Vertex-wise mixed modeling using QDECR

Erasmus MC — Universitair Medisch Centrum Rotterdam

Sander Lamballais, M. Arfan Ikram,
Meike W. Vernooij, Ryan L. Muetzel

Erasmus MC , Rotterdam, the Netherlands

Background

(video: https://qdecr.com/ohbm2020)

The cerebral cortex is commonly studied through surface-based methods by representing the cortical mantle as a vertex-based surface.

Most existing surface-based tools provide methods for vertex-wise generalized linear regression.

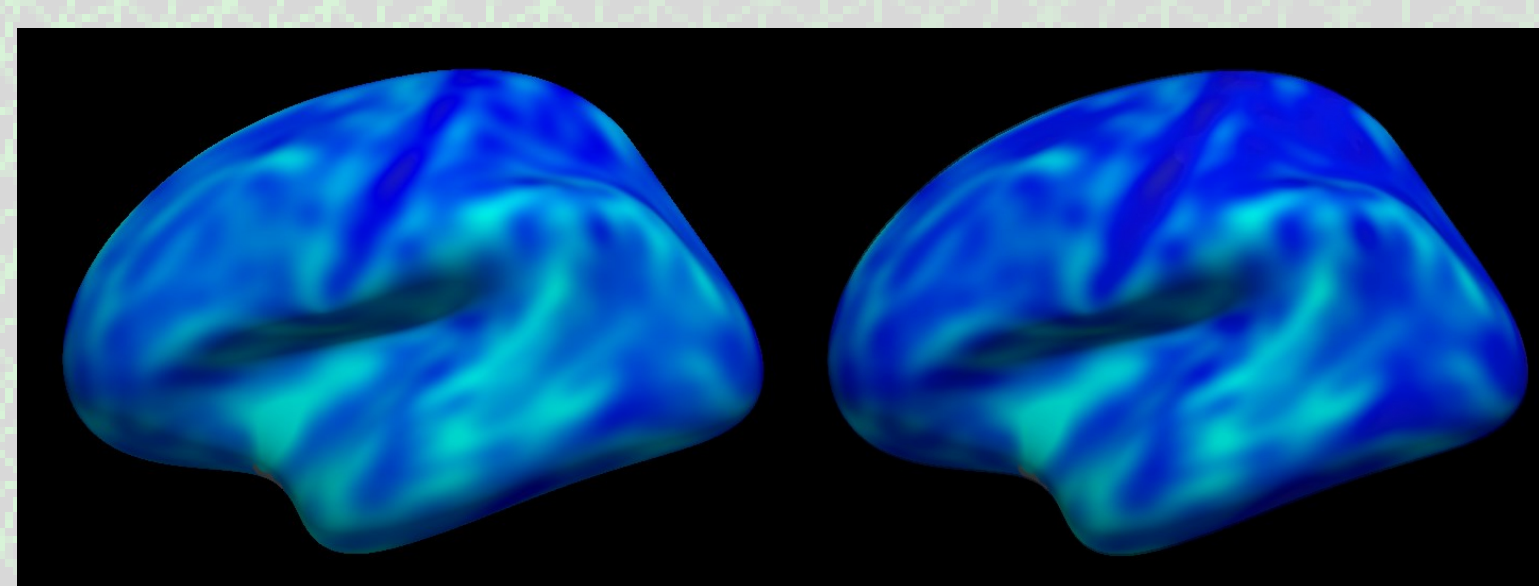However, certain study designs—such as those with repeated measures—benefit from mixed modeling.

