

# **The ANTs Longitudinal Cortical Thickness Pipeline**

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\*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)

## **Abstract**

Longitudinal studies of development 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 quantifying neurostructural changes. Longitudinal-specific strategies for acquisition and processing have potentially significant benefits including more consistent estimates of intra-subject parameters while retaining predictive power. 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) comprising 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 minimizes interpolation artifacts which simultaneously minimizes within-subject variability and maximizes between-subject variability. 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 machine learning 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, including neurodegenerative conditions such as Alzheimer’s disease [1, 2]. 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., [3–5]) and volumetric techniques (e.g., [6–9]). Of noted significance, and representing the former, is the well-known and highly utilized FreeSurfer software package [10–14].

In inferring developmental processes, many studies employ cross-sectional population sampling strategies despite the potential for confounding effects [15]. Large-scale studies involving longitudinal image acquisition of a targeted subject population, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI) [16], 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 [17]. For example, FSL’s SIENA (Structural Image Evaluation, using Normalization, of Atrophy) framework [18] for detecting atrophy between longitudinal image pairs 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 [19] in the context of hippocampal volumetric change where it was shown that interpolation-induced artifacts can artificially create and/or inflate effect size [20]. These insights and others have since been used for making specific recommendations with respect to longitudinal image data processing [17, 21–23].

In [17, 24] the authors motivated the design and implementation of the longitudinal FreeSurfer variant inspired by these earlier insights and 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 [25] and has been used in a variety of studies including pediatric cortical development [26], differential development in Alzheimer’s disease and fronto-temporal dementia [27], and fatigue in the context of multiple sclerosis [28].

In [29], 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 [30]. This proposed ANTs-based pipeline has since been directed at a variety of neuroimaging research topics including mild cognitive impairment and depression [31], short term memory in mild cognitive impairment [32], and aphasia [33]. Other authors extended the general framework to non-human studies [34, 35]. 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 the common practice of reorienting individual time point images to a single-subject template for unbiased processing induces interpolation 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-

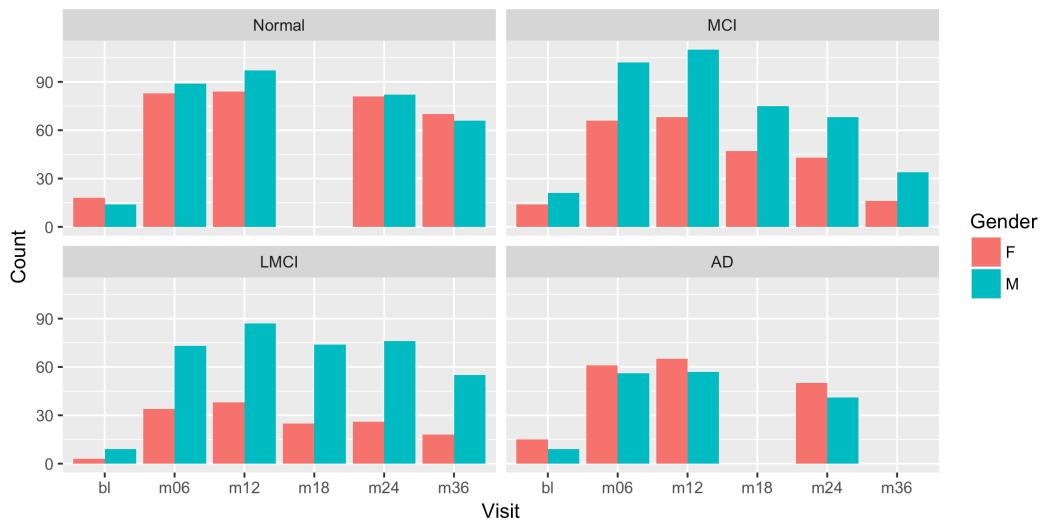
sectional effects. To explore these findings in a more clinically oriented context, we also use a machine learning-based training/prediction paradigm which demonstrates that the recommended longitudinal processing approach leads to improved predictive diagnostic accuracy over the alternative strategies, including cross-sectional processing.

