

# The ANTs Longitudinal Cortical Thickness Pipeline

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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-specific strategies for acquisition and processing have potentially significant benefits including the reduction of the inter-subject confound associated with 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 first phase of the Alzheimer's Disease Neuroimaging Initiative (ADNI-1) consisting of over 600 subjects with multiple time points from baseline to 36 months. We demonstrate that the single-subject template construction and native subject-space processing advantageously localizes data transformations and reduces interpolation artifacts and is the preferred processing strategy with respect to simultaneous minimization of within-subject variability and maximization of between-subject variability, respectively. It is further shown that optimizing these dual criteria leads to greater scientific interpretability in terms of tighter confidence intervals in calculated mean trends, smaller prediction intervals, and tighter confidence/credible intervals for determining cross-sectional effects. A complementary training/prediction evaluation provides additional evidence of the benefits of this framework.

*Keywords:* ANTs, Alzheimer's disease, bias, cortical thickness, interpolation, longitudinal processing

## Introduction

Quantification of brain morphology significantly facilitates the investigation of 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 studies involving longitudinal image acquisition of a targeted subject population, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI) [51], are designed to mitigate some of the relevant statistical issues. Analogously, much research has been devoted to exploring methodologies for properly exploiting such studies and avoiding various forms of processing bias [52]. For example, FSL’s SIENA (Structural Image Evaluation, using Normalization, of Atrophy) framework [53] for detecting atrophy between two time points avoids a specific type of processing bias by transforming the images to a midspace position between the two time points. As the authors point out “[i]n this way both images are subjected to a similar degree of interpolation-related blurring.” Consequences of this “interpolation-related blurring” were formally analyzed in [54] in the context of hippocampal volumetric change where it was shown that interpolation-induced artifacts can artificially inflate effect size [55]. These insights have since been used for making specific recommendations with respect to longitudinal image data processing [52, 56, 57].

In a series of papers [52, 58] the authors motivated the design and implementation of the longitudinal FreeSurfer variant partly inspired by these earlier insights and encapsulated by the overarching general principle of “treat[ing] all time points exactly the same.” It has since been augmented by integrated linear

mixed effects modeling capabilities [59] and has been used in a variety of studies including pediatric cortical development [60], differential development in Alzheimer’s disease and fronto-temporal dementia [61], and fatigue in the context of multiple sclerosis [62].

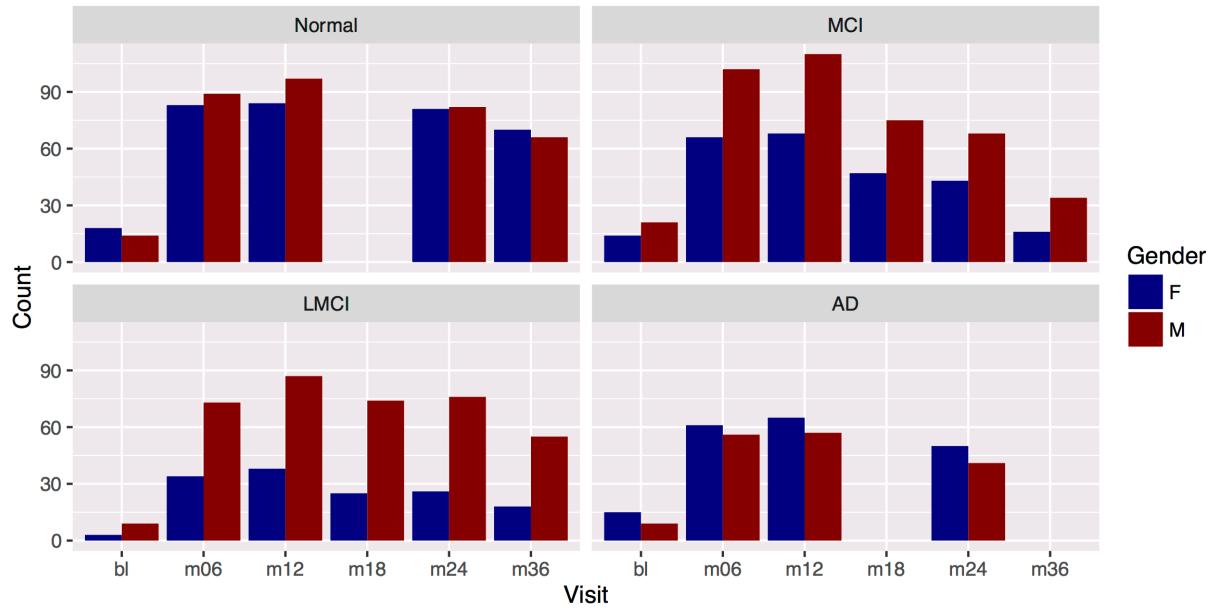
In [63], we introduced the Advanced Normalization Tools (ANTs) cortical thickness framework which leverages various pre-processing, registration, segmentation, and other image analysis tools that members of the ANTs and Insight Toolkit (ITK) open-source communities have developed over the years and disseminated publicly.<sup>1</sup> This proposed ANTs-based pipeline has since been directed at a variety of neuroimaging research topics including mild cognitive impairment and depression [64], short term memory in mild cognitive impairment [65], and aphasia [66]. In this work, we introduce the longitudinal version of the ANTs cortical thickness pipeline and demonstrate its utility on the publicly available ADNI-1 data set. In addition, we demonstrate that certain longitudinal processing choices have significant impact on measurement quality in terms of within-subject and between subject variances which, in turn, heavily impacts the scientific interpretability of results. Similar to other research illustrating the negative impact of interpolation effects on study results, we show that a common practice for unbiased processing induces a different set of problematic artifacts which guides processing choices for the proposed ANTs longitudinal pipeline. These choices for the ADNI-1 data produce tighter confidence intervals in calculated mean trends, smaller prediction intervals, and less varied confidence/credible intervals for discerning cross-sectional effects. To explore these findings in a more clinically oriented context, we use a machine learning-based training/prediction paradigm which demonstrates that the recommended longitudinal processing approach leads to improved predictive diagnostic accuracy over the alternative strategies.

