

# The ANTs Longitudinal Cortical Thickness Pipeline

Nicholas J. Tustison<sup>1,2</sup>, Andrew J. Holbrook<sup>3</sup>, Brian B. Avants<sup>4</sup>, Jared M. Roberts<sup>2</sup>, Philip A. Cook<sup>5</sup>,  
James R. Stone<sup>1</sup>, Daniel L. Gillen<sup>3</sup>, and Michael A. Yassa<sup>2</sup> for the Alzheimer's Disease  
Neuroimaging Initiative\*

<sup>1</sup>Department of Radiology and Medical Imaging, University of Virginia, Charlottesville, VA

<sup>2</sup>Department of Neurobiology and Behavior, University of California, Irvine, Irvine, CA

<sup>3</sup>Department of Statistics, University of California, Irvine, Irvine, CA

<sup>4</sup>Biogen, Cambridge, MA

<sup>5</sup>Department of Radiology, University of Pennsylvania, Philadelphia, PA

Corresponding author:

Nicholas J. Tustison

211 Qureshey Research Lab

Irvine, CA 92697-3800

540-383-2719

[ntustison@virginia.edu](mailto:ntustison@virginia.edu)

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## **Abstract**

Large-scale longitudinal studies of developmental progression or disease in the human brain have motivated the acquisition of large neuroimaging data sets and the concomitant development of robust methodological and statistical tools for insight into potential neurostructural changes. Longitudinal strategies for acquisition and processing have potentially significant benefits including the reduction of the inter-subject variability of corresponding cross-sectional studies. In this work, we introduce the open-source Advanced Normalization Tools (ANTs) cortical thickness longitudinal processing pipeline and its application on the Alzheimer's Disease Neuroimaging Initiative 1 data set consisting of over 600 subjects with multiple time points from baseline to 36 months. We show that single-subject template construction and native subject-space processing localizes data transformations and reduces interpolation artifacts, respectively, and is the preferred strategy for minimizing within-subject variability and maximizing between-subject variability. Furthermore, we demonstrate that these criteria lead to greater diagnostic predictive accuracy over other possible processing strategies. In the spirit of open-science, the ANTs software (including the longitudinal cortical thickness processing framework), regional data tables, and processing scripts are publicly available.

## Introduction

Quantification of brain morphology is invaluable for studying a wide range of neurological conditions with structural correlates (e.g., Alzheimer’s disease and frontotemporal dementia [1, 2], Parkinson’s disease [3], Williams syndrome [4], multiple sclerosis [5], autism [6], migraines [8], chronic smoking [9], alcoholism [10], cocaine addiction [11], schizophrenia [12], bipolar disorder [13], autism [6], marijuana use in adolescents [14], Tourette syndrome in children [15], scoliosis in female adolescents [16], heart failure [17], early-onset blindness [18], chronic pancreatitis [19], obsessive-compulsive disorder [20], ADHD [21], obesity [22], heritable [23] and elderly [24] depression, age [25], gender [26], untreated male-to-female transsexuality [27], handedness [28], intelligence [29], athletic ability [30], meditative practices [31], musical ability [32, 33], musical instrument playing [34], tendency toward criminality [35], childhood sexual abuse in adult females [36], and Tetris-playing ability in female adolescents [37]). Essential for thickness quantification are the many computational techniques which have been developed to provide accurate measurements of the cerebral cortex. These include various mesh-based (e.g., [38–40]) and volumetric techniques (e.g., [41–44]). Of noted significance, and representing the former, is the well-known and highly utilized FreeSurfer software package [45–49].

In inferring developmental processes, many of these studies employ cross-sectional population sampling strategies despite the potential for confounding effects [50]. Large-scale longitudinal studies, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI) [51], mitigate some of the relevant statistical issues. Similarly, much research has been devoted to exploring methodologies for exploiting such studies and avoiding various forms of processing bias [52]. Examples of the former include 4-D longitudinal segmentation [53, 54] and unbiased template creation [55, 56]. An example of the latter includes the bias associated with image spatial normalization to a designated coordinate system [57]. Briefly, interpolation-induced artifacts which occur during spatial normalization can artificially inflate effect size.