## Methods and materials

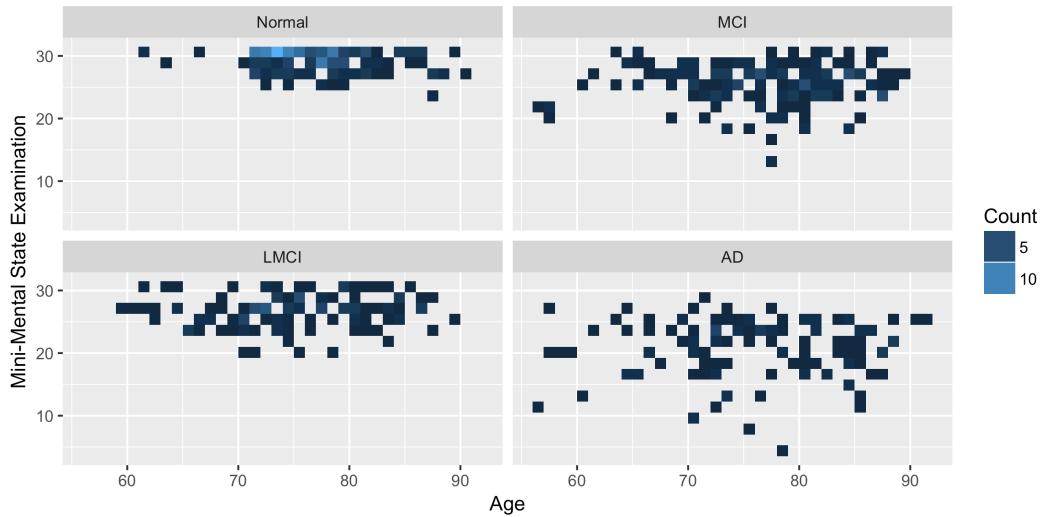
### ADNI-1 imaging data

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 [36] 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 [37]. 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 [29] (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 [38] 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 ( $n = \text{FIXME followup}$ ), 178 MCI subjects ( $n = \text{FIXME followup}$ ), 128 LMCI subjects ( $n = \text{FIXME followup}$ ), and 123 AD subjects ( $n = \text{FIXME followup}$ ).



**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”).



**Figure 2:** Age vs. Mini-mental examination (MMSE) scores for the ADNI-1 subjects by diagnosis providing additional demographic characterization for the subjects processed for this study.

Further breakdown of demographic information is given in Figures 1 and 2 to provide additional perspective on the data used for this work. **FIXME i think FIGURE 1 may be wrong or confusing. it looks like fewer than 30 subjects at baseline**

## ANTs cortical thickness

### *Cross-sectional processing*

A thorough discussion of the ANTs cross-sectional thickness estimation framework was previously discussed in [29]. As a brief review, given a T1-weighted brain MR image, processing comprises the following major steps (cf Figure 1 of [29]):

1. N4 bias correction [39],
2. brain extraction [40],
3. Atropos  $n$ -tissue segmentation [41], and

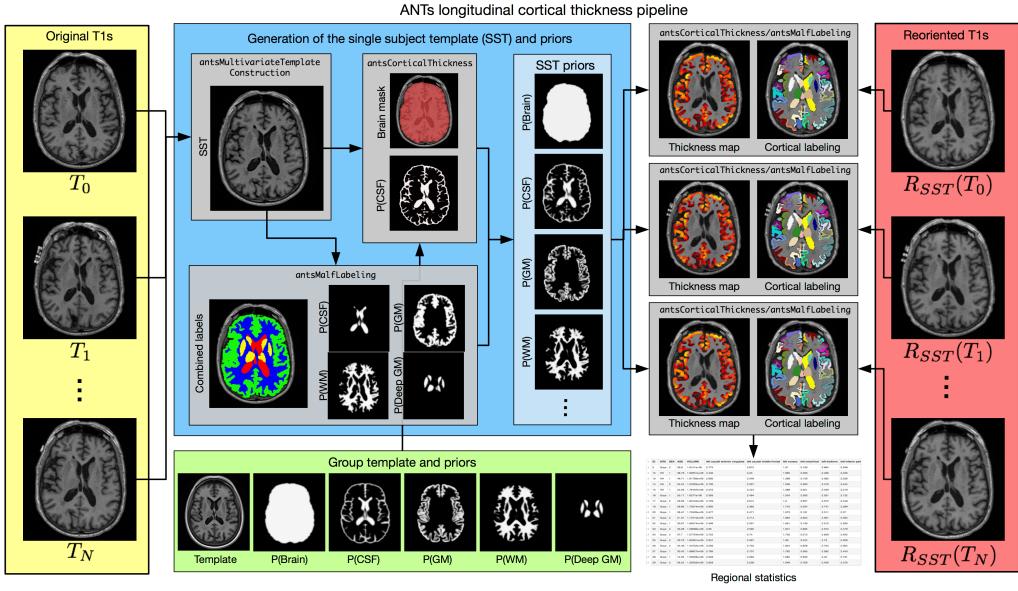
#### 4. cortical thickness estimation [8].

ROI-based quantification is achieved through the use of the joint label fusion approach of [42] and the use of the MindBoggle-101 data labeled using the Desikan–Killiany–Tourville (DKT) protocol [43] consisting of 31 labels per hemisphere (cf Table 1). This pipeline has since been enhanced by the implementation [44] of a patch-based denoising algorithm [45] as an optional preprocessing step and multi-modal integration capabilities (e.g., joint T1- and T2-weighted processing).