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

## Methods and materials

### ADNI-1 imaging data

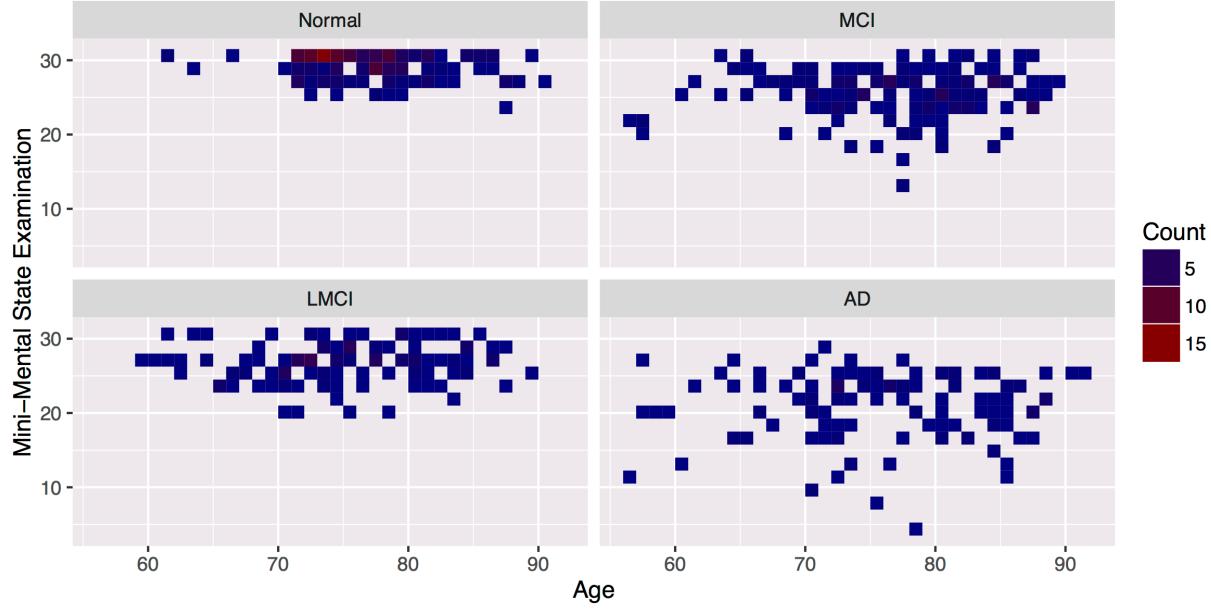


**Figure 1:** Demographic breakdown of the number of ADNI-1 subjects by diagnosis i.e., normal, mild cognitive impairment (MCI), late mild cognitive impairment (LMCI), and Alzheimer’s disease (AD). Within each panel we plot the number of subjects (by gender) per visit—baseline (“bl”) and  $n$  months (“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 [67] 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 [68]. As proposed, 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.

The ADNI-1 data was downloaded in May of 2014. The data was first processed using the ANTs cross-sectional cortical thickness pipeline [63] (4399 total images). Data was then processed using two variants of the ANTs longitudinal stream (described in the next section). In the final set of csv files (which we have made publicly available<sup>2</sup> in the github repository associated with this work), we only included time points for which clinical scores (e.g., MMSE) were available. In 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.

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



**Figure 2:** Age vs. Mini-mental examination (MMSE) scores for the ADNI-1 subjects by diagnosis.

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

#### *Cross-sectional processing*

A thorough discussion of the ANTs cross-sectional thickness estimation framework was previously discussed in [63]. As a brief review, given a T1-weighted brain MR image, processing comprises the following major steps (cf Figure 1 of [63]):

- N4 bias correction [69],
- brain extraction [70],
- Atropos  $n$ -tissue segmentation [71], and
- cortical thickness estimation [43].

ROI-based quantification is achieved through the use of the joint label fusion approach of [72] and the use of the MindBoggle-101 data labeled using the Desikan–Killiany–Tourville (DKT) protocol [73] consisting of 31 labels per hemisphere (cf Table 1). This pipeline has since been enhanced by the implementation [74] of a patch-based denoising algorithm [75] as an optional preprocessing step and multi-modal integration capabilities (e.g., joint T1- and T2-weighted processing).

**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.

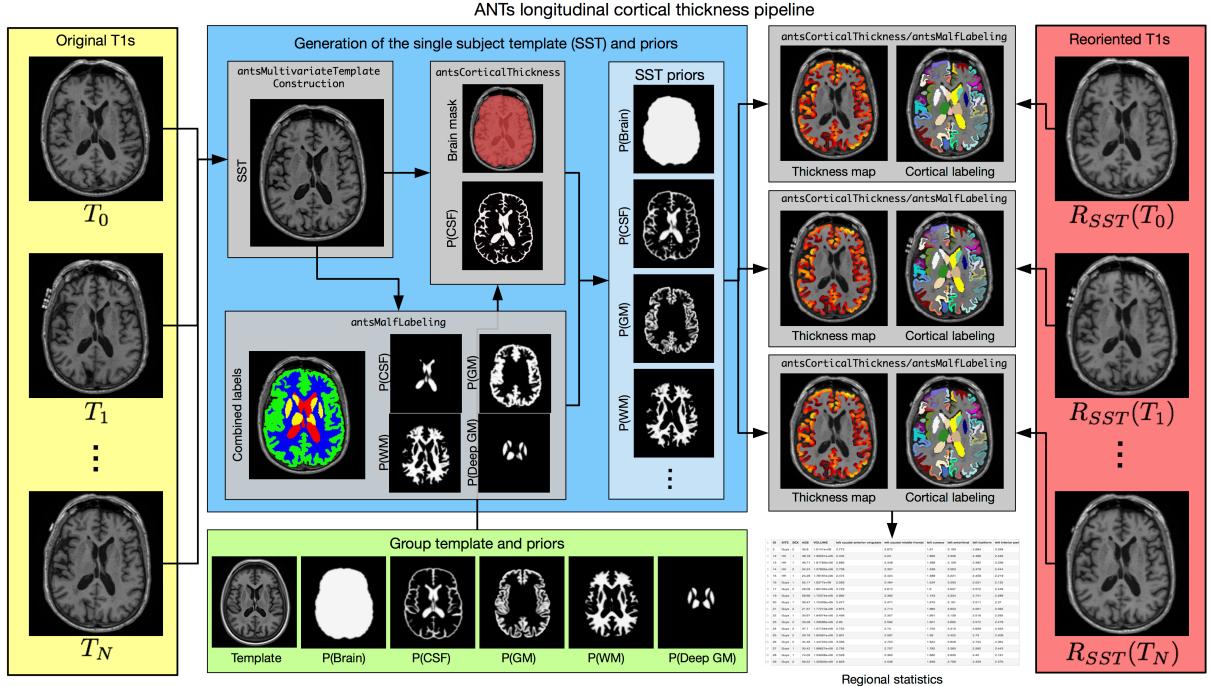
1) caudal anterior cingulate (cACC)	17) pars orbitalis (pORB)
2) caudal middle frontal (cMFG)	18) pars triangularis (pTRI)
3) cuneus (CUN)	19) pericalcarine (periCAL)
4) entorhinal (ENT)	20) postcentral (postC)
5) fusiform (FUS)	21) posterior cingulate (PCC)
6) inferior parietal (IPL)	22) precentral (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 summarized 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 [73] and compared with the corresponding 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 [76], MMRR [77], NKI [78], and OASIS [79]) were used to predict age and gender using linear and random forest [80] models. The resulting regional statistics (including cortical thickness, surface area [81], volumes, and Jacobian determinant values) were made available online.<sup>3</sup> These include the corresponding FreeSurfer measurements which are also publicly available for research inquiries (e.g., [82]). Since publication, this pipeline has been used in a number of cross-sectional studies (e.g., [83–85]).