Within QDECR[1,2], an R package for vertex-wise analyses, we created the qdecr_lmm function for the analysis of vertex-wise mixed models.
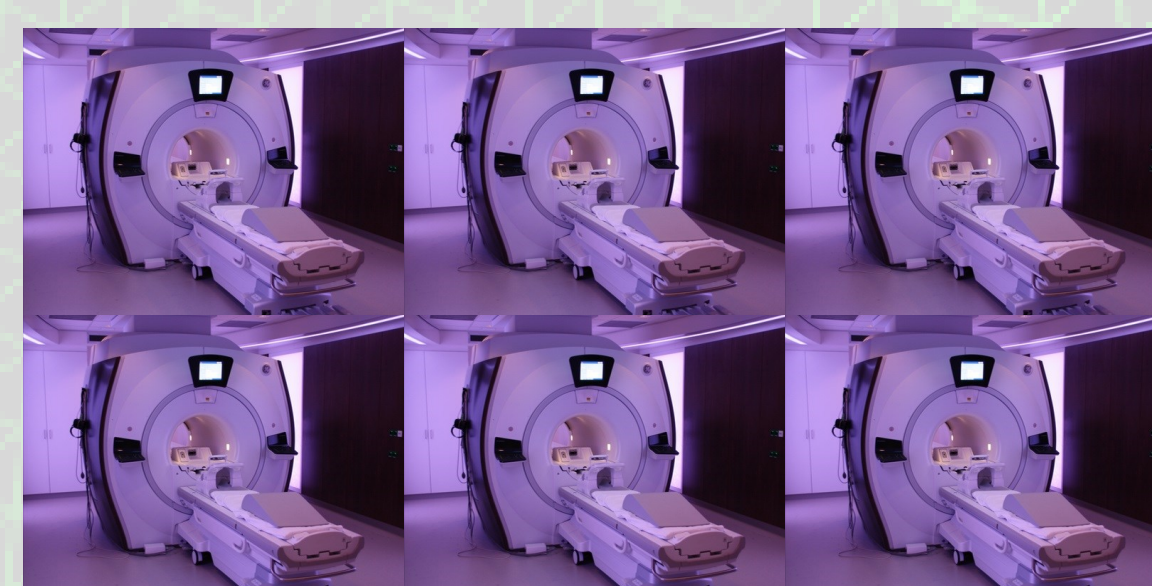
But why mixed models?

Mixed models contain both **fixed** and **random** effects. Fixed effects have effects that are assumed constant across individuals (e.g. age, sex) whereas random effects are not (e.g. time, scanner).

Two examples of designs that could benefit from mixed modeling:

Multiple time points   **Multiscanner studies**

Implementation

R is a programming language that focuses on statistical computing[3]. QDECR is an R package for surface-based, vertex-wise analyses[1,2]. QDECR links Freesurfer[4] surface-based output with phenotypic data to perform linear regression at each vertex. We created a function called `qdecr_lmm` that utilizes the existing QDECR modular structure to run linear mixed models.

The code is still in testing (alpha)

<u>Model</u>
The function `qdecr_lmm` creates a random intercepts model at every vertex. The model assumes compound symmetric covariance matrix, works with balanced and unbalanced data and is restricted to estimation of random intercepts.

<u>Data</u>
Freesurfer output data: Organized in one parent directory, or as one parent directory for each level of the random effect.
Phenotypic data: Long format data frame for unimputed, or several formats for multiple imputed datasets (see website).

<u>Formulas</u>
The `qdecr_lmm` model is specified using R formulas. The effect of sex on decline in vertex-wise cortical thickness with time is specified with two formulas:
Fixed effects: *qdecr_thickness ~ age_baseline + time * sex*
Random effects: *~ 1 | id*
These variables (apart from qdecr_thickness) should be present as column names in the phenotypic dataset. The `id` variable would refer to the identity column. `qdecr_thickness` denotes that the vertex-wise cortical thickness will be the outcome.

<u>Other</u>
The code can be parallelized across multiple cores to speed up the analysis. The code runs in about 10 minutes for a dataset of 2000 participants with 2 time points.

