# Spatio-temporal cortical brain patterns of Alzheimer's disease

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Degeneration of the human cortex is a complex, dynamic process which often spans decades. This degeneration can be evaluated on regions of interest (ROI) in the brain through probabilistic network analyses. However, current approaches for finding such networks have two major limitations; 1) Analyses at discrete age groups cannot appropriately account for connectivity dynamics over time, and 2) morphological tissue changes are seldom unified with connectivity networks, despite known dependencies. In this work we propose a dynamic wombling model to estimate ROI covariance networks dependent on age and compare these results with discrete age wombling. We applied our methods on the healthy controls (HC) and Alzheimer's disease (AD) groups from the Alzheimer's Disease Neuroimaging Initiative (ADNI) case study.

## Dynamic wombling model

Our probabilistic network approach unifies biomarker estimates through the fixed and random effects layers of the hierarchical model, contingent on the age dependent covariance network estimation via wombling. Wombling is the estimation of a symmetric binary matrix $W$, whose elements $w_{jk}$ = 1 denote ROI $j$ and $k$ covary with each other, and 0 otherwise. In this work we extend the traditional wombling model[1] to make $W$ be a function of participants baseline $Age_\alpha$. Let $\mathbb{I}$ be a $K \times K$ identity matrix, the dynamic wombling model is of the form

$$y_{irk} | b_{ik}, \boldsymbol{\beta}, \sigma^2 \sim N(\boldsymbol{x}_i\boldsymbol{\beta} + b_{ik}, \sigma^2) \quad \text{Fixed Effects}$$

$$\boldsymbol{b}_i | \sigma_s^2, Q_\alpha \sim MVN(\mathbf{0}, \sigma_s^2 Q_\alpha) \quad \text{Spatial Effects}$$

$$Q_\alpha^{-1} = \rho\left(\mathbb{I}\sum_{j=1}^{K} w_{kj} - W^\alpha\right) + (1-\rho)\mathbb{I}$$

$$w_{kj}^\alpha | \gamma_{kj}^0, \gamma_{kj}^1 \sim \text{Bern}(p_{kj}^\alpha)$$

$$p_{kj}^\alpha = \frac{\exp(\gamma_{kj}^0 + \gamma_{kj}^1 Age_\alpha)}{1 + \exp(\gamma_{kj}^0 + \gamma_{kj}^1 Age_\alpha)} \quad \text{Connectivity Age Effects}$$

Figure 1: Coloured rectangles show the dependencies among the hierarchical layers of the model. The response is the cortical thickness of brain region $k$, within participant $i$ who has $r$ replicates denoted by $y_{irk}$. Participant specific variables is $\boldsymbol{x}_i$, fixed effect vector and residual errors are denoted by $\boldsymbol{\beta}$ and $\sigma^2$. The spatial random effects for individual $i$ is $\boldsymbol{b}_i$ which follows a multivariate normal distribution with a spatially structured covariance matrix which is the product of the spatial scale parameter $\sigma_s^2$ and covariance matrix for baseline age $\alpha$, $Q_\alpha$. This matrix is a function of the covariance connectivity network $W^\alpha$ and fixed value $\rho \in (0,1)$. The value of $\rho$ denotes the strength of spatial dependence in the random effects[1], and in this work it's fixed to $\rho = 0.9$. Matrix parameters $\gamma^0$ and $\gamma^1$ in the logistic regression layer of the model determine the probability $(p_{kj}^\alpha)$ of a covariance link being present between regions $k$ and $j$ at baseline age $\alpha$.

## Analyses at discrete age groups

To benchmark our method with current brain network analyses which considers covariance networks at discrete age groups, we applied a simpler wombling model[1] on the ADNI cast study data on HC and AD groups. ROI connections with the largest change between young and old groups include the inferior temporal and parietal operculum for the HC group (top of Fig. 2) and the frontal gyrus and the parietal operculum for the AD (bottom of Fig. 2).