#### *Unbiased longitudinal processing*

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<sup>3</sup><https://github.com/ntustison/KapowskiChronicles>



**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, on the other hand, 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, 54, 58] and, to our knowledge, interpolation effects not previously made explicit.

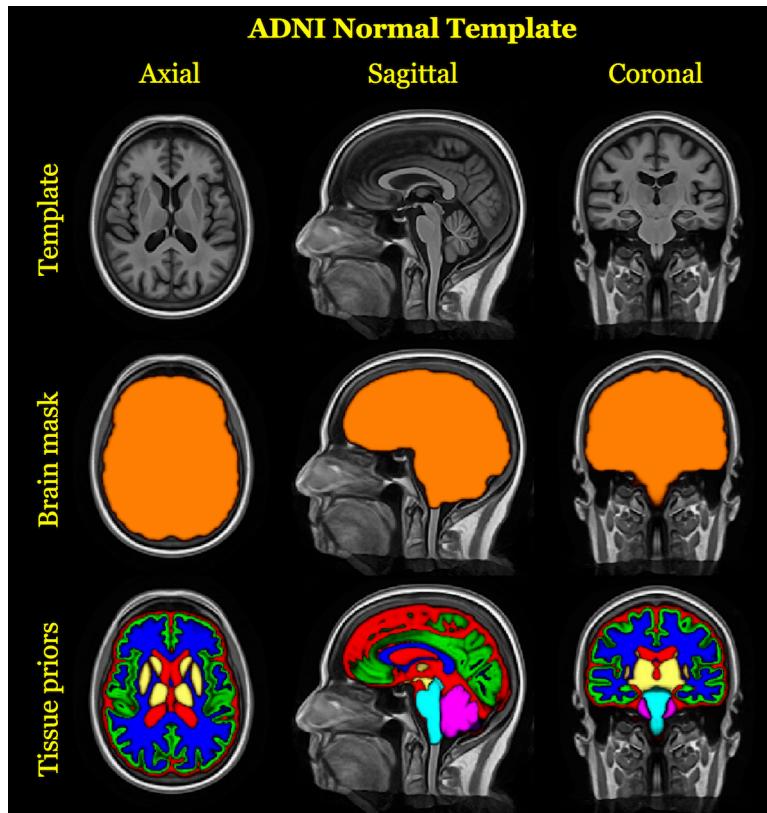
Given  $N$  time-point T1-weighted MR images, a group template, and group template prior probability maps (described below), the longitudinal pipeline consists of the following steps:

1. (Offline): Creation of the group template.
2. Creation of the single-subject template (SST).
3. Application of the ANTs cross-sectional pipeline to the SST.
4. Creation of the SST prior probability maps.
5. (Optional): Rigid transformation of each individual time point to the SST.
6. Application of the ANTs cross-sectional pipeline to each individual time-point image.
7. Joint label fusion to determine the cortical ROIs for analysis.

An overview of these steps is provided in Figure X which we describe in greater detail below.

**ADNI group template, brain mask, and tissue priors.** Prior to any individual subject processing, the group template is constructed from the population data [86]. For the ADNI-1 processing described in this work, we created a population-specific template from 52 cognitively normal ADNI-1 subjects. In addition, corresponding brain and tissue prior probability maps for the CSF, gray matter, white matter, deep gray matter, brain stem, and cerebellum were created as described in [63]. A brief overview of this process is also provided in the next section describing the single-subject template. Canonical views of the ADNI-1 template and corresponding auxiliary images are given in Figure X.

**Single-subject template, brain mask, and tissue priors.** Following the offline construction of the ADNI-1 group template and prior probability images, each subject undergoes identical processing. First, an average shape and intensity single subject template (SST) is created from all time point images [86] using the same protocol used to produce the ADNI-1 group template. Next, six probabilistic tissue maps (cerebrospinal fluid (CSF), gray matter (GM), white matter (WM), deep gray matter (striatum + thalamus), brain stem, and cerebellum) are generated in the space of the SST. This requires processing the SST through two parallel workflows. First, the SST proceeds through the standard cross-sectional ANTs cortical thickness pipeline which generates a brain extraction mask and the CSF tissue probability map,  $P_{Seg}(CSF)$ . Second, using a data



**Figure 4:** Top row: Canonical views of the template created from 52 cognitively normal subjects of the ADNI-1 database. The prior probability mask for the whole brain (middle row) and the six tissue priors (bottom row) are used to “seed” each single-subject template for creation of a probabilistic brain mask and probabilistic tissues priors during longitudinal processing.

set of 20 atlases from the OASIS data set that have been expertly annotated [73], a multi-atlas joint label fusion step (JLF) [72] 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) and JLF CSF estimate,  $P_{JLF}(CSF)$ , are used as the SST prior probabilities after smoothing with a Gaussian kernel ( $\sigma = 1mm$ ) whereas the CSF SST tissue 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 Gaussian kernel. Finally,  $P(CSF)$  is subtracted out from the other five tissue probability maps. The final version of the SST and auxiliary images enable 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.** In the FreeSurfer longitudinal stream, each time-point image is processed using the FreeSurfer cross-sectional stream. The resulting processed data from all time points is then used to create a mean, or median, single-subject template. Following template creation, each time-point image is rigidly transformed to the template space where it undergoes further processing (e.g., white and pial surface deformation). This reorientation to the template space “further reduce[s] variability” and permits an “implicit vertex correspondence” across all time points [52].

The ANTs longitudinal workflow shares some common aspects of its FreeSurfer analog but differs in others as outlined above. The first step for subject-wise processing involves the creation of an optimal mean shape/intensity template from all the time points [86]. For the cross-sectional ANTs processing, the group template and auxiliary images are used to perform tasks such as individual brain extraction and  $n$ -tissue segmentation prior to cortical thickness estimation [63]. However, for the longitudinal variant, the group template is used to create the SST auxiliary images. We then map the SST and corresponding probabilistic tissue maps to the native space of each time point where segmentation and cortical thickness is estimated. Note that this unbiased longitudinal pipeline is completely agnostic concerning ordering of the input time-point images, i.e. we “treat all time points exactly the same.”

During the initial development of this work, it was thought that rotating the individual time points to the SST would be of benefit, similar to FreeSurfer, in reducing variability, minimizing or eliminating possible orientation bias, and permitting a 4-D segmentation given that the underlying Atropos implementation is dimensionality-agnostic [71]. Regarding the latter, the possible benefit is potentially outweighed by the possibility of “over-regularization” [52] whereby smoothing across time reduces detection ability of large time point changes. Additionally, it is less than straightforward to accommodate irregular temporal sampling such as the acquisition schedule of the ADNI-1 protocol.

