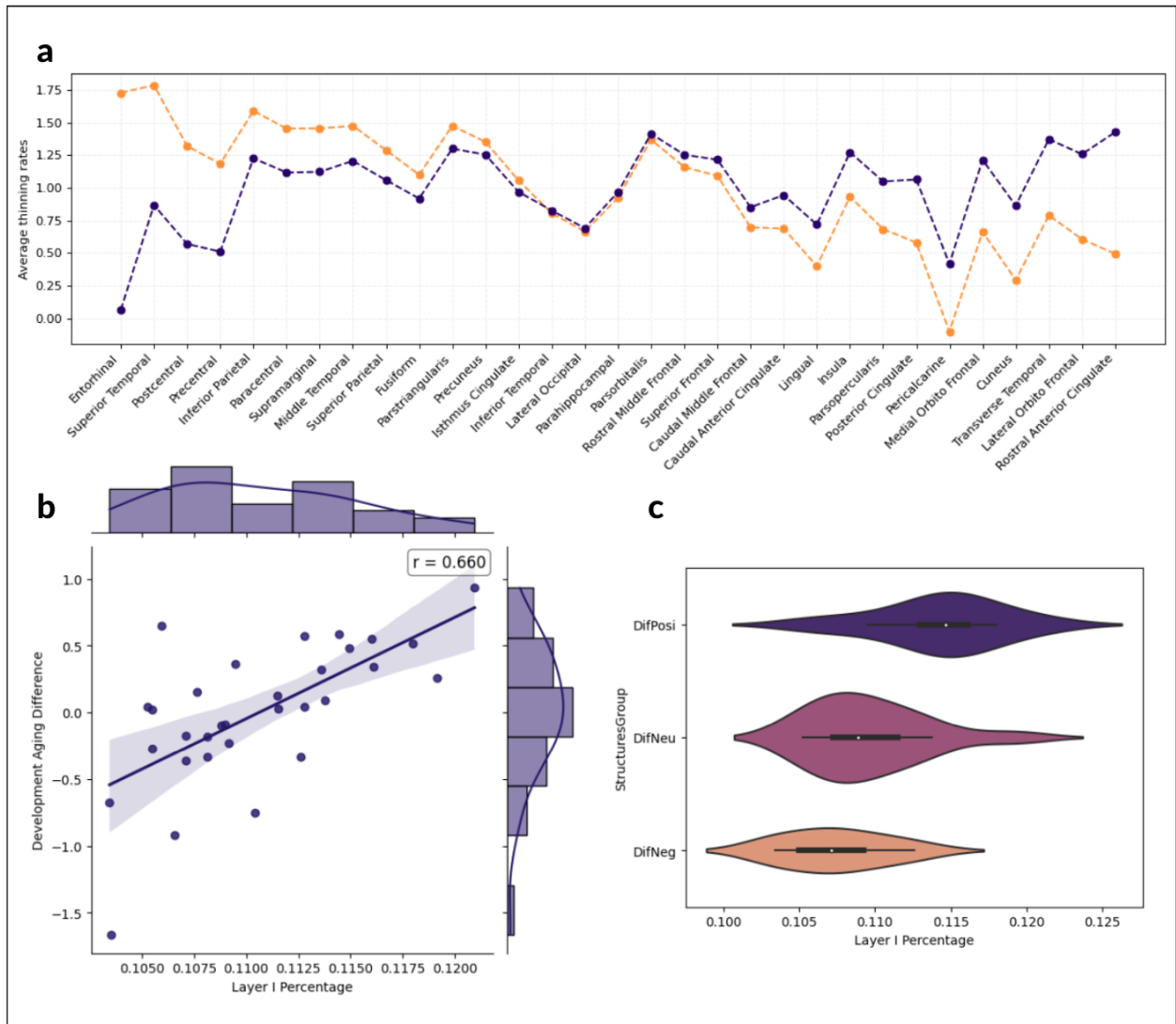


Figure 10: (a) Development aging difference calculated as a subtraction of normalized average thinning in development and aging stages for each cortical structure. (b) Scatter plot of development aging difference versus Layer I percentage, solid line indicates the linear regression ($r=0.66$). (c) Development aging difference clustered into three clusters: "negative difference (DifNeg)", "no difference (DifNeu)", and "positive difference (DifPosi)". Within each cluster the layer I fraction were on average 0.107, 0.110 and 0.114, respectively.

