

# The ANTs Longitudinal Cortical Thickness Pipeline

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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 and 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 measurements while retaining predictive power. In this work, we introduce the open-source Advanced Normalization Tools (ANTs) registration-based cortical thickness longitudinal processing pipeline and its application to 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 in these data that the single-subject template construction and same orientation processing results in a simultaneous minimization of within-subject variability and maximization of between-subject variability immediately estimable from a longitudinal mixed-effects modeling strategy. It is known from the statistical literature that optimizing these dual criteria leads to greater scientific interpretability in terms of tighter confidence intervals in calculated mean trends, smaller prediction intervals, and narrower confidence intervals for determining cross-sectional effects. This evaluation strategy is evaluated over the entire cortex, as defined by the Desikan-Killiany-Tourville labeling protocol, where comparisons are made with the cross-sectional and longitudinal FreeSurfer processing streams.

*Keywords:* Advanced Normalization Tools, FreeSurfer, interpolation, longitudinal mixed-effects, longitudinal processing

# 1 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]).

In inferring developmental processes, many studies employ cross-sectional population sampling strategies despite the potential for confounding effects [10]. Large-scale studies involving longitudinal image acquisition of a targeted subject population, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI) [11], 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 [12]. For example, FSL’s SIENA (Structural Image Evaluation, using Normalization, of Atrophy) framework [13] 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 [14] in the context of hippocampal volumetric change where it was shown that interpolation-induced artifacts can artificially create and/or inflate effect size [15]. These insights and others have since been used for making specific recommendations with respect to longitudinal image data processing [12, 16–18].

In [12, 19], 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 [20] and has been used in a variety of studies including pediatric cortical development [21], differential development in Alzheimer’s disease and fronto-temporal dementia [22], and fatigue in the context of multiple sclerosis [23]. [Although the FreeSurfer longitudinal processing stream is perhaps one of the most well-known, other important longitudinal-specific methodologies have been proposed for characterizing cortical morphological change.](#) Similar to FreeSurfer, cortical surfaces

are generated in [24, 25] permitting vertex-wise quantitation of thickness and thickness change. Application to early infants in [24] further demonstrate the utility of targeted longitudinal considerations.

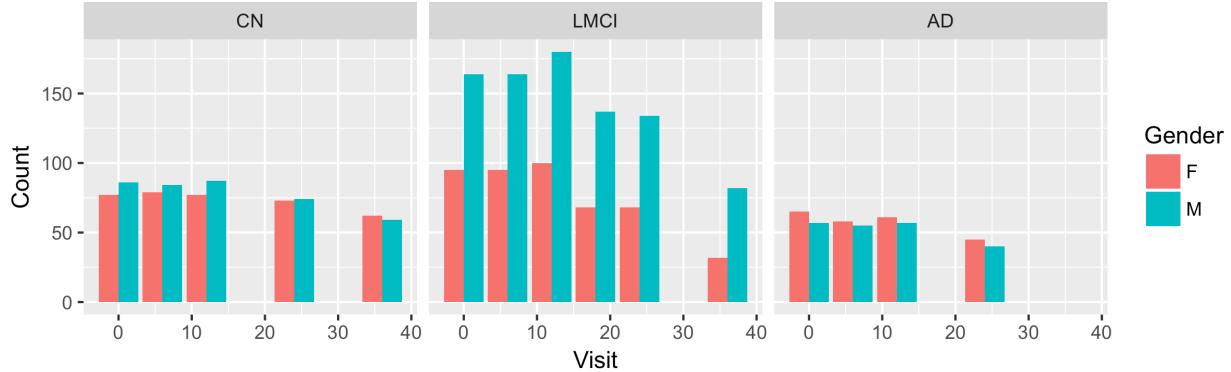
We introduced the Advanced Normalization Tools (ANTs) cortical thickness pipeline in [26] which leverages various pre-processing, registration, segmentation, and other image analysis tools that members of the ANTs and Insight Toolkit (ITK) open-source communities have developed over the years and disseminated publicly [27]. This proposed ANTs-based pipeline has since been directed at a variety of neuroimaging research topics including mild cognitive impairment and depression [28], short term memory in mild cognitive impairment [29], and aphasia [30]. Other authors have extended the general framework to non-human studies [31, 32].

In this work, we introduce the longitudinal version of the ANTs [registration-based](#) 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 is known to impact the scientific interpretability of results, produce tighter confidence intervals in calculated mean trends, smaller prediction intervals, and less varied confidence/credible intervals for discerning cross-sectional effects. Similar to previously outlined research, we show that reorienting individual time point images to a single-subject template has a favorable performance effect which guides processing choices for the proposed ANTs longitudinal pipeline.