In [58], we introduced the Advanced Normalization Tools (ANTs) cortical thickness framework which leverages various pre-processing, registration, segmentation, and other image analysis tools that members of the ANTs and Insight Toolkit (ITK) communities have developed over the years and disseminated as open-source.<sup>1</sup> This proposed ANTs-based pipeline has since been directed at a variety of neuroimaging topics including mild cognitive impairment and depression [59], short term memory in mild cognitive impairment [60], and aphasia [61]. In this work, we introduce the ANTs longitudinal cortical thickness pipeline and use it to process the ADNI1 data set. We demonstrate that certain longitudinal processing choices have significant impact on

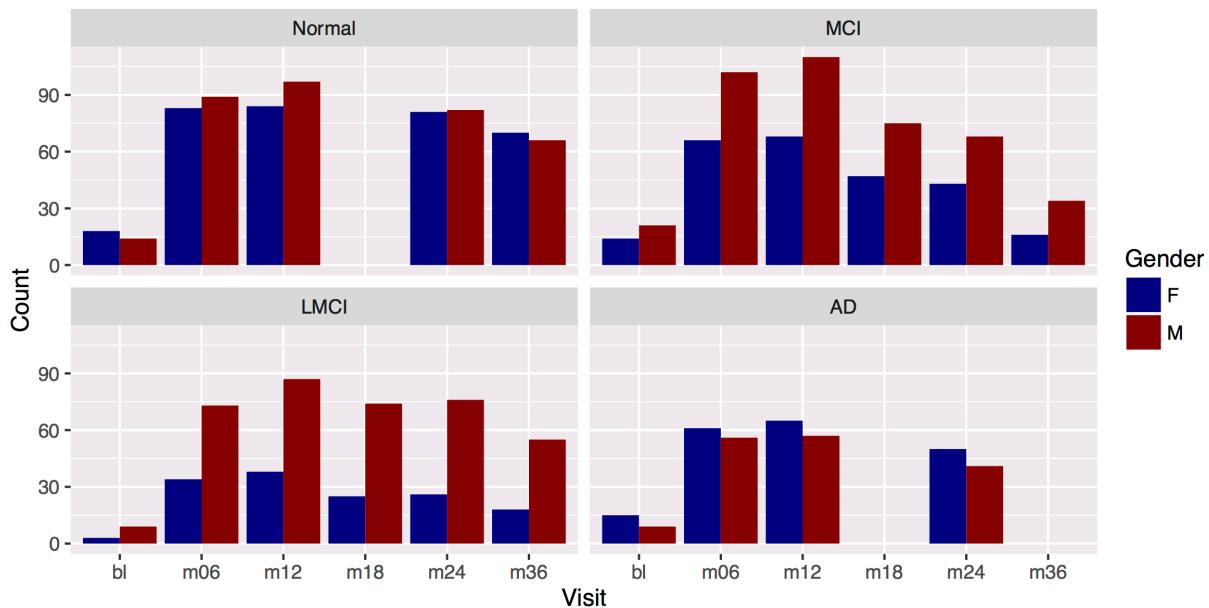
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<sup>1</sup><https://github.com/stnava/ANTs>

measurement quality in terms of within-subject and between subject variances which, in turn, heavily impacts the clinical interpretability of results.