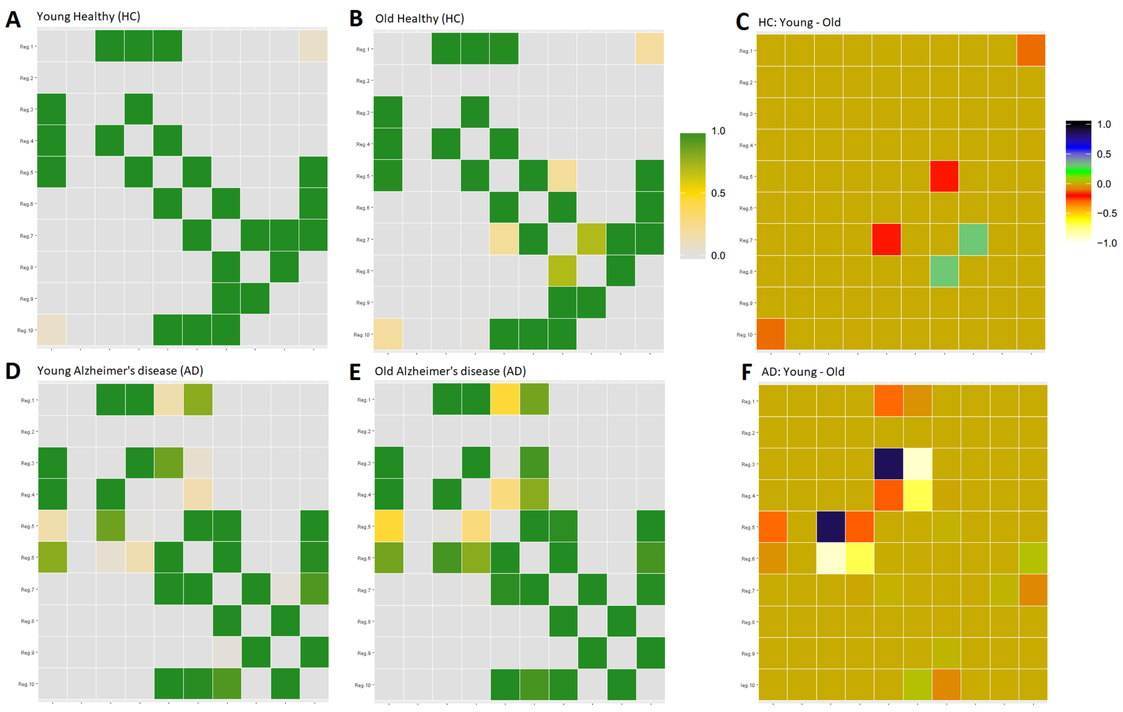


Figure 2: Covariance connectivity matrices results from the wombling algorithm for HC (top) and AD (bottom) diagnosis groups. Posterior means for data partitioned into young (age < 75, **A** and **D**) and old (age > 75, **B** and **E**) age ranges for HC and AD groups. Differences between young and old posterior means for HC (**C**) and AD (**F**) groups. The 10 ROI's considered in this work are the; (1) Supramarginal, (2) Entohirnal area, (3) Superior frontal gyrus, (4) Angular gyrus, (5) Parietal Operculum, (6) Superior temporal gyrus, (7) Middle temporal gyrus, (8) Inferior temporal gyrus, (9) Posterior cingulate gyrus and (10) the Insula.

## Dynamic wombling on healthy and AD patients

The marginal posterior probabilities over age $(p_{jk}^\alpha)$ and 80% credible intervals for selected connections are shown in Fig. 3 for HC (**A**) and AD (**B**) groups. Unlike the discrete analyses, which only provides information on the presence or absence of links, dynamic wombling estimates the age and length of time taken for connections to alter (if at all) while taking into account network uncertainty.

There is a posterior probability greater than 0.75 in the HC group of a link being present between the middle temporal gyrus and posterior cingulate over ages 60 to 90. In contrast with the AD group, which shows a decreasing probability as age increases. By age 75 and onwards, the probability of a connection between the same regions drops to less than 0.12.

For the first time in brain network research, network heterogeneity over age is estimated via a single model. The insight from this analyses shows the complex probabilistic patterns of brain covariance over age, and how they differ for healthy ageing and Alzheimer's disease progression.