Proof of principle

To demonstrate the vertex-wise mixed model, we utilize T_1-weighted images from 2 time points of 2000 participants of the Rotterdam Scan Study[5]. The images were processed through Freesurfer 6.0[4]. The surface-based cortical thickness maps were registered to fsaverage space and were spatially smoothed with a 10 mm FWHM Gaussian Filter.
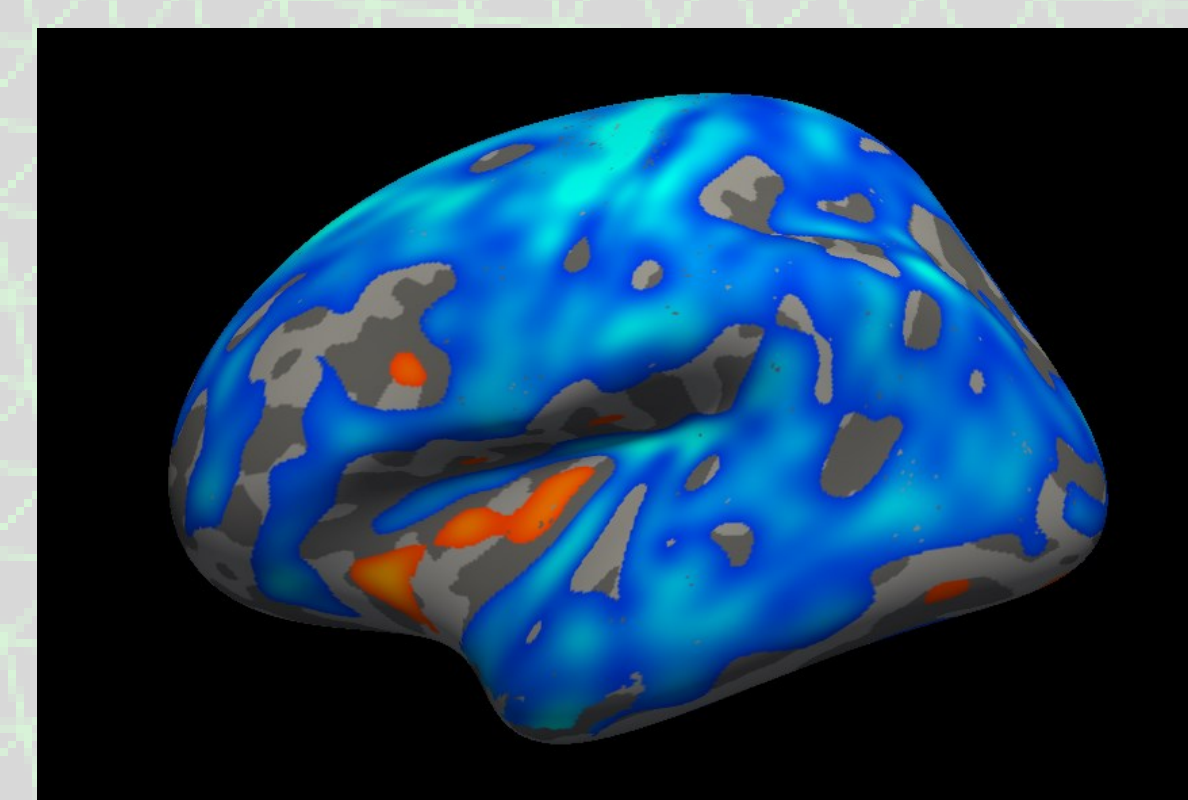
Research aim: To assess how sex and age affect cortical thickness

```
vw <- qdecr_lmm(qdecr_thickness ~ age + sex, id = "im",
          data = dd, random = ~1|id,
          hemi = "lh", project = "test")
```