Structures can be separated by a positive difference between thinning rates in development and thinning rates in aging, a negative difference, and no difference at all. The positive difference represents more thinning in aging than in development, the negative difference represents more thinning in development than in aging and no difference represents the same rates of thinning in both stages of life [figure 10a]. Layer I percentage had the highest correlation with the difference (Pearson correlation of -0.64) [figure 10b]. Furthermore, we analyzed the correlation of all variables studied with thinning in the three stages of life. Layer I percentage was the only feature with an opposite correlation in the first and final stages of life with thinning (correlation of -0.34 in development, 0.8 in mid-life, 0.30 in aging). Cortical structures showed varied responses to thinning at different stages of development and aging, with a statistically significant difference between groups in layer I percentage ($p=0.003$). Therefore, we calculated the layer I percentage averages for each group of structures - positive difference, no difference and negative difference - and found that they have distinct compositions of layer I - $10.7 \pm 0.1\%$ (mean \pm s.e.m.) in the positive difference, $11.0 \pm 0.1\%$ in the no difference and $11.4 \pm 0.1\%$ in the negative difference [figure 10c].

4. Discussion

4.1. Modeling Cortical Thickness: Insights and Implications

As the literature suggests, age has a high importance in all the models to explain cortical thickness. To the best of our knowledge, previous works were able to explain 0.59 of the thickness variance [27]. In our thickness model, we hypothesize that cortical cytoarchitectonic organization influences the different thickness in cortical regions. We did four model architectures to test this hypothesis, and we were able to explain 0.87 of the mean thickness of a cortical structure.

Figure 3 shows cortical thickness variation across cortical regions. The presence of minimal inter-individual variation in certain brain structures could highlight their fundamental and evolutionarily conserved roles. In contrast, larger variations in other structures underscore the brain's adaptability and the potential influence of genetic, environmental, and developmental factors on individual differences in cognition and behavior.

To understand the importance of cytoarchitectonic organization, the localization features were represented by atlas Economo, atlas DKT, and the BigBrain database percentage of each cortical layer by cortical structure. The three atlases have the highest shap values in the models and convey similar information. Adding more than one does not enhance performance, as they all contribute with spatial information related to a coordinated system of localization.

In Figure 4, we presented the performance results of four distinct models, aiming to address key distinct methods to model thickness. First, we differentiated between training a model for the prediction of cortical mesh vertex thickness and predicting the average thickness across different brain structures. We encounter challenges in adequately explaining vertex-wise outcomes (Model B) due to potential noise interference or the need for additional variables to capture the intra-variance of cortical structure.

After that, we explored the performance of creating a single model to cover all structures collectively or adopting multiple models, each tailored to a specific brain structure. The approach represented by Model C, employing a separate model for each cortical structure, performed similarly to the more general approaches. This similarity between the models can be attributed primarily to the tree-based nature of the model, where the addition of more information corresponds to creating an additional branch within the tree, ultimately not impacting its performance.

Additionally we explored if training with the thickness of each vertex (Model D) was better than training with the averages for each brain structure (Model A) when evaluated equally i.e. evaluating considering the average thickness of each brain structure. Both approaches yielded equivalent performances, indicating that the data loss resulted by averaging thickness before training did not result in worse predictions.

In terms of the model's features, their relevance provides valuable insights into the factors influencing cortical thickness [Figure 5]. Notably, Layer V consistently emerges as the most relevant layer. Layer V, known as the internal pyramidal layer, is

composed of neurons responsible for efferent pathways, facilitating the transmission of information from the cortex to external regions. It plays a pivotal role in critical connections, such as the corticospinal tract and links to subcortical regions. The importance of this layer could be due to a variety of factors, such as functional roles, neuronal density, cognitive functions, developmental processes, and structural connectivity. Layer V is known to be central in various brain functions, including motor control, sensory integration, and the integration of information from different brain regions. Changes in functions and efficiency could alter the proximity and connectivity of neurons in this layer, which could influence their cortical thickness. Variations in cortical thickness can impact the density of neurons within layer V more than in other layers, making it a marker of cortical thickness variation.

Other features to be noted are age and curvature. Our study both confirms their importance and innovatively ranks them within the same model. However, it's consistently observed that, in all models, these features exhibit lower relevance in comparison to the dominant influence of Layer V.

Addressing the study's limitations yields valuable insights. It is fundamental to be aware that SHAP values are designed to expose correlations within predictive machine learning models, and discovering these correlations does not imply causation. Predictive models assume constant behavior and stable correlation patterns. To investigate causation, we need to conduct experiments to establish causal relationships, rather than relying solely on observed correlations.

One inherent limitation of cortical thickness measurements is their susceptibility to changes in the white matter/gray matter contrast within the brain. When this contrast fluctuates with age, it can introduce a source of bias into the cortical thickness assessments. In essence, as individuals grow older, alterations in the appearance of white and gray matter in brain scans may occur, potentially impacting the precision and reliability of the cortical thickness measurements we obtain [41].