## 2 Methods and materials

### 2.1 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 [33] 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 [34]. As proposed, collection goals were 200 elderly cognitively normal subjects collected at 0, 6, 12,



**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”).

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.

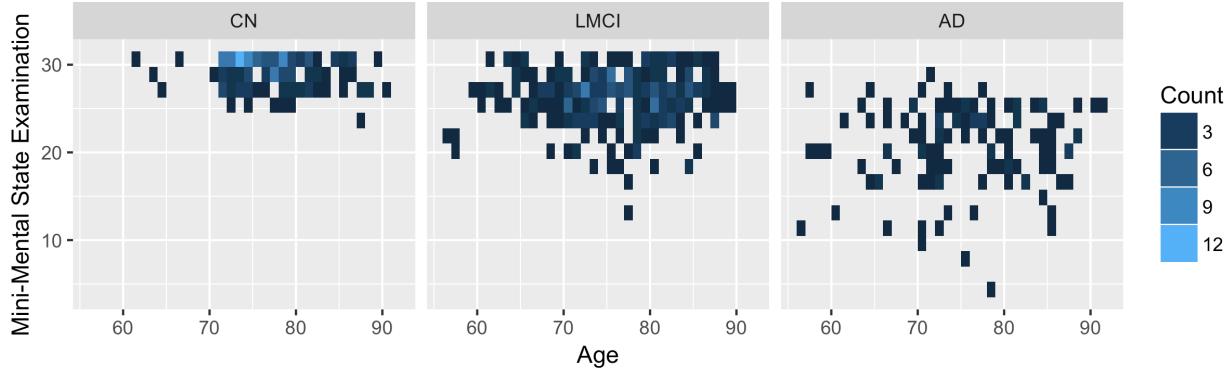
The ADNI-1 data was downloaded in May of 2014 and first processed using the ANTs cross-sectional cortical thickness pipeline [26] (4399 total images). Data was then processed using two variants of the ANTs longitudinal stream (described in the next section). In the final set of csv files (which we have made publicly available in the github repository associated with this work [35]), 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 with one or more follow-up image acquisition appointments. Further breakdown of demographic information is given in Figures 1 and 2 to provide additional perspective on the data used for this work.

## 2.2 ANTs cortical thickness

### 2.2.1 Cross-sectional processing

A thorough discussion of the ANTs cross-sectional thickness estimation framework was previously provided in [26]. As a brief review, given a T1-weighted brain MR image, processing comprises the following major steps (cf Figure 1 of [26]):

1. N4 bias correction [36],



**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.

2. brain extraction [37],
3. Atropos  $n$ -tissue segmentation [38], and
4. [registration-based](#) cortical thickness estimation [8].

ROI-based quantification is achieved through joint label fusion [39] of the cortex coupled with the MindBoggle-101 data. These data use the Desikan–Killiany–Tourville (DKT) labeling protocol [40] to parcellate each cortical hemisphere into 31 anatomical regions (cf Table 1). This pipeline has since been enhanced by the implementation [41] of a patch-based denoising algorithm [42] as an optional preprocessing step and multi-modal integration capabilities (e.g., joint T1- and T2-weighted image processing).

For evaluation, voxelwise regional thickness statistics were summarized based on the DKT parcellation scheme. Test-retest error measurements were presented from a 20-cohort subset of both the OASIS [43] and MMRR [44] data sets and compared with the corresponding FreeSurfer thickness values. Further evaluation employed a training/prediction paradigm where regional cortical thickness values generated from 1205 images taken from four publicly available data sets (i.e., IXI [45], MMRR, NKI [46], and OASIS) were used to predict age and gender using linear and random forest [47] models. The resulting regional statistics (including cortical thickness, surface area [48], volumes, and Jacobian determinant values) were made available online [49]. These include the corresponding FreeSurfer measurements which are also publicly available for research inquiries (e.g., [50]). Since publication, this framework has been used in a number of studies (e.g., [51–53]).

**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)	

### 2.2.2 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 longitudinal studies which takes into account various bias issues previously discussed in the literature [12, 14, 19].

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



**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-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 “ANTs 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 “ANTs SST”. For regional thickness values, regional labels are propagated to each image using a given atlas set (with cortical labels) and joint label fusion.