Inspecting the significant clusters can be done with the `summary` function. Surfaces can be viewed in FreeView with the `freeview` function. Below the examples for the fixed effects of age and sex:
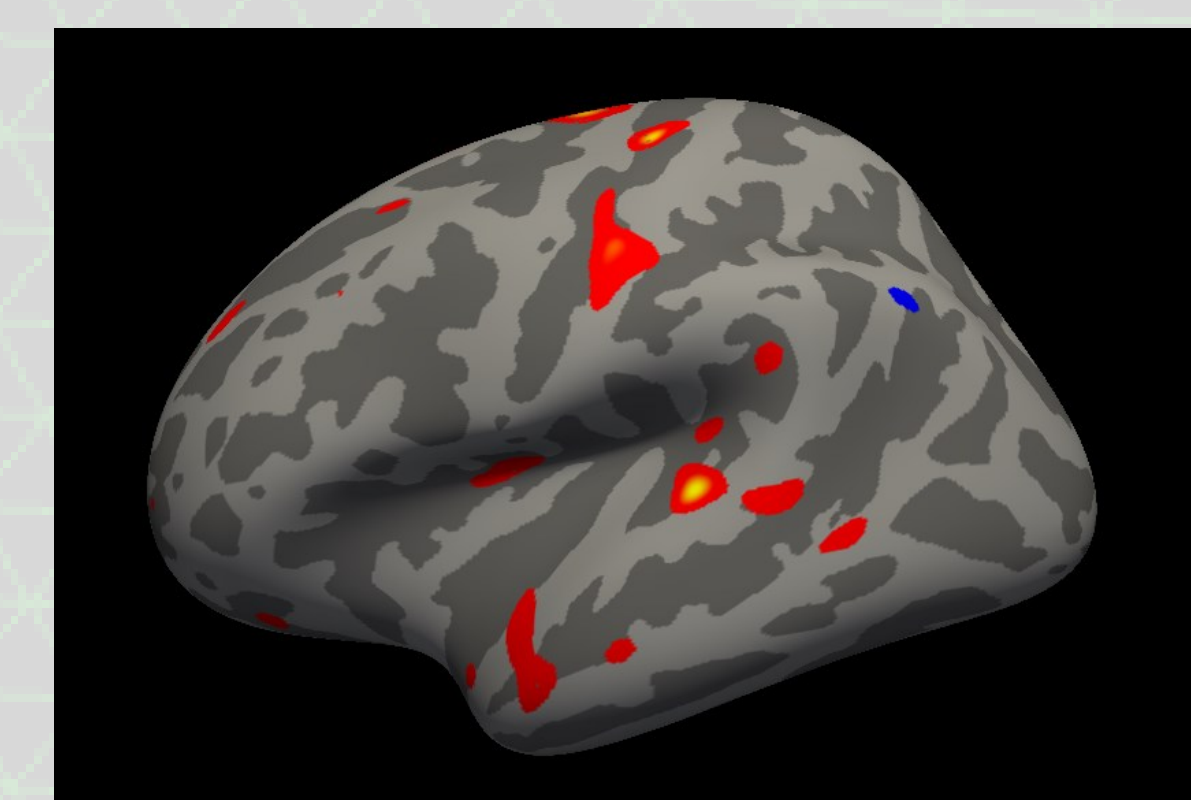
Age (time-covarying)   **Sex**
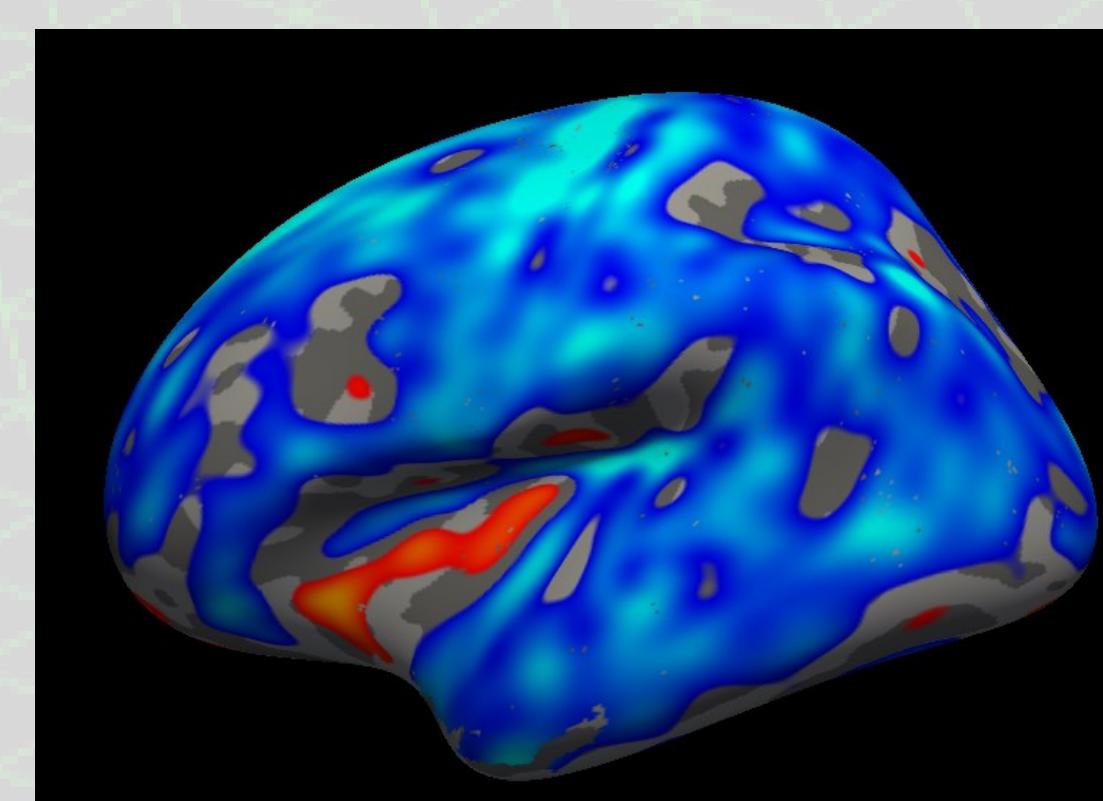freeview(vw, "age")   freeview(vw, "sexFemale")

To save out random intercepts, the `save_random` argument of `qdecr_lmm` has to be set to `TRUE`.