Future works could also consider other aspects. Firstly, expanding the dataset to encompass greater diversity and a broader age spectrum would bolster the robustness of our findings. Secondly, exploring alternative atlases for analysis may yield additional perspectives. Furthermore, the incorporation of data from various modalities, including functional connectivity, and examining different hierarchical levels, such as genomics, would provide a more comprehensive understanding of the topic. One crucial dimension not addressed by these models is the study of temporal derivatives in cortical thickness, which provides valuable insights into how thinning progresses over the lifespan. We have undertaken this analysis and will discuss our findings in the following section.

Investigating cortical thickness is of paramount importance in neuroscience due to its capacity to yield insights into the structural integrity of the cerebral cortex, a region integral to higher cognitive functions. These inquiries aspire to enhance our comprehension of the connection between cortical thickness and cognitive processes, potentially informing the development of therapeutic strategies for neurological and psychiatric disorders, and aiding in our understanding of how the brain processes information.

4.2. Modeling Cortical Thinning: Insights and Implications

We used different mathematical modeling techniques and a multiscale dataset to predict cortical thinning at different stages of life and cortical regions. We demonstrate that cortical thinning encodes a link between pruning and cognitive decline in healthy aging. Spatial variables' contributions to thinning are strongly conditioned to life stages.

The finding corroborates with the known fact that the frontal lobe has delayed development behavior throughout life compared to the other lobes [28]. SHAP tools allow us to: identify high-magnitude but low-frequency nonlinear contributions to thinning, highlight distinct variable subgroups with shared contributions and identify nonlinear interaction effects among each variable.

In the literature, there are different studies that defend that age, curvature, cytoarchitecture and localization were correlated with the magnitude of thinning, but that was no information about the extent of their contribution when considered together. Our work analyzes the interaction between these variables and confirms their importance.

Thinning exhibits varying degrees of intensity throughout the stages of development and aging, with more pronounced thinning occurring at the beginning and towards the later stages of life. Age and location are key factors influencing this thinning phenomenon. Interestingly, a model that only considers temporal features performs similarly to a model that takes into account both temporal and spatial features. Moreover, focusing on location provides good results and enhances the comprehensibility of the findings.

The distinctive patterns observed in each lobe's thinning behavior and its relationship with age reveal that certain lobes are more impacted during development, while others are more affected in old age. This underscores the existence of a connection between temporal and spatial information. This relationship can be attributed to the varying functions of these lobes and how they are influenced over the course of one's lifetime. For instance, the lobes more affected during development - Insula, Limbic, and Occipital lobes - are associated with emotions and vision. While the less affected during development - Temporal and Frontal lobes - play roles in language, memory, and other cognitive functions and are the most affected in old age. Notably, the parietal lobe, responsible for sensory integration, does not exhibit a prominent relationship with thinning.

Layer I was the most relevant in our study, its thickness plays a central role in explaining cortical thinning in development and aging. This layer does not have many neuronal bodies, its composition is primarily of glial cells and axons. It is the primary target of corticocortical and subcortical projections that mediate top-down or context dependent sensory perception [42-44]. Our data showed that regions with higher layer I thickness had a higher thinning during development and smaller thinning during aging.

Our results could indicate that pruning and cognitive decline in healthy aging are processes guided by the same type of cortical component. We pose the argument that pruning in development occurs more in regions with more corticocortical connections and subcortical projections, while in cognitive decline in healthy aging, these are the regions that remain more preserved and thin less. This concept elucidates a coherent

pattern in the context of cognitive alterations occurring throughout development and aging.

The integration of cytoarchitectonic data with magnetic resonance imaging, provides estimations about an individual's brain while they are alive. An estimation that represents an innovative aspect of this research. The finding of a link between pruning and cognitive decline in healthy aging elucidates the advantages of an integrative neuroscience approach and the implementation of merging different scale databases, using appropriate mathematical methods. It will be discussed in the following sections.

Several limitations and possible direct extensions of this work should be highlighted. First it's essential to recognize that the atlas employed in this study is dated, yet it has the main advantage of being the most focused on cytoarchitectural information. Additionally, the information on cytoarchitecture was based on an indirect measure and estimation from a single 65-year-old male, which limits the generalizability of the results. Future research should aim to include data from a wider range of ages and both genders to better understand the underlying mechanisms of brain organization. Another possible limitation is the lack of inclusion of functional data in the analysis, as the study mainly focused on the spatial and temporal variables. Therefore, future research should explore the integration of functional and structural data to gain a more comprehensive understanding of brain function and organization. Lastly, increasing the amount of data used in this study would help improve the reliability and validity of the findings.