Most significantly, though, reorienting each time point image to the SST has significant detrimental measurement effects in which interpolation bias induces artificial anatomical changes and these changes correlate significantly with specific regions. Since we are measuring the thickness of the highly convoluted cortex involving measurements on the order of  $2 - 8\text{mm}$  from images with  $\sim 1\text{mm}^3$  voxels, these artificial changes significantly effect clinically related criteria of measurement quality such as confidence intervals and predictability. This is discussed further in Results.

**Joint label fusion and pseudo-geodesic for large cohort labeling.** Cortical thickness ROI-based analyses are performed using joint label fusion [72] and whatever cortical parcellation scheme is deemed appropriate for the specific study. The brute force application of the joint label fusion algorithm would require  $N$  pairwise registrations for each time point image where  $N$  is the number of atlases used. This would require a significant computational cost for a relatively large study such as ADNI. Instead, we use the “pseudo-geodesic” approach for mapping atlases to individual time point images. The transformations between the atlas and the group template are computed offline. With that set of transforms, we are able to concatenate a set of existing transforms from each atlas through the group template, to the SST, and finally to each individual time point.

## Statistical evaluation

To quantify the relative performance of the cross-sectional and longitudinal processing methods as a biomarker we considered a summary measure related to intra-class correlation. Specifically, we said that one processing 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 estimable from the longitudinal mixed-effects model () outlined below.

Longitudinal mixed-effect (LME) models comprise a well-established and widely used class of regression models designed to estimate cross-sectional and longitudinal linear associations between quantities while accounting for subject specific trends. As such, these models are useful for the analysis of longitudinally collected cohort data. Indeed, [59] provide an introduction to the mixed-effects methodology in the context of longitudinal neuroimaging data and compare it empirically to competing methods such as repeated measures ANOVA. For more complete treatments of the subject matter, see [87] and [88]. LME models are also useful for estimating and comparing within-subject and between-subject variability after conditioning out systematic time trends in longitudinally measured data. In the context of the current investigation, by fitting simple LME models

to the data resulting from cross-sectional and longitudinal processing techniques, we are able to quantify the relative performance of each approach with respect to within-subject, between-subject, and total variability in a way that [89] only hint at in their exposition of their longitudinal, FreeSurfer based methodology.

As previously noted we observed yearly cortical thickness measurements from sixty-two separate regions of interest. To assess the above variability-based criteria while accounting for changes that may occur through the passage of time, we used a Bayesian LME 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

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

Specification of parameters in the above prior distributions reflect commonly accepted diffuse priors [REFERENCE]. In this model,  $\tau_k$  represents the between-subject standard deviation, and  $\sigma_k$  represents the within-subject standard deviation, conditional upon time. For each region  $k$ , the quantity of interest is thus the ratio

$$r^k = \frac{\tau_k}{\sigma_k}, \quad k = 1, \dots, 62. \quad (2)$$

This ratio is at the heart of classical statistical discrimination methods as it features both in the ANOVA methodology and in Fisher's linear discriminant analysis. These connections are important since the utility of cortical thickness as a biomarker lies in the ability to discriminate between patient sub-populations with respect to clinical outcomes. It is also similar to the intra-class correlation coefficient [87]. The posterior distribution of  $r^k$  was summarized via the posterior median. Where the posterior distributions were obtained using the Stan probabilistic programming language [90].

For each processing method, we performed sixty-two independent, region-specific regressions. In order to compare results between methods, we considered the quantities

$$\delta^k = r_l^k - r_c^k, \quad \text{and} \quad \delta_{norm}^k = \frac{r_l^k - r_c^k}{r_l^k + r_c^k}, \quad (3)$$

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.

As a further assessment of utility as a biomarker, we used LME models and cortical thickness measurements of the entorhinal cortex to demonstrate how these variability criteria relate to potential scientific analyses. First, we used model () to show that a greater ratio of between-subject to within-subject variability results in tighter confidence and credible intervals on the slope parameter  $\beta$ . This result indicates more confidence with respect to mean trends over time that are of common interest when comparing subpopulations of patients. Second, we showed that smaller within-subject variability corresponds to smaller prediction intervals when predicting a subject's cortical thickness levels at future visits. This is important when considering regional cortical thickness measures as candidate biomarkers. Third, we use a simple linear regression model to compare the relationship between total variance and uncertainty with respect to cross-sectional effects. To do so, we regress baseline cortical thickness in the entorhinal cortex (EC) over baseline AD diagnostic status:

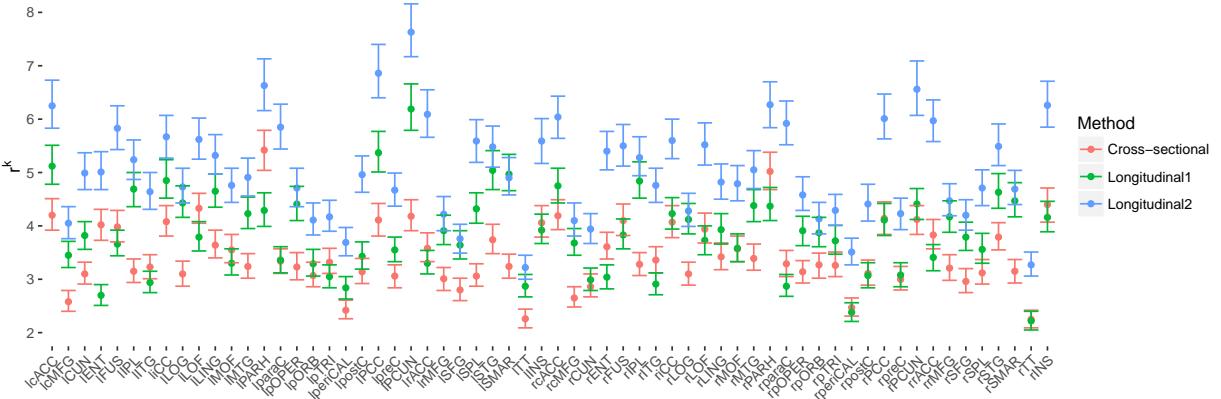
$$ECCT_i = \beta_0 + \beta_1 AD_i + \epsilon_i . \quad (4)$$

In general, lower total variability corresponds to tighter confidence/credible intervals for cross-sectional covariate effects, and hence higher certainty when evaluating linear associations between quantities such as cortical thickness and AD status. If total variability is similar across processing methods, we would expect to see credible intervals of roughly the same size.

## Results

This section presents processing method performance in 62 brain regions with respect to the variance ratio defined in (2) before demonstrating some ways in which different aspects of variability affect confidence in prediction and estimation.

Figure (5) provides resulting 95% credible intervals for the distributions of region specific variance ratios  $r^k = \tau_k/\sigma_k$ . Each processing method has its own color: blue, the color of the second longitudinal method, runs along the upper portions of the figure, rarely intersecting with green, the color of the first longitudinal method; green and orange, the color corresponding to the cross-sectional method, mix with each other nearer to the middle and bottom of the figure. The placement of the methods with respect to each other is meaningful. The higher the method, the larger the variance ratio corresponding to that method, and hence the greater discriminative capacity for the data corresponding to that processing method. Therefore, Figure (5) may be considered as evidence for method Longitudinal 2 [NEED TO COME UP WITH LABELS FOR THESE] providing higher quality data than that provided by the other methods. Looking past the strong performance of the second longitudinal method, the first longitudinal method and the cross-sectional method perform similarly to one another: Longitudinal 1 performs better in some regions, and the cross-sectional method performs better in others.