For evaluation, voxelwise 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 [43] 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 [46], MMRR [47], NKI [48], and OASIS [49]) were used to predict age and gender using linear and random forest [50] models. The resulting regional statistics (including cortical thickness, surface area [51], volumes, and Jacobian determinant values) were made available online [52]. These include the corresponding FreeSurfer measurements which are also publicly available for research inquiries (e.g., [53]). Since publication, this framework has been used in a number of studies (e.g., [54–56]).

#### *Unbiased longitudinal processing*

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



**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, in the individual time point's native space (denoted as “Longitudinal-native” in the text). Optionally, one can rigidly transform the time-point images prior to segmentation and cortical thickness estimation (right column, red panel). This alternative processing scheme is referred to as “Longitudinal-SST”. For regional thickness values, regional labels can be propagated to each image using a given atlas set and cortical parcellation scheme.

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

longitudinal studies which takes into account various bias issues previously discussed in the literature [17, 19, 24].

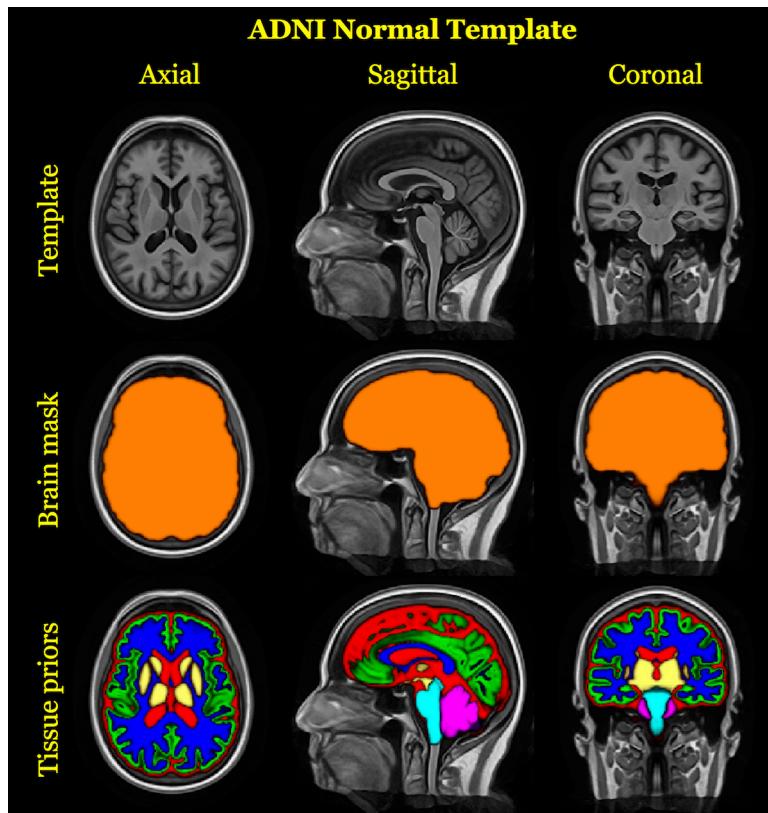
Given  $N$  time-point T1-weighted MR images (and, possibly, other modalities) and representative images to create a population-specific template and related images, the longitudinal pipeline consists of the following steps:

1. (Offline): Creation of the group template and corresponding prior probability images.
2. Creation of the unbiased single-subject template (SST).
3. Application of the ANTs cross-sectional pipeline to the SST. This processes the SST based on the group template.
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 – with SST as reference template – to each individual time-point image. This processes individual time points based on the SST yet also allows concatenation of transforms to the group template.
7. Joint label fusion to determine the cortical ROIs for analysis.

An overview of these steps is provided in Figure 3 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 representative population data [57]. For the ADNI-1 processing described in this work, we created a population-specific template from 52 cognitively normal ADNI-1 subjects. 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 [29]. A brief overview of this process is also provided in the section concerning creation of the single-subject template. Canonical views of the ADNI-1 template and corresponding auxiliary images are given in Figure 4.

**Single-subject template, brain mask, and tissue priors.** With 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



**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.

from all time-point images using the same protocol [57] 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 set of 20 atlases from the OASIS data set that have been expertly annotated [43], a multi-atlas joint label fusion step (JLF) [42] is performed to create individualized probability maps for all six tissue types. Five of the 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 (isotropic,  $\sigma = 1mm$ ) 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 time point of the original longitudinal image series.