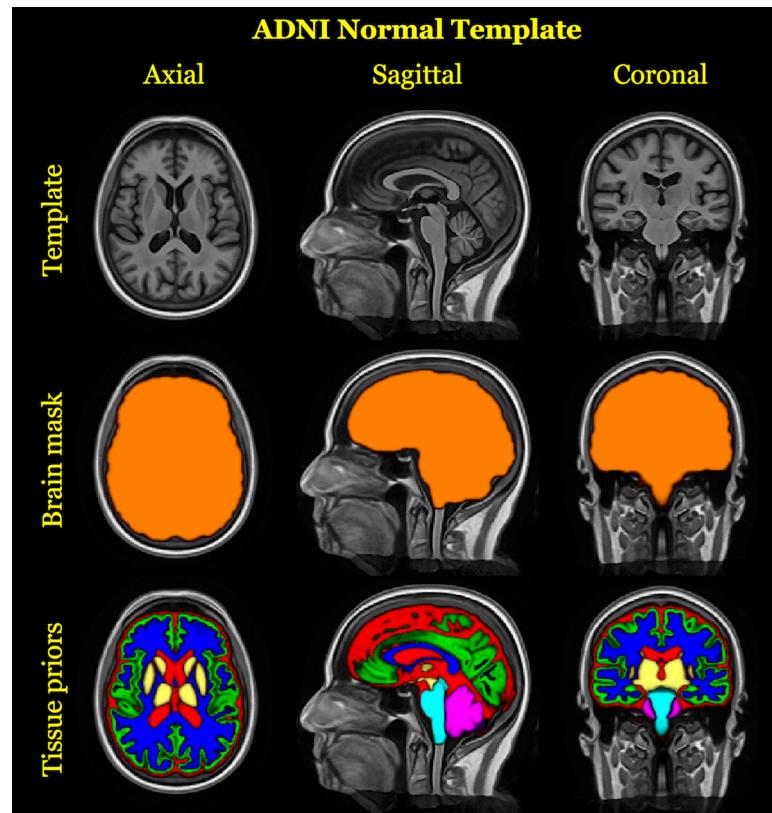
of the following steps:

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 cortical thickness pipeline [26] to the SST *cwith the group template and priors as input.*
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 cortical thickness pipeline [26], with the SST as the reference template, to each individual time-point image. *Input includes the SST and the corresponding spatial priors made in Step 3.*
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 [54]. 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 [26]. 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 from all time-point images using the same protocol [54] 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



**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.

been expertly annotated and made publicly available [40], a multi-atlas joint label fusion step (JLF) [39] 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 the 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. Note that the unique treatment of the CSF stems from the fact that the 20 expertly annotated atlases only label the ventricular CSF. Since cortical segmentation accuracy depends on consideration of the external CSF, the above protocol permits such inclusion in the CSF prior probability map.

The final version of the SST and auxiliary images enable unbiased, non-linear 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 from all the time points for that individual [54]. 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 [26]. However, in the longitudinal variant, the SST serves this purpose. We thus deformably map the SST and its priors to the native space of each time point where individual-level 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.” Based on outcomes involving previously processed data sets (including ADNI-2), we chose to employ the denoising algorithm [42] for all ANTs-based 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 [12].

The ANTs framework also permits rotation of the individual time point image data to the SST, similar to FreeSurfer, for reducing variability, minimizing or eliminating possible orientation bias, and permitting a 4-D segmentation given that the underlying Atropos segmentation implementation is dimensionality-agnostic [38]. Regarding the 4-D brain segmentation, any possible benefit is potentially outweighed by the occurrence of “over-regularization” [12] 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.

**Registration-based cortical thickness.** The underlying registration-based estimation of cortical thickness, Diffeomorphic Registration-based Estimation of Cortical Thickness (DiReCT), was introduced in [8]. Given a probabilistic estimate of the cortical gray and white matters, diffeomorphic-based image registration is used to register the white matter probability map to the combined gray/white matter probability map. The resulting mapping defines the diffeomorphic path between a point on the gray/white matter interface and the gray matter boundary. Cortical thickness values are then assigned at each spatial location within the cortex by integrating along the diffeomorphic path starting at each gray/white matter interface point and ending at the gray matter/CSF boundary. A more detailed explanation is provided in [8] with the actual implementation provided in the class `itk::DiReCTImageFilter` available as part of the ANTs library.