**Figure 5:** 95% credible intervals of the region specific variance ratios  $r^k = \tau_k/\sigma_k$  are presented for each processing method. The second longitudinal method dominates the others: its point estimates—posterior median—are greater than those of the other processing methods; and its credible intervals only overlap with those of the first longitudinal method once and never overlap with those of the cross-sectional method. These results suggest that data obtained using the Longitudinal 2 method have greater discriminative capacity than data obtained using the other methods.

Data quality translates directly to quality of statistical results and the scientific conclusions derived therefrom.

Hence, data with good variance and precision properties will benefit statistical analyses in multiple ways. To demonstrate these benefits, we focus on data from the entorhinal cortex and present three different aspects of variability and their statistical upshots. Table (2) presents different aspects of model variability and shows their relationships to uncertainty in prediction and estimation. Model variability is shown in terms of point estimates (posterior medians) for different functions of the variance terms from model (0). Predictive and estimation uncertainty takes the form of credible interval widths and predictive variance. The larger these quantities, the more uncertainty, and hence the less definite the scientific conclusions reached. Both raw and normalized results are presented. For each quantity, the cells corresponding to highest performance are colored green, and those corresponding to worst performance are colored red.

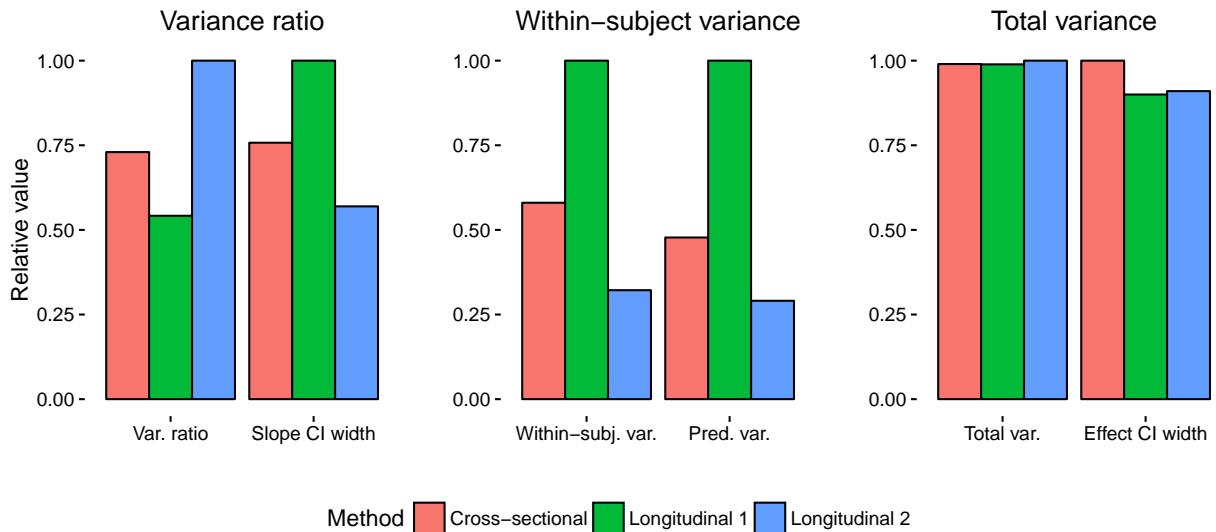
**Table 2:** Processing methods and EC statistical results

Method	$\frac{\tau}{\sigma}$	CI width <sup>1</sup>	$\sigma^2$	Variance <sup>2</sup>	$\sigma^2 + \tau^2$	CI width <sup>3</sup>
<b>Cross-sectional</b>						
<i>unnormalized</i>	3.82	0.0026	0.07	0.07	1.02	0.46
<i>normalized</i>	0.73	0.76	0.58	0.48	0.99	1
<b>Longitudinal 1</b>						
<i>unnormalized</i>	2.83	0.0034	0.11	0.15	1.02	0.41
<i>normalized</i>	0.54	1	1	1	0.99	0.90
<b>Longitudinal 2</b>						
<i>unnormalized</i>	5.23	0.0019	0.04	0.04	1.03	0.42
<i>normalized</i>	1	0.57	0.32	0.29	1	0.91

On the left of Table (2), the variance ratio is presented alongside the width of the credible interval corresponding to the slope parameter  $\beta$  from model (0). In general, a higher ratio of between-subject and within-subject variances implies greater precision when estimating trends and associations through time. As expected from the previous results regarding the ratio of between- and within-subject variability, the second longitudinal method yields the smallest credible interval on the slope parameter.

In the middle of Table (2), within-subject variability is presented alongside predictive variance, i.e. the median for each subject-specific empirical variance when predicting EC cortical thickness 6 months out from last observation. As might be expected these two quantities track closely to each other, since prediction variability is an amalgam of within-subject variability and uncertainty in model parameters. Again, the second Longitudinal method performs best, and the first performs worst.

Finally, the right side of Table (2), compares total variance to the width of credible intervals pertaining to the cross-sectional association of AD diagnosis and EC cortical thickness as modeled in Equation (4). As total variance rises, so too does uncertainty in cross-sectional effects. However, all three processing methods achieve roughly the same amount of total variability, so no trend is visible. It is interesting to observe that for this particular example the lower bound of the second longitudinal is farther from the null effect of zero when compared to the other two approaches. That is, despite having marginally greater total variance, the distance from zero for the credible interval corresponding to the second longitudinal method is 0.81, whereas the distances for the first longitudinal and cross-sectional methods are 0.75 and 0.70, respectively. Figure (6) displays the normalized results.



**Figure 6:** Aspects of model variance (see Section ??) are compared with credible interval sizes and variance in predictions. Values are normalized by the largest quantity, and processing methods are distinguished by color and ordering. On the left, the variance ratio  $r = \tau/\sigma$  is compared to the width of credible interval for the slope term of model (4). In the middle, within-subject variance  $\sigma^2$  is compared to predictive variance. On the right, total variance  $\sigma^2 + \tau^2$  is compared to width of credible interval for the cross-sectional association of AD status with EC cortical thickness.