## Methods and materials

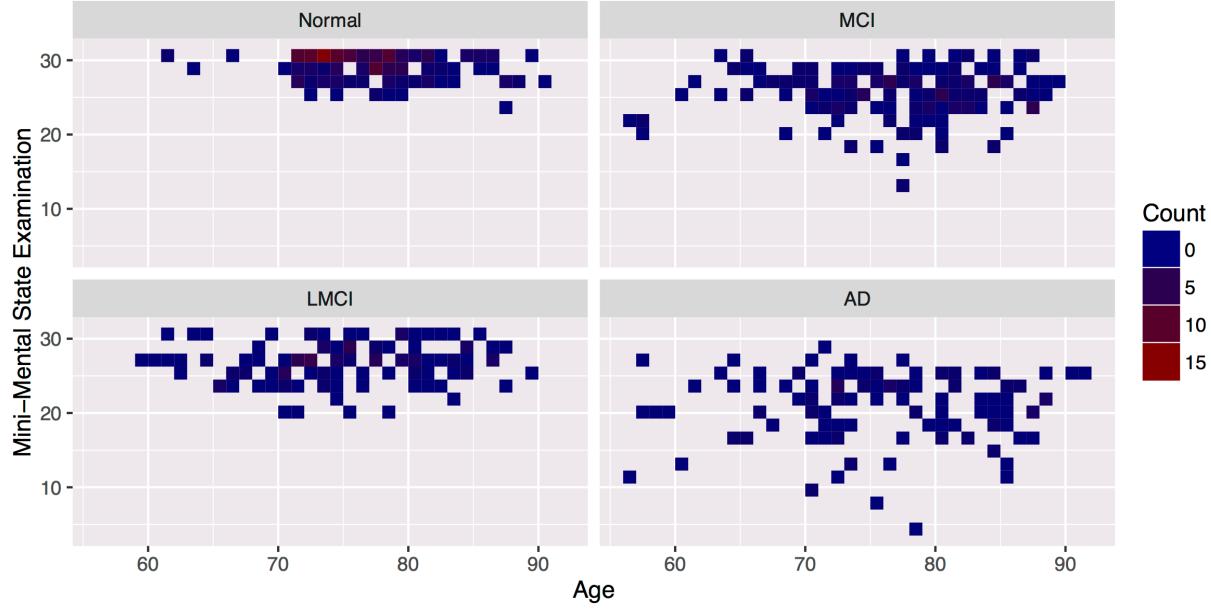
### Longitudinal ADNI imaging data



**Figure 1:** Demographic breakdown of the number of ADNI subjects by diagnosis i.e., normal, mild cognitive impairment (MCI), late mild cognitive impairment (LMCI), and Alzheimer’s disease (AD). Within each panel we plot the number of subjects (by gender) per visit—baseline (“bl”) and  $n$  months (“mn”).

The strict protocol design, large-scale recruitment, and public availability of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) makes it an ideal data set for evaluating the ANTs longitudinal cortical thickness pipeline. An MP-RAGE [62] sequence for 1.5 and 3.0 T was used to collect the data at the scan sites. Specific acquisition parameters for 1.5 T and 3.0 T magnets are given in Table 1 of [63]. Originally, collection goals were 200 elderly cognitively normal subjects collected at 0, 6, 12, 24, and 36 months; 400 MCI subjects at risk for AD conversion at 0, 6, 12, 18, 24, and 36 months; and 200 AD subjects at 0, 6, 12, and 24 months.

We downloaded the ADNI1 data in May of 2014. The data was first processed using the ANTs cross-sectional cortical thickness pipeline [58] (4399 total images). Data was then processed using the ANTs longitudinal stream (described in the next section) only including data for which at least two time points were available. In the final set of csv files we only included time points for which clinical scores (e.g., MMSE) were available. In



**Figure 2:** Age vs. Mini-mental examination (MMSE) scores for the ADNI subjects by diagnosis.

total, we included 186 elderly cognitive normals, 178 MCI subjects, 128 LMCI subjects, and 123 AD subjects. A further breakdown of demographic information is given in Figure X. Similarly, in Figure X, we show the 2-D distribution of age vs. mini-mental examination (MMSE) scores taken at the month 12 visit across diagnoses for the subjects analyzed.

### ANTs Cortical thickness estimation

#### Cross-sectional processing

A thorough discussion of the ANTs cross-sectional thickness estimation framework was previously discussed in [58]. Briefly, given a T1-weighted brain MR image, processing comprises the following five major steps (cf Figure X of [58]):

- N4 bias correction [64],
- brain extraction [65],
- Atropos six-tissue segmentation [66], and
- cortical thickness estimation [43].

ROI-based quantification is achieved through the use of the joint label fusion approach of [67] and the use of the MindBoggle-101 data labeled using the Desikan–Killiany–Tourville (DKT) protocol [68] consisting of 31 labels per hemisphere (cf Table 1). This pipeline has since been enhanced by the implementation [69] of a

patch-based denoising algorithm [70] as an optional preprocessing step and multi-modal integration capabilities.

**Table 1:** The 31 cortical labels (per hemisphere) of the Desikan-Killiany-Tourville atlas. The ROI abbreviations from the R `brainGraph` package are given and used in later figures.