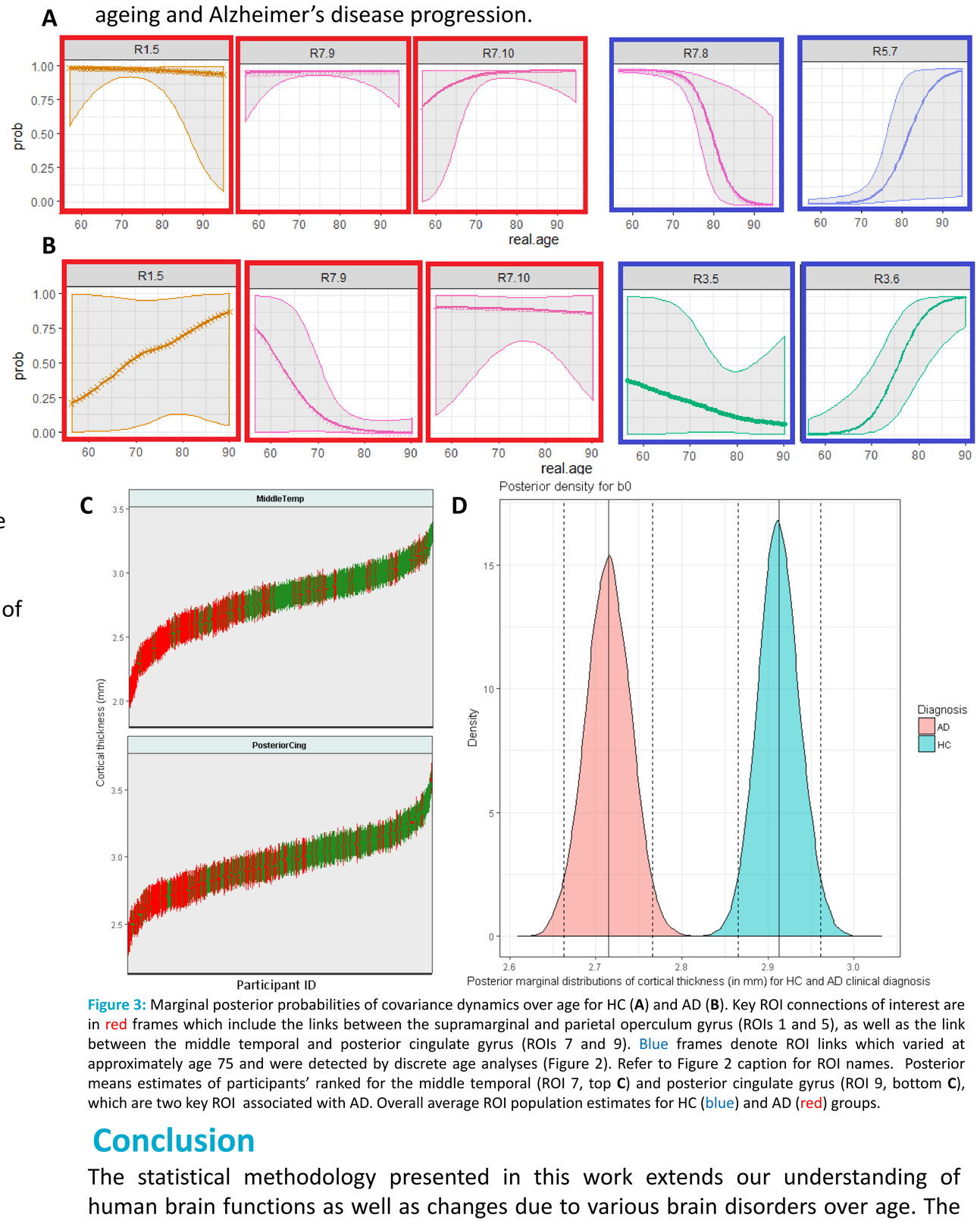


Figure 3: Marginal posterior probabilities of covariance dynamics over age for HC (**A**) and AD (**B**). Key ROI connections of interest are in red frames which include the links between the supramarginal and parietal operculum gyrus (ROIs 1 and 5), as well as the link between the middle temporal and posterior cingulate gyrus (ROIs 7 and 9). Blue frames denote ROI links which varied at approximately age 75 and were detected by discrete age analyses (Figure 2). Refer to Figure 2 caption for ROI names. Posterior means estimates of participants' ranked for the middle temporal (ROI 7, top **C**) and posterior cingulate gyrus (ROI 9, bottom **C**), which are two key ROI associated with AD. Overall average ROI population estimates for HC (blue) and AD (red) groups.

## Conclusion

The statistical methodology presented in this work extends our understanding of human brain functions as well as changes due to various brain disorders over age. The analyses presented in this work will help practitioners choose suitable statistical methods to identify key points in time when brain covariance connections change, in addition to morphological tissue estimates, which could potentially allow for targeted therapeutic interventions.

**FOR FURTHER INFORMATION**

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**REFERENCES**

[1] Cespedes et. al. (2017), *A Bayesian hierarchical approach to jointly model structural biomarkers and covariance networks* , ePrints 112807, https://eprints.qut.edu.au/112807/

[2] Leroux BG et. al. *Estimation of disease rates in small areas: a new mixed model for spatial dependence.* Statistical models in Epidemiology the Environment, and Clinical Trials, Elizabeth M & Berry D. (eds). Springer (2000); 179-191

[3] Simpson et. al. (2013), *Analyzing complex functional brain networks: fusing statistics and network science to understand the brain,* Statistics Surveys, **7:1**

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