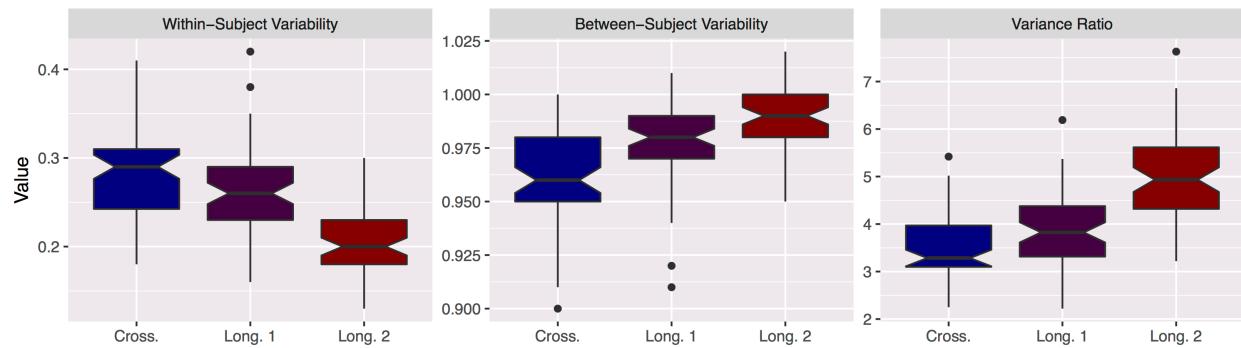
## (SUBSECTION TO REMOVE) Comparison of ANTs cortical thickness pipelines

As described previously, we employ a number of criteria to evaluate the performance of the ANTs cortical thickness longitudinal pipeline with the original cross-sectional workflow described previously [63]. Further, we look at two variants of the longitudinal pipeline: the first where each time point image is reoriented to the SST prior to segmentation and cortical thickness estimation (denoted as “longitudinal 1”) and the second

where each time point is processed in native space (denoted as “longitudinal 2”).

#### *Within-subject/between-subject variability*

Maximizing the between-subject variability while simultaneously minimizing the within-subject variability minimizes the overlap between groups implying a more significant effect of the condition separating the groups. In Figure X, we provide a general overview of how each of these three measurements compare across the three different ANTs pipeline variants over the 62 DKT regions. This illustrates the superiority of the longitudinal 2 pipeline where processing occurs in native space. It is also interesting to note that longitudinal 1 is an improvement over the cross-sectional processing in that, overall, it reduces both types of variability.

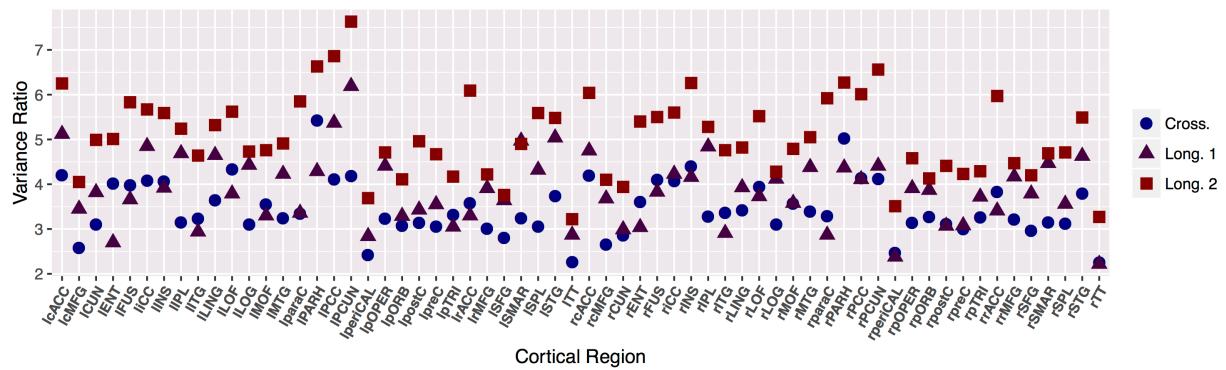


**Figure 7:** Notched box plots showing the distribution of the within-subject variability, between subject variability, and ratio of the between-subject variability and within-subject variability for each of the 62 DKT regions. Note that the “better” measurement maximizes this latter ratio.

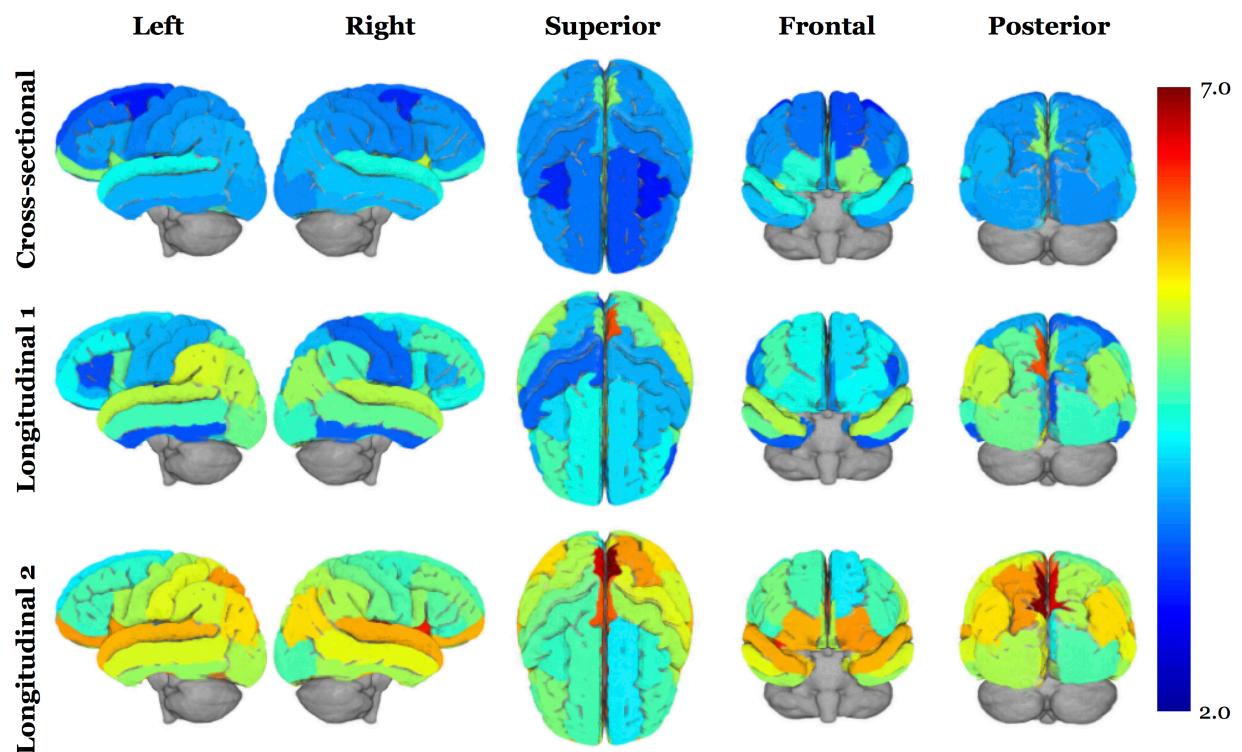
Further insights can be gleaned by looking at the ratio measurements per region (see Figure X). On a per region basis, longitudinal 2 outperforms both the cross-sectional and longitudinal 1 pipelines. Although longitudinal 1 is superior for the majority of the DKT regions over cross-sectional processing, exceptions include the left and right entorhinal, left and right fusiform, left and right inferior temporal, left and right paracentral, left and right parahippocampal, left and right posterior anterior cingulate, left lateral orbitofrontal, left medial orbitofrontal, left pars triangularis, right cuneus, right insula, right isthmus cingulate, right pericalcarine, right posterior cingulate right precentral, right postcentral, and right transverse temporal.