1) caudal anterior cingulate (cACC)	17) pars orbitalis (pORB)
2) caudal middle frontal (cMFG)	18) pars triangularis (pTRI)
3) cuneus (CUN)	19) pericalcarine (periCAL)
4) entorhinal (ENT)	20) postcentral (postC)
5) fusiform (FUS)	21) posterior cingulate (PCC)
6) inferior parietal (IPL)	22) precentral (preC)
7) inferior temporal (ITG)	23) precuneus (PCUN)
8) isthmus cingulate (iCC)	24) rostral anterior cingulate (rACC)
9) lateral occipital (LOG)	25) rostral middle frontal (rMFG)
10) lateral orbitofrontal (LOF)	26) superior frontal (SFG)
11) lingual (LING)	27) superior parietal (SPL)
12) medial orbitofrontal (MOF)	28) superior temporal (STG)
13) middle temporal (MTG)	29) supramarginal (SMAR)
14) parahippocampal (PARH)	30) transverse temporal (TT)
15) paracentral (paraC)	31) insula (INS)
16) pars opercularis (pOPER)	

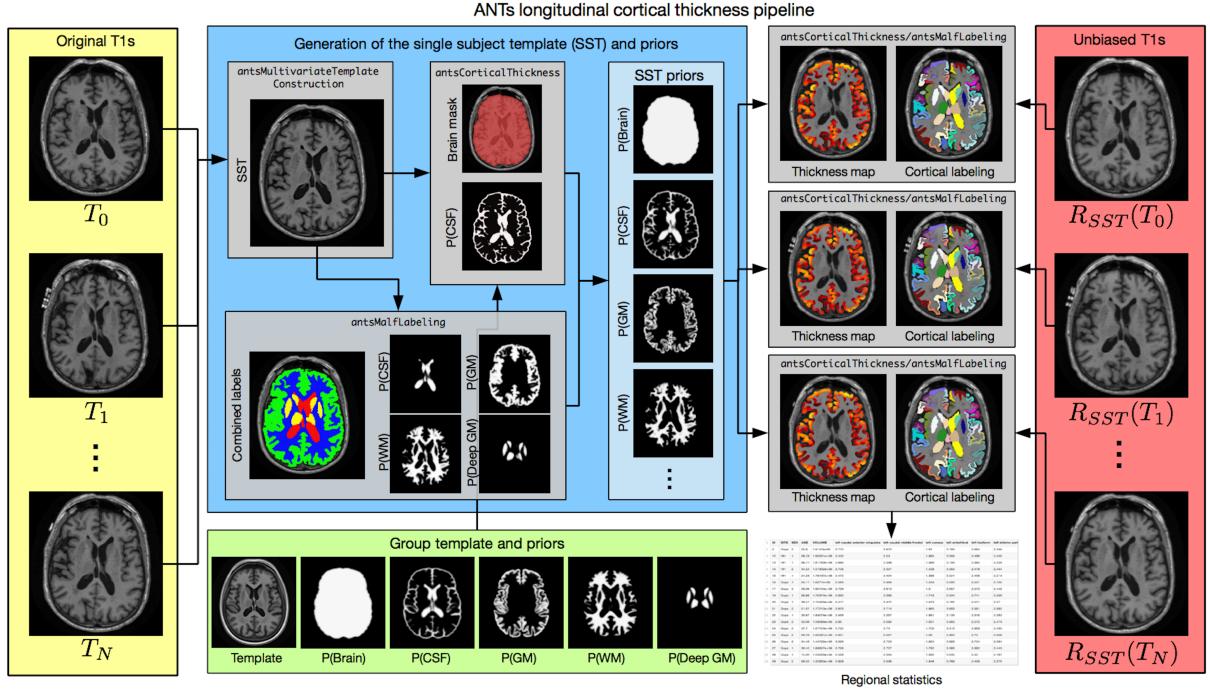
For evaluation, regional thickness statistics were calculated based on the DKT parcellation scheme. Test-retest error measurements were presented from a cohort of 20 atlases taken from the OASIS data set which had been manually labeled [68] and compared with the analogous FreeSurfer thickness values. Further evaluation employed a training/prediction paradigm whereby DKT regional cortical thickness values generated from 1205 images taken from four publicly available data sets (i.e., IXI [71], MMRR [72], NKI [73], and OASIS [74]) were used to predict age and gender using linear and random forest models. Although repeatability was comparable between the two packages, predictive accuracy was improved with ANTs versus FreeSurfer.