**Individual time point processing.** The first step for subject-wise processing involves creating the SST i.e. the optimal mean shape/intensity template from all the time points for that individual [57]. 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 [29]. However, in the longitudinal variant, the SST serves this purpose. We thus map the SST and its priors to the native space of each time point where individual-level seg-

mentation 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 an option allowing for rotation of 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 segmentation implementation is dimensionality-agnostic [41]. Regarding the 4-D brain segmentation, any possible benefit is potentially outweighed by the occurrence of “over-regularization” [17] 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.

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 [17]. The ANTs longitudinal workflow shares some common aspects of its FreeSurfer analog but differs in others as outlined above.

**Joint label fusion and pseudo-geodesic for large cohort labeling.** Cortical thickness ROI-based analyses are performed using joint label fusion [42] 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 (e.g., [58]). 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

Following the above description, there are three major processing choices for using ANTs to perform a longitudinal cortical thickness study. Given its commonality, we could simply use the cortical thickness processing [29]. This has the advantage of requiring significantly less computation but does not address the various issues due to general cross-sectional sampling alluded to earlier. The second processing option is to reorient each time-point image to the SST similar to FreeSurfer which addresses such issues as orientation bias. The third option is to process each time-point image in its native space while maintaining the use of the SST and probability images. Although the latter is susceptible to possible orientation bias, it minimizes the effects of interpolation artifacts. We denote these alternatives as:

- **Cross-sectional.** Process each subject’s time point independently using the cross-sectional pipeline originally described in [29].
- **Longitudinal-SST.** Rigidly transform each subject to the SST and then segment and estimate cortical thickness in the space of the SST.
- **Longitudinal-native.** Segment and estimate cortical thickness in the native space.

In this section we describe the statistical framework for evaluating each option.

### *Regional within-subject and between-subject variance*

To quantify the relative performance of these cross-sectional and longitudinal processing methods, 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 (1) 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, [25] 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 [59] and [60]. 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 [61] hint at in their exposition of the longitudinal FreeSurfer stream.

As previously noted we observed a longitudinal sampling of cortical thickness mea-

surements from 62 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

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

Specification of variance priors to half-Cauchy distributions reflects commonly accepted practice in the context of hierarchical models [62]. 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

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

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 [59]. The posterior distribution of  $r^k$  was summarized via the posterior median where the posterior distributions were obtained using the Stan probabilistic programming language [63].

### *Entorhinal cortical thickness variability*

The entorhinal cortex (EC) is one of the earliest regions to exhibit tau pathology in the Alzheimer’s brain and is one of the first regions to show signs of neurodegenerative change [64–67]. In the ADNI sample, EC cortical thickness was the most powerful measure of structural change both in aMCI and AD brains [68]. EC thinning was also found to precede and predict hippocampal atrophy [69] and to predict conversion to AD with the greatest accuracy [70]. Thus, we chose the EC to be the target of an additional focused analysis to determine the relative utility of the different pipelines for measuring thickness in this particular region. It is worthy of note that the EC also presents a special challenge as its medial location in the brain makes it very difficult to segment from neighboring vasculature. Thus, it is particularly vulnerable to segmentation errors which can inflate its thickness. Our choice of EC as a region to demonstrate proof of concept was thus motivated both by its selective vulnerability to neurodegenerative processes as well as the difficulty of its segmentation.

As a further assessment of utility as a biomarker, we used LME models and cortical thickness measurements of the EC to demonstrate how these variability criteria relate to potential scientific analyses. First, we used model (1) 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:

$$ECCT_i = \beta_0 + \beta_1 AD_i + \epsilon_i . \quad (3)$$

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.

#### *Diagnostic prediction via extreme gradient boosting*

As mentioned earlier, an important component of our previously reported cross-sectional comparative evaluation [29] incorporated a statistical modeling approach for predicting basic subject demographics (i.e., age and gender) from the summary DKT regional cortical thickness values. We used a similar evaluation strategy in this work with the ADNI-1 data. We built statistical models from cortical thickness values for predicting the ADNI-specified diagnosis. However, instead of using the regional cortical thickness values for all time points directly, we used the longitudinal cortical thickness values for each DKT region of each subject to compute a subject-specific, region-specific rate-of-thickness-change measurement generated from simple linear regression of the available data. Thus, for each subject, we calculated a single set of 62 slope coefficients,  $\zeta = \{\zeta_1, \zeta_2, \dots, \zeta_{62}\}$ , and a single diagnosis of cognitively normal, MCI, LMCI, or AD. Note that the diagnosis for each subject did not change over the course of the image acquisition schedule permitting this particular evaluative strategy. This classification scenario yields the following model:

$$DIAGNOSIS \sim \sum_{k=1}^{62} \zeta_k \quad (4)$$

The motivating idea is that regional thinning is accelerated in some regions versus

others which should be reflected in the assigned diagnostic category [68, 69].