#### *Clinically-based assessment of measurement quality*

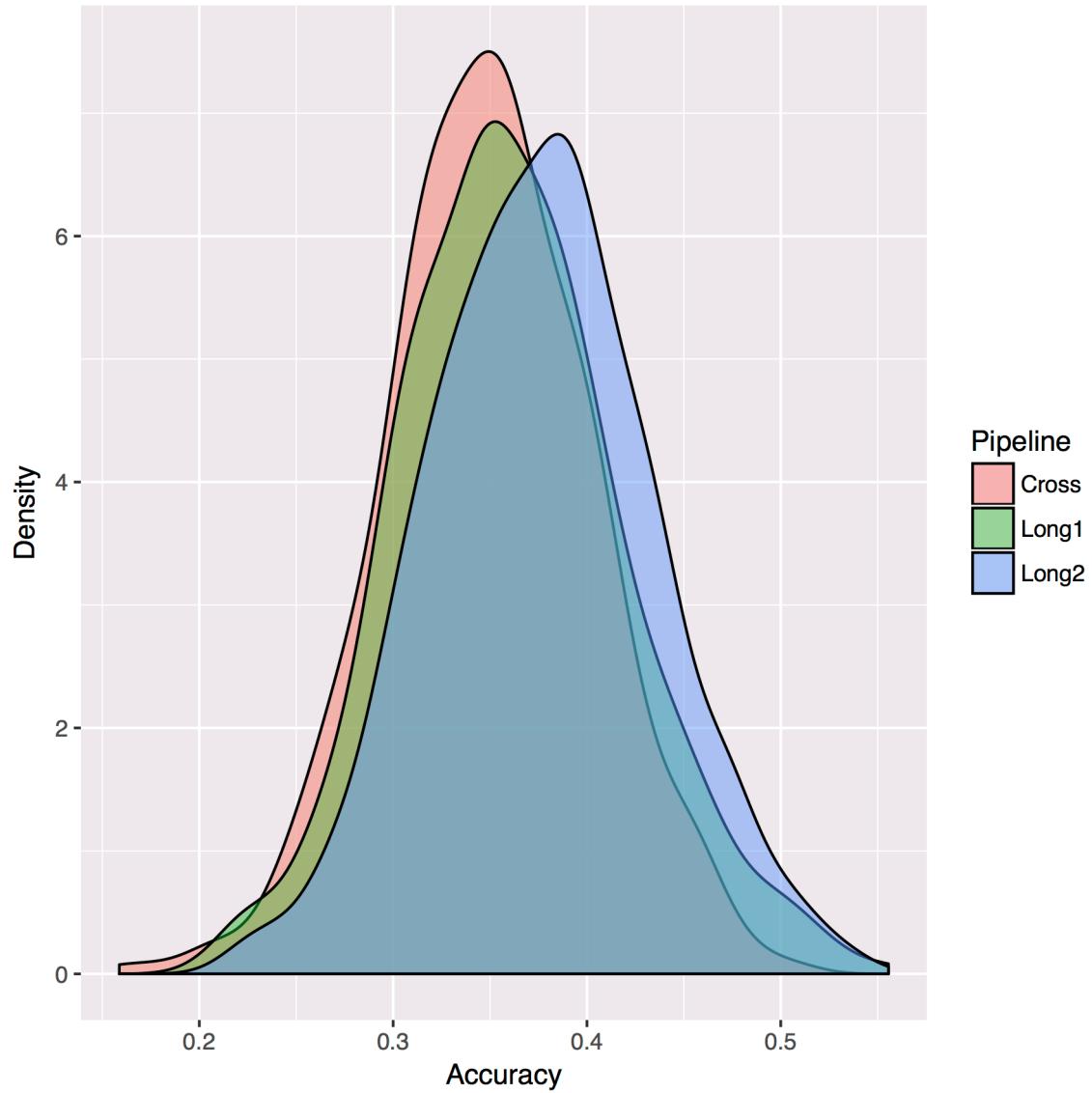
A clinically-based prediction strategy was performed to evaluate the quality of the cortical thickness measurements produced by each pipeline. The rate of thickness change determined over the set of subject imaging visits was used as a feature set for predicting diagnosis. The basic idea is that regional thinning is accelerated in some regions versus others which should be reflected in the assigned diagnostic category.



**Figure 8:** Per region quantities of the variance ratio (between-subject and within subject variability). These values are plotted spatially in Figure X.