Research aim: To assess how sex associates with thickness change over time

```
vw <- qdecr_lmm(qdecr_thickness~age_baseline + sex*time,
          id = "im", data = dd, random = ~1|id,
          hemi = "lh", project = "test")
```
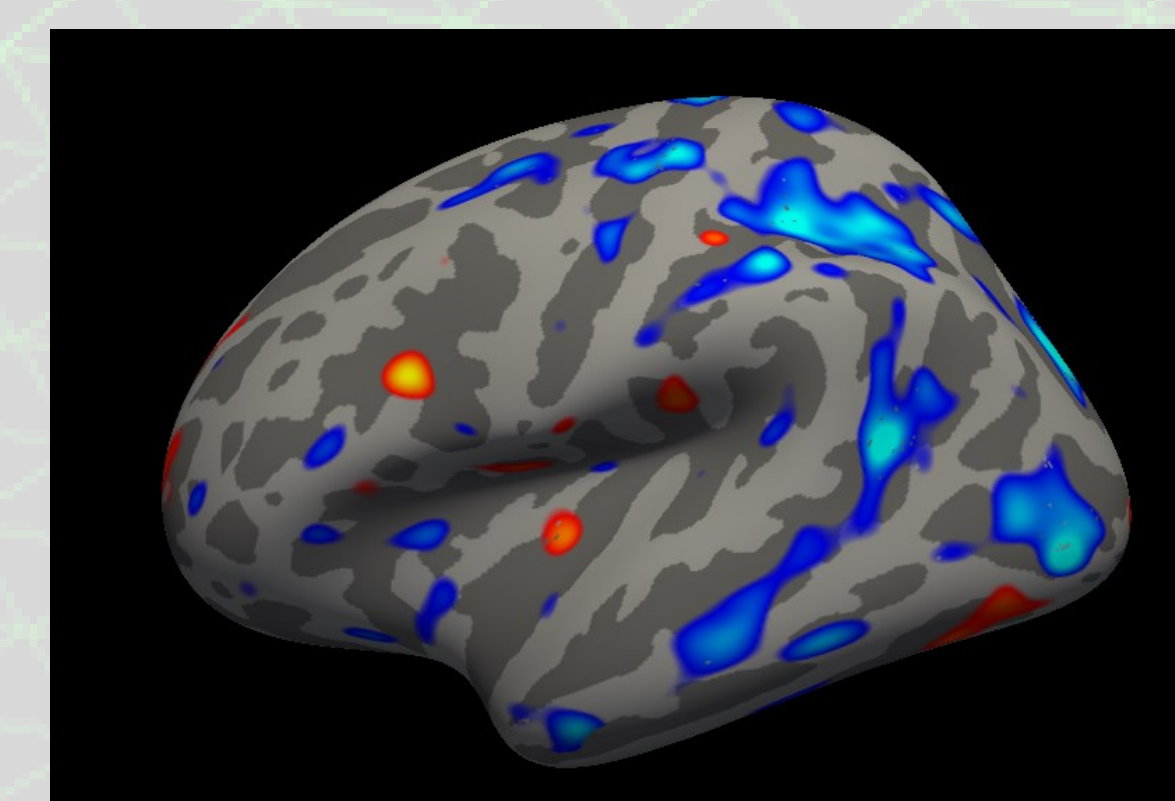
Age (baseline)   **Sex:time interaction**
freeview(vw, "age_baseline")   freeview(vw, 4)

Discussion

The `qdecr_lmm` function implements vertex-wise mixed modeling, and thus provides the opportunity to analyze longitudinal and hierarchical vertex-wise data using R.

The code will be made available under the GPL-3 license once testing is complete.

References

1. https://qdecr.com
2. Lamballais S, Muetzel RL. Code Ocean 2020. doi: 10.24433/CO.2177760.v1
3. https://www.R-project.org/
4. Fischl B. NeuroImage, 2012. doi: 10.1016/j.neuroimage.2012.01.021
5. Ikram M et al. Eur J Epi, 2015. doi: 10.1007/s10654-015-0105-7

www.qdecr.com   slamballais/QDECR   s.lamballaistessensohn@erasmusmc.nl   @slamballais