For model construction, we used extreme gradient boosting, which is a well-performing, out-of-the-box classifier implemented in the XGBoost [71] package for the R project. Although there are many options available for classification, we chose this particular technique due to our recent interest in other projects based on its various successes in other fields.<sup>1</sup> An additional advantage is that XGBoost provides the “gain” quantity which describes “the improvement in accuracy brought by a feature to the branches [of the tree or iteration] it is on [71].” These can be reviewed for clinical plausibility of the results.

## Results

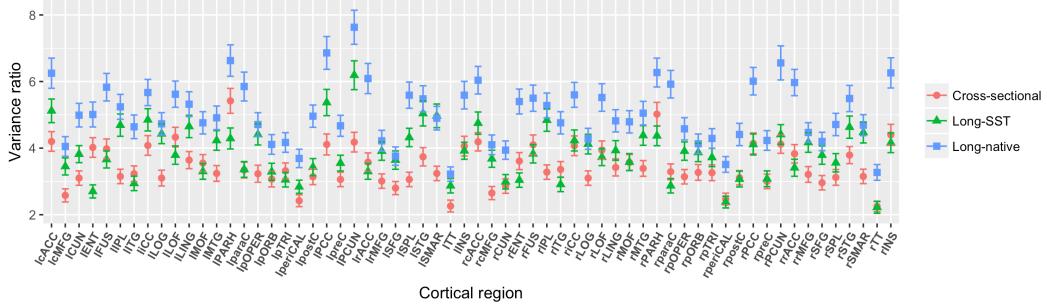
Based on the evaluation design described in the previous section, we compare the performance of the three processing approaches (Cross-sectional, Longitudinal-SST, and Longitudinal-native) as applied to the ADNI-1 data. Specifically, we demonstrate how the variance ratio defined in Equation (2) illustrates ways in which different aspects of variability affect confidence in prediction and estimation.

### *Regional within-subject and between-subject variance*

Our first evaluation strategy was to use LME models to quantify the between-subject and within-subject variance with the expectation that maximizing the former while minimizing the latter optimizes measurement quality in terms of prediction and confidence intervals. Figure 5 provides the resulting 95% credible intervals for the distributions of region-specific variance ratios  $r^k = \tau_k/\sigma_k$  for each of the three methods. The placement of the methods with respect to each other is meaningful. The supe-

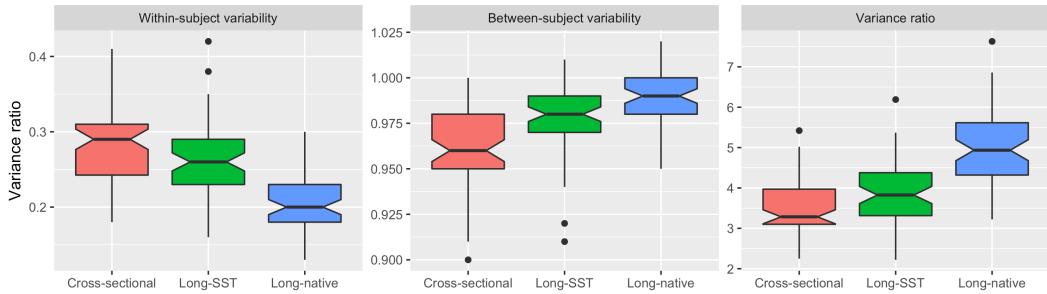
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<sup>1</sup><http://stat-computing.org/awards/jmc/winners.html>