**Joint label fusion and pseudo-geodesic for large cohort labeling.** Cortical thickness ROI-based analyses are performed using joint label fusion [39] 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 non-linear 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., [55]). The transformations between the atlas and the group template are computed offline. With that set of non-linear 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 for estimating regional labels for each image.

## 2.3 Statistical evaluation

Based on the above ANTs pipeline descriptions, there are three major variants for cortical thickness processing of longitudinal data. We denote these alternatives as:

- **ANTs Cross-sectional** (or **ANTs Cross**). Process each subject’s time point independently using the cross-sectional pipeline originally described in [26].
- **ANTs Longitudinal-SST** (or **ANTs SST**). Rigidly transform each subject to the SST and then segment and estimate cortical thickness in the space of the SST.
- **ANTs Longitudinal-native** (or **ANTs Native**). Segment and estimate cortical thickness in the native space.

For completeness, we also include a comparison with both the cross-section and longitudinal FreeSurfer v5.3 streams respectively denoted as “FreeSurfer Cross-sectional” (or “FS Cross”) and “FreeSurfer Longitudinal” (or “FS Long”).

## 2.4 Cross-sectional and longitudinal evaluation strategies

Possible evaluation strategies for [cross-sectional methods](#) have employed manual measurements in the histological [56] or virtual [57] domains but would require an inordinate labor effort for collection to be comparable with the size of data sets currently analyzed. Other quantitative measures representing “reliability”, “reproducibility”, or, more generally, “precision” can also be used to characterize such tools. For example, [58] used FreeSurfer cortical thickness measurements across image acquisition sessions to demonstrate improved reproducibility with the longitudinal stream over the cross-sectional stream. In [59] comparisons for ANTs, FreeSurfer, and the proposed method were made using the range of measurements and their correspondence to values published in the literature. However, none of these precision-type measurements, *per se*, indicate the utility of a pipeline-specific cortical thickness value as a potential biomarker.

For example, Figure 8 in [26] confirms what was found in [59] which is that the range of ANTs cortical thickness values for a particular region exceeds those of FreeSurfer. However, for the same data, the demographic predictive capabilities of the former was superior to that of the latter. Thus, better assessment strategies are necessary for determining clinical utility. For example, the intra-class

correlation (ICC) coefficient used in [26] demonstrated similarity in both ANTs and FreeSurfer for repeated acquisitions despite the variance discrepancy between both sets of measurements.

This is understood with the realization that the ICC takes into account both inter-observer and intra-observer variability.

Similarly, evaluation strategies for longitudinal studies have been proposed with resemblance to those employed for cross-sectional data such as the use of visual assessment [24], scan-rescan data [12, 25], and 2-D comparisons of post mortem images and corresponding MRI [25]. In addition, longitudinal methods offer potential for other types of assessments such as the use of simulated data (e.g., atrophy [12, 25], infant development [24]) where "ground-truth" is known and, regression analysis of longitudinal trajectories of regional cortical thickness [60].

## 2.5 Within-subject and between-subject variance

For a longitudinal biomarker to be effective at classifying subpopulations, it should have low within-subject variation and high between-subject variation. Without this, subpopulation distinctions would not be possible (e.g., if measurements within the subject vary more than those between subjects). A summary measure related to the ICC statistic [61] is used to quantify this intuition for assessing relative performance of these cross-sectional and longitudinal ANTs pipeline variants along with the cross-sectional and longitudinal FreeSurfer streams. Specifically, we use longitudinal mixed-effects (LME) modeling to quantify pipeline-specific between-subject and within-subject variabilities where comparative performance is determined by maximizing the ratio between the former and the latter. Such a quantity implies greater within-subject reproducibility while distinguishing between patient sub-populations (e.g., Alzheimer's disease diagnosis). As such this amounts to higher precision when cortical thickness is used as a predictor variable or model covariate in statistical analyses upstream.

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, [20] provides 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 [61] and [62]. 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 [63] hint at in their exposition of the longitudinal FreeSurfer stream.

As previously noted we observed a longitudinal sampling of cortical thickness measurements from the 62 parcellated cortical DKT regions. 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 the time point indexed by  $j$ . Under the Bayesian paradigm we utilized a model of the form

$$\begin{aligned} Y_{ij}^k &\sim N(\alpha_i^k + \beta_i^k t, \sigma_k^2) \\ \alpha_i^k &\sim N(\alpha_0^k, \tau_k^2) \quad \beta_i^k \sim N(\beta_0^k, \rho_k^2) \\ \alpha_0^k, \beta_0^k &\sim N(0, 10) \quad \sigma_k, \tau_k, \rho_k \sim \text{Cauchy}^+(0, 5) \end{aligned} \tag{1}$$

where specification of variance priors to half-Cauchy distributions reflects commonly accepted best practice in the context of hierarchical models [64]. They concentrate mass near zero but have heavy tails, meaning small variance values are expected but large variance values are not prohibited. Even so, results demonstrated robustness to parameter selection.