The resulting regional statistics (including cortical thickness, surface area [75], volumes, and Jacobian determinant values) are available online.<sup>2</sup> These include the corresponding FreeSurfer measurements which are also

<sup>2</sup><https://github.com/ntustison/KapowskiChronicles>

publicly available for research studies (e.g., [76]). Since publication this pipeline has been used in a number of cross-sectional studies (e.g., [77–79]).

### Unbiased longitudinal processing



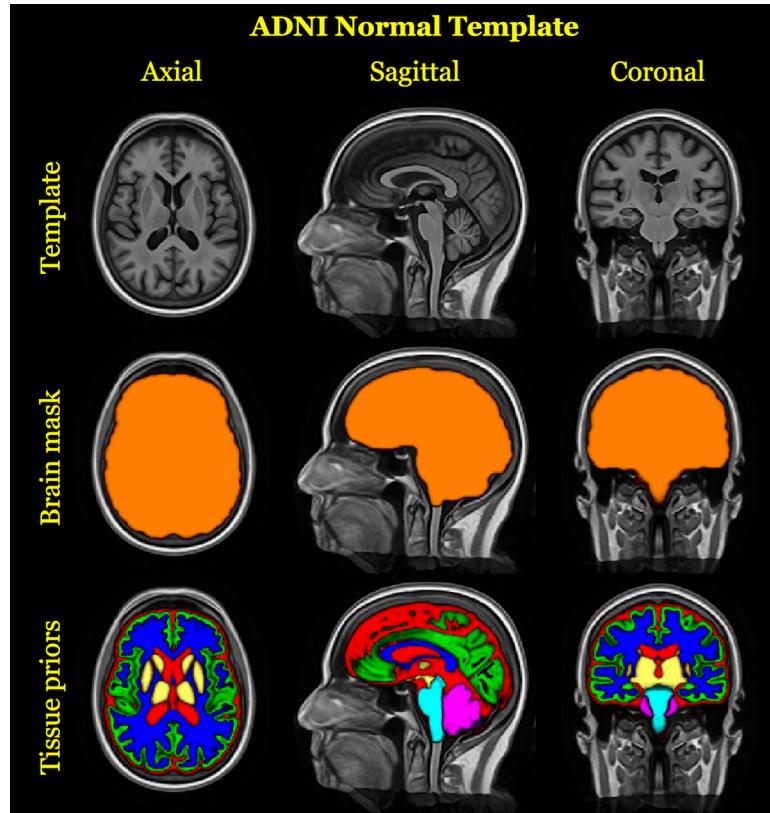
**Figure 3:** Diagrammatic illustration of the ANTs longitudinal cortical thickness pipeline for a single subject with  $N$  time points. From the  $N$  original T1-weighted images (left column, yellow panel) and the group template and priors (bottom row, green panel), the single-single subject template (SST) and auxiliary prior images are created (center, blue panel). These subject-specific template and other auxiliary images are used to generate the individual time-point cortical thickness maps. Optionally, one can rigidly transform the time-point images prior to segmentation and cortical thickness estimation (right column, red panel). For regional thickness values, regional labels can be propagated to each image using a given atlas set and cortical parcellation scheme.

Given certain practical limitations (e.g., subject recruitment and retainment), as mentioned earlier, many researchers employ cross-sectional acquisition and processing strategies for studying developmental phenomena. Longitudinal studies can significantly reduce inter-subject measurement variability. The ANTs longitudinal cortical thickness pipeline extends the ANTs cortical thickness pipeline for longitudinal studies which takes into account various bias issues previously discussed in the literature [52, 56, 57]. Given  $N$  time-point T1-weighted MR images and a group template and prior probability maps (described below), the longitudinal pipeline consists of the following steps:

1. Create single-subject template (SST) and prior probability maps.
2. (Optional): Transform each individual time point to the SST.
3. Apply the ANTs cross-sectional pipeline to each individual time-point using SST-based priors.

An overview of these steps is provided in Figure X which we describe in greater detail below. One of the most significant findings presented below is that the common step of transforming each individual time point to the SST is suboptimal in that the corresponding interpolation effects decrease the quality of cortical thickness measurements over segmentation and cortical thickness estimation in native space.