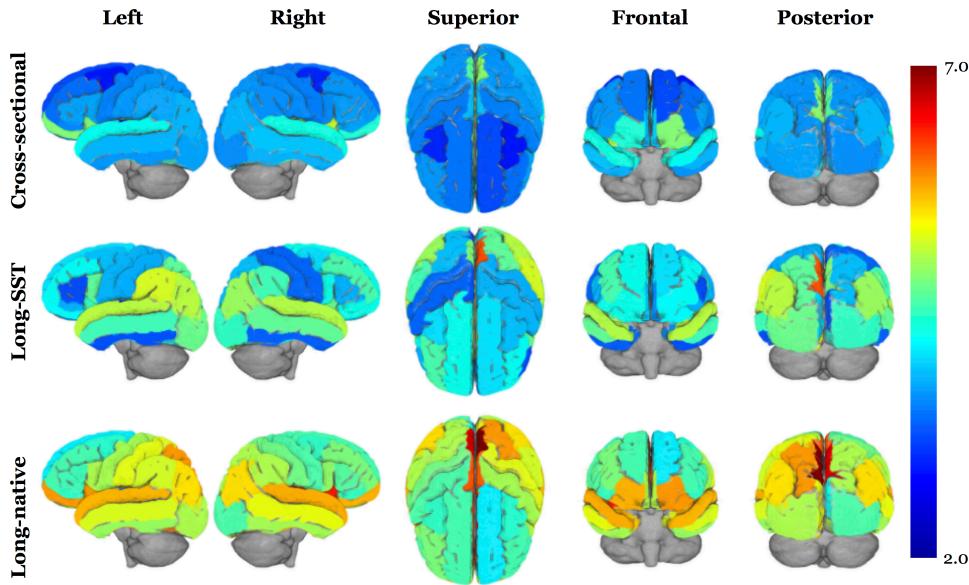
**Figure 5:** 95% credible intervals of the region-specific variance ratios  $r^k = \tau_k/\sigma_k$  are presented for each processing method. The Longitudinal-native method dominates the others: its point estimates—posterior median—are greater than those of the other processing methods; and its credible intervals scarcely overlap with those of Longitudinal-SST and never overlap with those quantities calculated from the cross-sectional method. These results suggest that the cortical thickness values obtained using Longitudinal-native have greater discriminative capacity than the thickness values obtained using the other two methods.

prior method is designated by larger variance ratios and has the greater discriminative capacity for the data corresponding to that processing method.



**Figure 6:** 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.

Longitudinal-native has the highest ratio variance across all 62 regions over the two alternative methods. It rarely overlaps with Longitudinal-SST and never with Cross-sectional. In contrast, even though Longitudinal-SST has a greater number of superior ratio values across the regions relative to the Cross-sectional, 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 rostral 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.



**Figure 7:** 3-D volumetric rendering of the regional variance ratio values on the generated ADNI template. The higher variance ratios indicate greater between-subject to within-subject variability.

The plot in Figure 6 shows a relative summary of all the regional quantities for all three variance measurements (within-subject, between-subject, and variance ratio) via notched box plots. These relative distributions show that both between-subject

and within-subject quantities contribute to the disparities in the ratio evaluation metric. Finally, we overlay the variance ratio values on the corresponding regions of a 3-D rendering of the ADNI template (Figure 7) to provide an additional visual comparison between the methods. Therefore, Figures 5, 6, and 7 may be considered as evidence for method Longitudinal-native providing higher quality data than those provided by the other methods.

#### *Entorhinal cortical thickness variability*

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

Method	$\frac{\tau}{\sigma}$	CI width	$\sigma^2$	Variance	$\sigma^2 + \tau^2$	CI width
<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>Long-SST</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>Long-native</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

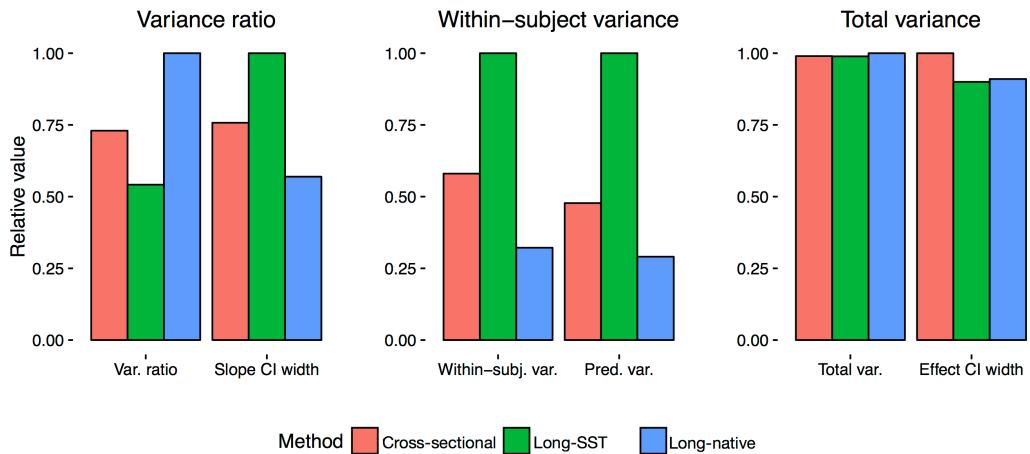
Data quality translates directly to quality of statistical results and the scientific conclusions derived therefrom. Hence, data with good variance and precision properties will benefit statistical analyses in multiple ways. To demonstrate these benefits, we focus on data from the entorhinal cortex and 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 differ-

ent functions of the variance terms from Model (1). 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.