4.3. Modeling Frameworks Beyond Single-Dimension Analysis

Combining multiscale models, ensemble models, and SHAP (Shapley Additive Explanations) can be highly beneficial as a comprehensive framework for modeling. Each of these approaches offers unique advantages and can complement one another in various ways.

Multiscale models are advantageous for capturing and incorporating information at different levels of granularity or resolution. They enable the exploration of complex relationships across multiple scales, thereby providing a more holistic understanding of the underlying phenomena [29]. By considering multiple scales, these models can uncover patterns and dependencies that may be overlooked by single-scale approaches. Integrating multiscale modeling into the framework can enhance the model's ability to capture intricate interactions and nuanced dynamics.

Ensemble models, on the other hand, leverage the strength of multiple individual models to improve overall predictive performance and robustness. By combining the predictions of diverse models, such as different algorithms or variations in model parameters, ensembles can mitigate the limitations of any single model and enhance overall accuracy and generalizability. Ensemble models also provide the advantage of capturing uncertainty and offering more reliable predictions through the aggregation of multiple perspectives.

SHAP, as a model interpretability technique, allows for a deeper understanding of how individual variables contribute to the model's output. It provides feature importance rankings and additive explanations, enabling the identification of influential variables and

the quantification of their impact on the model's predictions. SHAP values also facilitate the analysis of variable interactions, elucidating complex relationships between features. By incorporating SHAP into the modeling framework, it becomes possible to gain insights into the underlying factors driving the model's predictions and enhance the interpretability and transparency of the model.

When used together, these three methods form a comprehensive framework that encompasses different aspects of modeling. An important thing to notice is that ensembles and SHAP can handle multicollinearity, which is essential as is inevitable when using it together with a multiscale framework. The combination of multiscale modeling, ensemble techniques, and SHAP-based interpretability can lead to improved predictive performance, better understanding of underlying processes, and enhanced model interpretability. This integrated approach allows for a more thorough exploration of complex datasets, robust modeling, and deeper insights into the relationships and contributions of variables, making it a valuable framework for various applications in data analysis and decision-making.

This framework provides several advantages over traditional univariate analysis and parametric methods in statistics. Traditional univariate analysis focuses on examining individual variables in isolation, which may fail to capture the complex relationships and interactions among multiple variables. In contrast, the framework allows for multivariate analysis, enabling the exploration of dependencies and interactions between multiple variables simultaneously [45]. This multivariate approach is particularly beneficial when dealing with datasets that exhibit multicollinearity, where variables are highly correlated with each other. Multiscale models, within this framework,

can handle multicollinearity by considering variables at different scales or levels of granularity, thereby providing a more accurate and comprehensive analysis.

Moreover, traditional parametric methods often rely on specific assumptions about the data distribution and model structure, which may not hold in real-world scenarios. These assumptions, such as normality and homoscedasticity, may limit the applicability and robustness of the model. However, the framework incorporating multiscale models, ensemble models, and SHAP is not constrained by these assumptions and can handle nonlinearity, heteroscedasticity, and other complexities present in the data. By leveraging machine learning techniques, this framework offers greater flexibility and adaptability to the inherent characteristics of complex datasets, leading to improved modeling accuracy and interpretability.

4.4. Data-Driven Modeling in the Context of Open Science and Big Data

The discussion of the modeling framework should not overlook the critical importance of considering the broader context of Open Science and its intricate connection to the expansive domain of Big Data. While the modeling framework provides a powerful toolset for analyzing complex datasets, it is equally imperative to address the underlying data infrastructure and purpose within which the modeling framework operates. By acknowledging the context of Open Science and its relationship to Big Data, researchers can establish a solid foundation for the development and implementation of innovative modeling approaches. Open Science is a movement that promotes the open sharing of

scientific research and data. It emphasizes transparency, collaboration, and accessibility in the scientific process. With the advent of Big Data, Open Science has gained momentum as researchers have access to vast amounts of data from various sources. Big Data refers to extremely large and complex datasets that cannot be easily managed, analyzed, or processed using traditional methods. In this context, a large amount of data enables researchers to explore new avenues of discovery and develop general models that can provide comprehensive explanations across different scientific disciplines.