**Figure 9:** 3-D volumetric rendering of the variance ratio values plotted in Figure X.

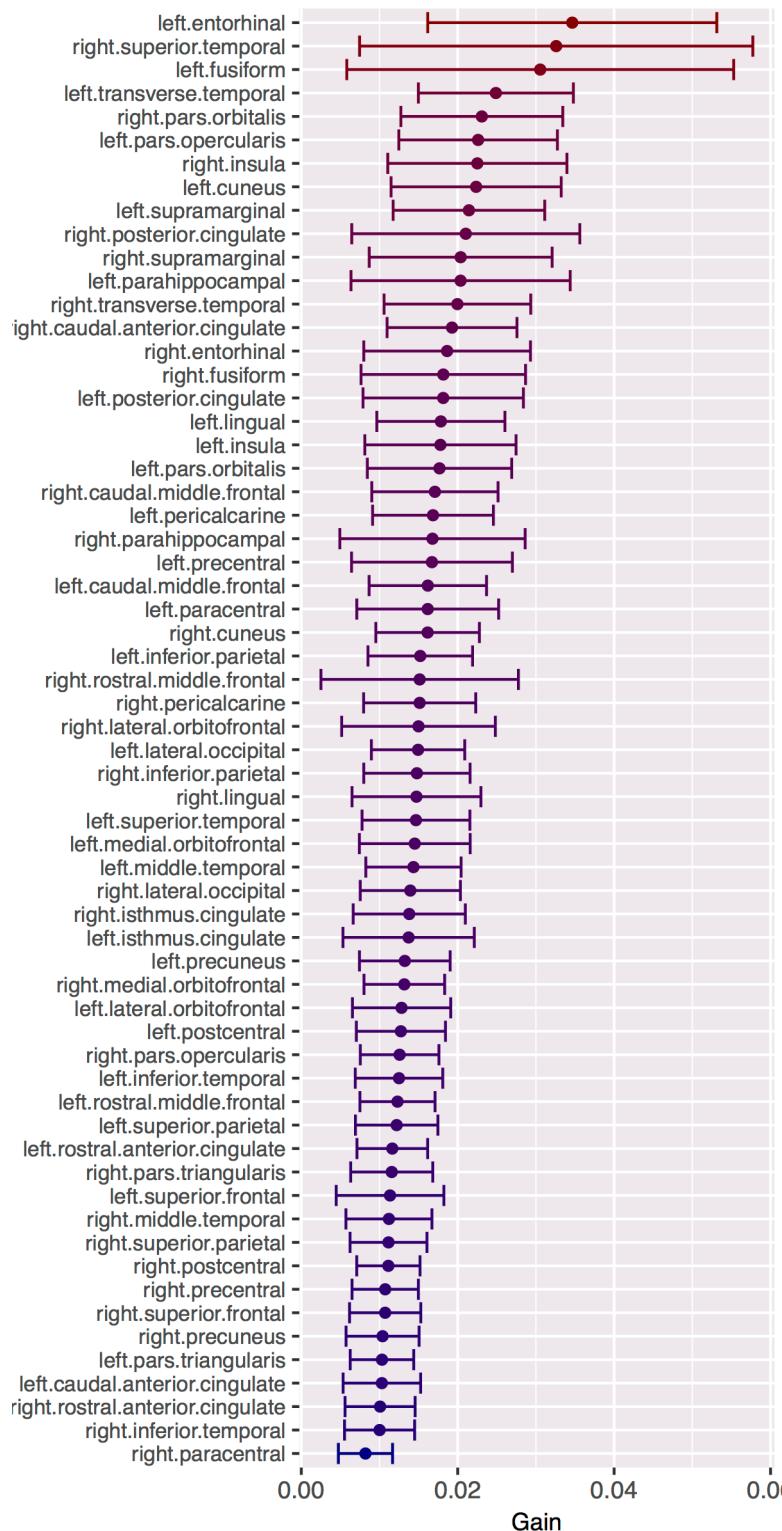


**Figure 10:** Density plot of the accuracy for each of the three pipeline choices. Accuracy was determined from the confusion matrices that were calculated for each of the 500 iterations. Using Tukey multiple comparisons of means at a 95% family-wise confidence level, the adjusted p-values were: Long1 – Cross = 0.067, Long2 – Cross < 1e-6, Long2 – Long1 = 0.00019.

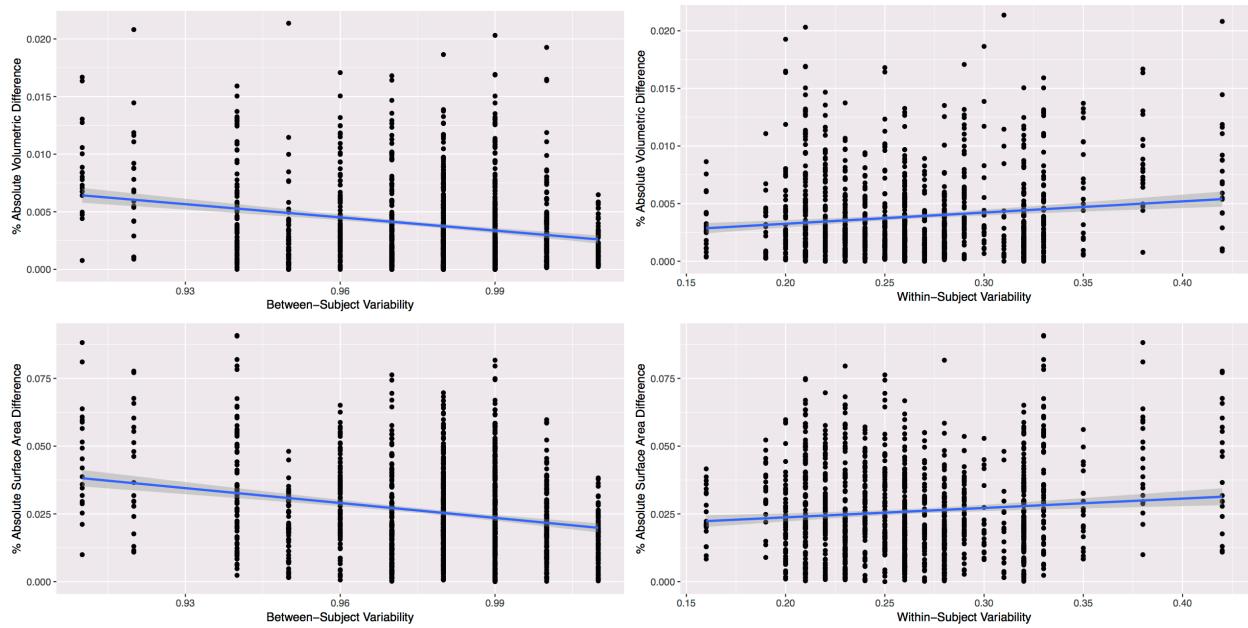
For each of 500 permutations, an extreme gradient boosting model [91] was constructed from 90% of the cortical thickness slope data corresponding to each pipeline. Based on previous experience, parameters of these models were chosen from the default parameters which included a gradient step of 0.6 and 100 iterations (or trees). The resulting models were then used to predict on the remaining 10% of the data. The resulting accuracy distributions are plotted in Figure X and compared statistically using Tukey's range test which indicated increasing performance Cross-sectional < Longitudinal 1 < Longitudinal 2. These models also provide means for assessing feature "importance" through the "Gain" values which describes "the improvement in accuracy brought by a feature to the branches [of the tree or iteration] it is on."

#### *Interpolation effects associated with Longitudinal 1 processing*

The subset of regions where the longitudinal 1 < cross-sectional in terms of the variance ratio caused us to investigate this issue further. Considering the only difference between longitudinal 1 and longitudinal 2 is the reorientation to the SST, our exploration focused on the effects of interpolation. Specifically, we suspected that interpolation artificially changes the anatomy (i.e., volume and surface area) which results in additive noise to the thickness measurements and that this effect varies spatially. To test this, we used the 20 DKT atlases [92] which were sampled from the OASIS data set. An optimal mean/shape template [86] was created from this cohort to which each T1-weighted image was rigidly registered. Using the resulting rigid transform, the label map of 62 regions was warped to the space of the template (similar in spirit to the protocol characterizing longitudinal 1) using nearest neighbor interpolation (check on this). Calculation of the volumes (by summing up the volume of each voxel) and surface areas (using a well-performing digitally-based surface estimator [81]) for each of the 62 regions were calculated both before and after transformation to the template. We then computed the percent change for each of the two anatomical measures and correlated those with the per subject variability which is plotted in Figure X.



**Figure 11:** The “gain” measurements of the extreme gradient boosting models for the Longitudinal 2 processing.



**Figure 12:** The between-subject variability (left) and within-subject variability (right) versus the volumetric (top) and surface area (bottom) measurements. Note that each of these correlations are significant ( $p < 0.001$ )

## **Discussion**

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