**ADNI normal group template.** Prior to any subject processing, the group template is generated from the population data [55] or one can use one of our publicly available templates [58]. For ADNI processing we created an ADNI-specific template from 52 normal subjects. We employed the brain extraction method described in [65] to create a corresponding probabilistic brain extraction map. We also generated six tissue prior probability maps for the CSF, gray matter, white matter, deep gray matter, brain stem, and cerebellum.



**Figure 4:** Top row: Canonical views of the template created from 52 normal subjects of the ADNI database. The prior probability mask for the whole brain (middle row) and the 6 tissue priors (bottom row) are used to “seed” each SST during longitudinal processing.

**Single-subject template, brain mask, and tissue priors.** Following the offline construction of the group template and prior probability images, each subject undergoes similar processing. First, an average shape and intensity single subject template (SST) is created from all time point images [55]. Subsequent processing segments the SST into six probabilistic tissues classes: cerebrospinal fluid (CSF), gray matter (GM), white matter (WM), deep gray matter (striatum + thalamus), brain stem, and cerebellum. This requires processing the SST through two parallel workflows. First, the SST proceeds through the standard ANTs cortical thickness pipeline which generates a brain extraction mask and the CSF posterior probability map. Second, using a data set of expert annotations [68], a multi-atlas joint label fusion step [67] is performed to create individualized probability maps for all tissue types. The five JLF probabilistic tissue estimates (GM, WM, deep GM, brain stem, and cerebellum) are used as the SST prior probabilities after smoothing with a standard deviation = 1 mm Gaussian kernel whereas the CSF SST prior probability is derived as a combination of the JLF and segmentation CSF estimates, i.e.,  $P(CSF) = \max(P_{Seg}(CSF), P_{JLF}(CSF))$ , also smoothed with the same smoothing operation. This final version of the SST enables unbiased mappings to the group template, subject-specific tissue segmentations, region of interest volumes and cortical thickness maps for each of the original time series images.

**Individual time point processing.** The T1-weighted image at each time point is rigidly aligned to the template and processed through cross-sectional cortical thickness pipeline using the SST template and auxiliary images (brain extraction mask and tissue priors).

Each time point image is then rigidly aligned to the SST. The SST prior probability maps are created using a protocol combining brain extraction and a six-tissue segmentation and a six-label joint label fusion processing of the SST. After the SST template priors are created, each time point image is rigidly aligned to the template to reduce the effect of coordinate system or interpolation bias.

**Pseudo-geodesic for large cohort labeling.** The cortical ROIs from the DKT atlases are propagated to each time point using a “pseudo-geodesic” mapping and joint label fusion.

## Statistical methods

We used a simple statistical principle to compare performance between cross-sectional and longitudinal processing methods. We said that one method outperforms the other when it does a better job minimizing within-subject variability and maximizing between-subject variability in cortical thickness measurements. Such a quality implies greater within-subject reproducibility while distinguishing between patient subpopulations. As such this will amount to higher precision when cortical thickness is used as a predictor variable or model

covariate in statistical analyses upstream. This criterion is immediately assessable in terms of estimates associated to the longitudinal mixed-effects model outlined below.

As previously noted we observed yearly cortical thickness measurements from sixty-two separate regions of interest. To assess the above variance criterion while accounting for changes that may occur through the passage of time, we used a hierarchical Bayesian model for parameter estimation. Let  $Y_{ij}^k$  denote the  $i^{th}$  individual's cortical thickness measurement corresponding to the  $k^{th}$  region of interest at measurement  $j$ . Under the Bayesian paradigm we utilized a model of the form

$$\begin{aligned} Y_{ij}^k &\sim N(\alpha_i^k + \beta^k t, \sigma_k^2) \\ \alpha_i^k &\sim N(\alpha_0^k, \tau_k^2) \quad \alpha_0^k, \beta^k \sim N(0, 10) \quad \sigma_k^2, \tau_k^2 \sim \text{Cauchy}^+(0, 5) \end{aligned} \tag{1}$$

Specification of parameters in the above prior distributions reflect commonly accepted diffuse priors.  $\tau_k^2$  represents the between-subject variance parameter, and  $\sigma_k^2$  represents the within-subject variance parameter. For each region, the quantity of interest is thus the ratio  $r^k = \frac{\tau_k^2}{\sigma_k^2}$ . This ratio is closely related to the intraclass correlation coefficient [80]. The posterior distribution of  $r^k$  was summarized via the posterior median. Where the posterior distributions were obtained using Stan probabilistic programming language [81].