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 (1). 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, Longitudinal-native 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 the 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 Longitudinal-native method performs best whereas Longitudinal-SST 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 (3). 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

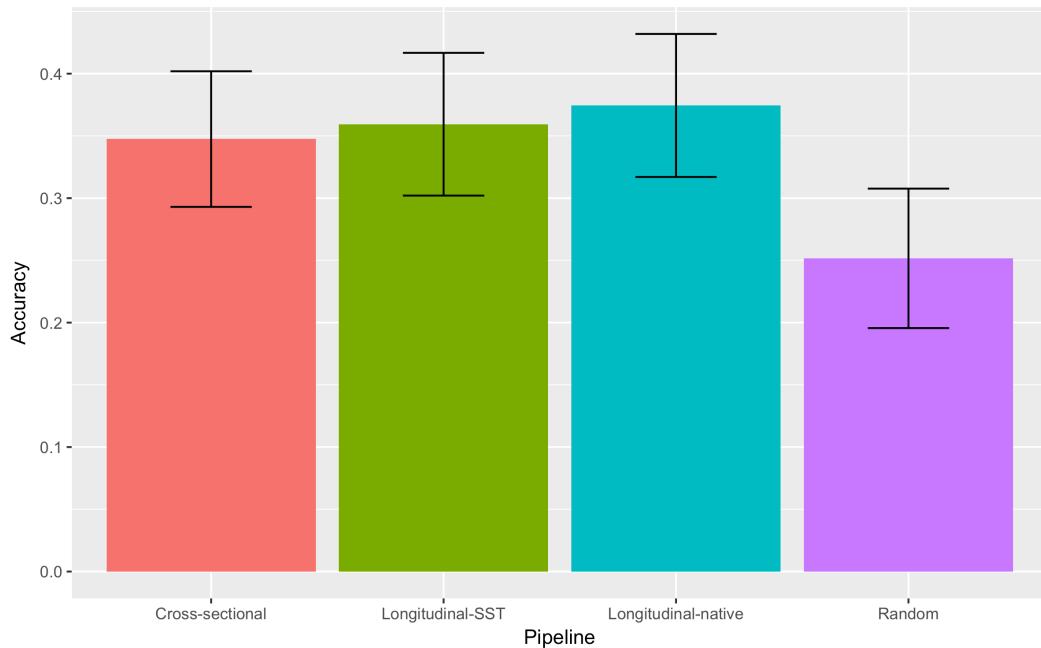


**Figure 8:** Aspects of model variance are compared with credible interval sizes and variance in predictions. Values are normalized by the largest quantity, and processing methods are distinguished by color and ordering. On the left, the variance ratio  $r = \tau/\sigma$  is compared to the width of credible interval for the slope term of Model (1). 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.

is, despite having marginally greater total variance, the distance from zero for the credible interval corresponding to Longitudinal-native is 0.81, whereas the distances for Longitudinal-SST and Cross-sectional are 0.75 and 0.70, respectively. Figure 8 displays the normalized results.

#### *Diagnostic prediction via extreme gradient boosting*

A clinically-based prediction strategy was performed to evaluate the quality of the cortical thickness measurements produced by each method. 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.



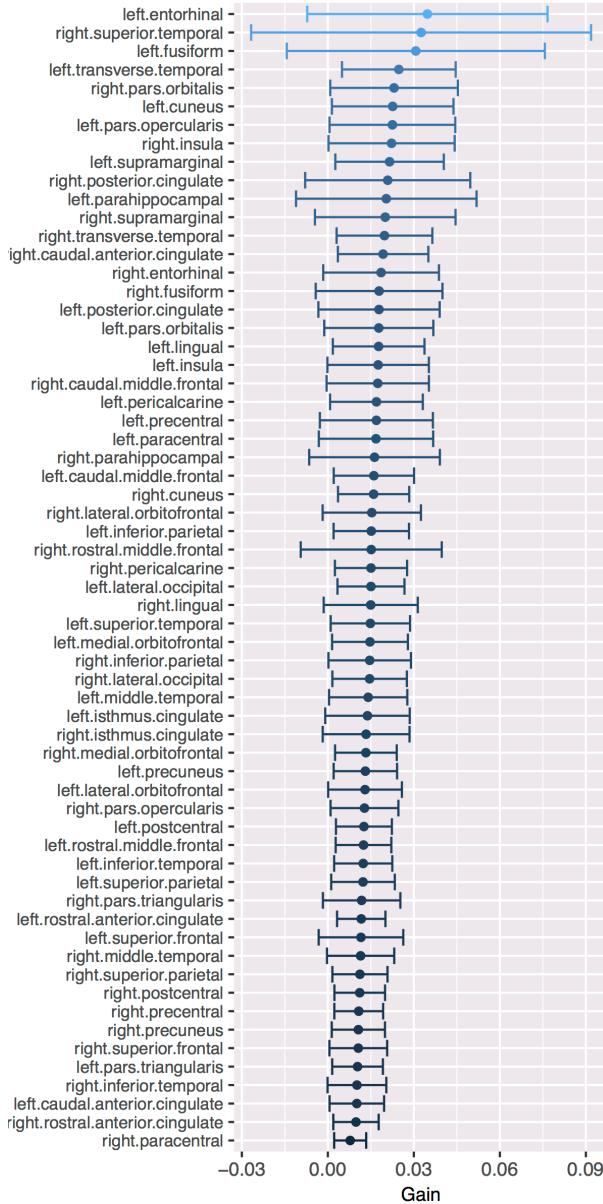
**Figure 9:** Bar plot of the accuracy for each of the three pipeline choices along with the distribution summary produced from random guessing. Accuracy was determined from the confusion matrices that were calculated for each of the 1000 iterations. Using Tukey multiple comparisons of means at a 95% family-wise confidence level, the adjusted p-values were: Longitudinal-SST – Cross-sectional  $< 1e - 4$ , Longitudinal-native – Cross-sectional  $< 1e - 6$ , Longitudinal-native – Longitudinal-SST  $< 1e - 6$ .