Open Science is characterized by principles such as open access to research articles, open data sharing, and open collaboration. It promotes the sharing of research findings and data openly and freely, allowing others to verify, reproduce, and build upon the work. Open Science encourages the use of preprints, where researchers can share their findings before formal peer review. It also encourages the use of open-source tools and software to facilitate collaboration and reproducibility. Through these characteristics, Open Science aims to foster transparency, accountability, and innovation in the scientific community.

Access to standardized data is a crucial aspect of Open Science. The FAIR principles (Findable, Accessible, Interoperable, and Reusable) provide a framework for making data more accessible and usable. Findability ensures that data can be easily located and identified by using standardized metadata and persistent identifiers. Accessibility ensures that data can be retrieved and accessed by humans and machines, removing any technical or legal barriers. Interoperability enables data integration and exchange by using common standards and formats. Reusability ensures that data can be utilized for multiple purposes with clear usage licenses and proper

documentation. By adhering to the FAIR principles, data becomes more discoverable and usable, facilitating collaboration and enabling the development of general models.

Another important aspect that results from the open science and big data context is the possibility of merging data from various sources allowing researchers to create multi-level and multi-modal models. Multi-level models consider different levels of analysis, such as individual, group, or population levels, to provide a comprehensive understanding of a phenomenon. By integrating data from different levels, researchers can uncover complex relationships and interactions. Similarly, multi-modal models combine data from multiple sources, such as imaging, genetic, behavioral, or environmental data, to capture the complexity of a phenomenon. By merging data, researchers can gain more global and general explanations, as they can integrate different phenomena and consider multiple factors simultaneously. This approach enhances our understanding of complex systems and facilitates the development of more comprehensive models. Linking different fields of neuroscience is challenging but not impossible and worthwhile. Integrating knowledge and data from various branches of neuroscience, such as cognitive neuroscience, computational neuroscience, and clinical neuroscience, can provide a more holistic understanding of the brain and its functions. Open Science, with its emphasis on collaboration and data sharing, can facilitate such integration by creating a platform for interdisciplinary research.

The combination of Open Science and Machine Learning has the potential to create integrative and high-performing models. Machine Learning techniques can

leverage the vast amount of openly accessible data to develop predictive models, uncover patterns, and generate novel insights. Open Science provides the foundation for sharing and utilizing these models, enabling researchers from diverse backgrounds to collaborate and build upon each other's work. By integrating Open Science practices with Machine Learning approaches, we can accelerate scientific progress, facilitate interdisciplinary collaborations, and foster the development of more accurate and comprehensive models in various fields of research.

5. Conclusion

In conclusion, our study has provided insights into the neurobiological mechanisms underlying cortical thinning during development, mid-life, and aging. By incorporating information from cytoarchitecture, curvature, and age, our model successfully predicts cortical thinning variations, explaining 84% of the observed variation. Age emerges as the most influential feature in the cortical thinning model, followed by layer I thickness, cortical thickness at 10 years old, and layer IV thickness.

Our findings reveal that regions with increased layer I thickness experience more pronounced thinning during development but exhibit less thinning during aging. Moreover, regions undergoing greater thinning during pruning in the developmental stage show a reduced level of thinning throughout the aging process. These results shed light on the complex interplay between different factors and highlight the dynamic nature of cortical thinning across the lifespan.

Additionally, we investigated the optimal method for modeling cortical thickness and compared vertex-level and brain-structure-level approaches. Our analysis demonstrated that the brain-structures model outperformed the vertex-level approach in predicting cortical thickness. This finding emphasizes the importance of considering the structural organization of the brain when studying cortical thinning and suggests that a broader perspective encompassing brain regions yields more accurate predictions.

Furthermore, our study contributes to the advancement of neuroscience research by integrating data from various fields through the merger of different-scale databases

and employing appropriate mathematical methods. This modeling framework serves as a tool for understanding the fundamental processes involved in brain development, aging, and neurodegenerative disorders, paving the way for future interventions and therapeutic strategies aimed at preserving brain health and optimizing cognitive function across the lifespan.

In summary, our research provides a comprehensive understanding of cortical thinning, highlighting the significant role of age and specific cortical layers in this process. The identification of regions exhibiting distinct thinning patterns during development and aging enhances our knowledge of the underlying mechanisms and offers potential targets for interventions. The adoption of a brain-structure-based modeling approach further refines our predictions, enhancing the accuracy and applicability of cortical thickness modeling. Ultimately, our work contributes to the broader field of neuroscience by integrating data from diverse sources, fostering a deeper comprehension of brain development, aging, and neurodegenerative disorders.

6. Data availability

The datasets generated and analyzed during the current study are available at <https://github.com/tamiresco/inbrainlab/data>.

7. Code availability

All code is available at <https://github.com/tamiresco/inbrainlab>.

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