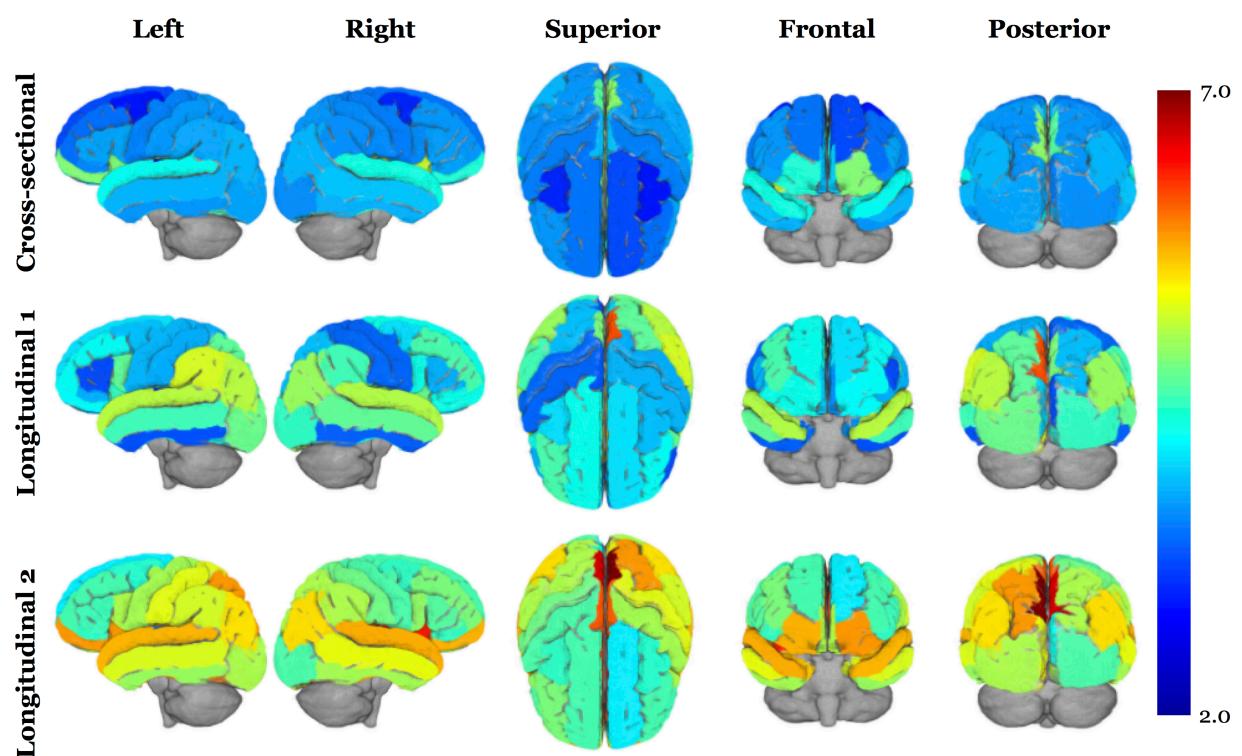
For each processing method we performed sixty-two independent regressions. In order to compare results between methods, we considered the quantity  $\delta^k = r_l^k - r_c^k$  and  $\delta_{norm}^k = \frac{r_l^k - r_c^k}{r_l^k + r_c^k}$ , denoting the variance ratio for the longitudinal method minus that of the cross-sectional method and the normed difference between ratios, respectively (cf Figure ??). Since a large  $r^k$  implies a higher between-subject to within-subject variability ratio, a positive estimate of  $\delta^k$  that is large in magnitude implies that the longitudinal processing method is preferable to the cross-sectional method. Conversely, a negative estimate that is large in magnitude implies that the cross-sectional processing method is preferable to the longitudinal method.

## Results

### Discussion

#### Subsection 1

And a sweet equation:



**Figure 5:** 3-D volumetric rendering of the normed difference of the longitudinal variance ratio minus the cross-sectional variance ratio specified for each of the 62 cortical regions.

$$\exp^{-i\pi}=-1$$

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