Using the model described by Equation (4), we compared the classification capabilities of each of the three pipelines. For each of  $N$  iterations, the data was randomly split 90/10 (i.e., 90% training and 10% testing) and used to construct three diagnostic classification models from the training data, one for each pipeline. The testing data portion and the corresponding prediction sets were used to construct confusion matrices from which diagnostic accuracy was calculated. Chosen XGBoost model parameters deviating from the default were: number of trees = number of iterations (“nrounds”) = 100 and gradient step (“eta”) = 0.3, based on parameter tuning on a small data subset over all three pipelines.

The resulting accuracy distribution summaries are plotted in Figure 9 and compared statistically using Tukey’s range test which indicated increasing performance Cross-sectional < Longitudinal-SST < Longitudinal-native. These models also provide means for assessing feature importance through the “gain” values. The gain plot is given in Figure 10. The information offered by the gain plot is consistent with what we know about selective vulnerability of brain regions to AD-related neurodegeneration [2]. For example, medial temporal regions such as the entorhinal and parahippocampal cortices are near the top offering the most diagnostic information, whereas regions such as paracentral cortices are near the bottom, offering very little diagnostic information.

## Discussion

Herein we detailed the ANTs longitudinal cortical thickness framework which was designed to take advantage of longitudinal data acquisition protocols while accounting for the various bias issues that have been associated with processing such data. Over 600 subjects from the well-known longitudinal ADNI-1 data set with diagnoses



**Figure 10:** At each iteration of the extreme gradient boosting optimization, the accuracy of the model is dependent on splitting the current tree on a single feature to correct any remaining misclassifications. The improvement in accuracy derived from each feature split is quantified by the gain. The gain measurements of the extreme gradient boosting models for the ANTs longitudinal-native processing. We average over all iterations and each training/testing run to produce the mean value for each feature plotted above. The bar and whiskers for each feature represents a single standard deviation of the average gain over all the training/testing runs.

distributed between cognitively normal, MCI, LMCI, and AD were processed through the original ANTs cross-sectional framework [29] and two longitudinal variants. One of the variants, Longitudinal-SST, is similar to the FreeSurfer longitudinal stream in that each time-point image is reoriented to an unbiased single-subject template for subsequent processing. Longitudinal-native, in contrast, estimates cortical thickness in the native space while also using tissue prior probabilities generated from the SST.

Comparative assessment utilized LME models to determine the between-subject to within-subject variance ratios over the 62 regions of the brain defined by the DKT parcellation scheme where higher values indicate greater discriminative capacity. In these terms, Longitudinal-native was clearly the best performer. Longitudinal-SST outperformed Cross-sectional over the majority of regions. Regional disparities point to increases in both between-subject and within-subject variances which might be an additional interpolation artifact. In other words, interpolation potentially has a systematic but regionally varying effect. Investigation of this issue is the subject of future research.

Additional assessments included similar variance quantification in the EC and diagnostic prediction using extreme gradient boosting models. The former evaluation was motivated by the prominence of the EC as a biomarker in AD progression whereas the latter coupled a simplistic assumption of AD progression with modern machine learning techniques similar in spirit to what we did in our previous work [29]. Both assessments supported the findings of the first assessment in demonstrating the superiority of Longitudinal-native. These findings promote longitudinal analysis considerations and motivates such techniques over cross-sectional methods for longitudinal data despite the increase in computational costs.

The longitudinal thickness framework is available in script form within the ANTs software library along with the requisite processing components. All generated data used

for input, such as the ADNI template and tissue priors, are available upon request. As previously mentioned, we also make available the csv files containing the regional thickness values for all three pipelines.

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