In this model,  $\tau_k$  represents the between-subject standard deviation, and  $\sigma_k$  represents the within-subject standard deviation, conditional upon time and  $\beta_k^i$  denotes the subject-specific slopes of cortical atrophy. For each region  $k$ , the quantity of interest is thus the ratio

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

The posterior distribution of  $r^k$  was summarized via the posterior median where the posterior distributions were obtained using the Stan probabilistic programming language [65]. Specifically, the R

interface to Stan was used to calculate the point estimates of the LME model (1) for cortical thickness across the different pipelines using the default parameters. The csv files containing the regional cortical thickness values for all five pipelines, the Stan model file, and the R script to run the analysis and produce the plots are all located in the github repository created for this work [35].

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. In particular, [66] (Sections 9.6.2 and 9.6.5) demonstrate the role that randomness and measurement error in explanatory variables play in statistical inference. When the explanatory variable is fixed but measured with error (as is plausible for cortical thickness measurements), the within-subject variance divided by the between subject variance is proportional to the bias of the estimated linear coefficient when the outcome of interest is regressed over the explanatory variable (Example 9.2). In short, the larger the  $r^k$ , the less bias for future statistical analyses based upon the cortical thickness data. When the explanatory variable is considered random and is measured with error (a common assumption in the measurement error literature [67, 68], this bias is expressed as attenuation of regression coefficient estimates to zero by a multiplicative factor  $r^k/(1 + r^k)$  (Example 9.3). Thus, larger  $r^k$  means less less attenuation bias and hence more discriminative capacity. Note that effect estimator bias is not the only problem—the residual variance is increased by a factor proportional to  $r^k/(1 + r^k)$  ([66], Chapter 3). The same authors refer to the combination of bias and added variance as a ‘double whammy’. Indeed, a worse reliability ratio causes greater bias in multiple linear regression in the presence of collinearity and even biases the estimators for other covariates, progression through time included (cf [68], Section 3.3.1). The same authors state that this bias is typical even in generalized linear models (Section 3.6) and continue to use the ratio as a measure of reliability even in the longitudinal context (Section 11.9).

## 3 Results

All imaging data were processed through the five processing streams (i.e., FS Cross, FS Long, ANTs Cross, ANTs SST, and ANTs Native) on the high performance computing cluster at the University of California, Irvine. The scripts that were used to process these data are provided in [35]. Based on the evaluation design described in the previous section, we compare the performance of these five approaches when applied to the ADNI-1 data.

### 3.1 Regional cortical atrophy rates based on diagnosis

Shown in Figure 5 are regional box plots based on the distribution of slope values for each of the five longitudinal pipelines. These regional slopes values are further grouped by diagnosis (i.e., CN vs. LMCI vs. AD) to illustrate the feasibility of the measurements based on known general trends of varying cortical atrophy rates in the ADNI population [69]. All pipelines show the greatest atrophy rates in the AD subpopulation over the entire brain including those specifically related to "ground zero" in Alzheimer's disease, e.g., the entorhinal and parahippocampal regions [70]. Similarly, those subjects with a diagnosis of LMCI exhibit increased cortical thickness decline compared with cognitively normal subjects.

### 3.2 Cortical within-subject and between-subject thickness variability

The LME model defined in (1) was used 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 6 provides the resulting 95% credible intervals for the distributions of region-specific variance ratios  $r^k = \tau_k/\sigma_k$  for each of the five pipelines. The superior method is designated by larger variance ratios and has the greater discriminative capacity for the data corresponding to that processing method.

ANTs SST has the highest ratio variance across most of the 62 regions over the other methods. It rarely overlaps with ANTs Native and never with ANTs Cross. In contrast to the majority of FreeSurfer regional ratio variances (from both FS Cross and FS Long) which are smaller than those

of the ANTs pipelines, FS Long has larger ratio values for the EC region with the only overlap in the credible intervals with ANTs SST.

The plot in Figure 7 shows a relative summary of all the regional quantities for all three variance measurements (within-subject, between-subject, and variance ratio) via 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 8) to provide an additional visual comparison between the methods. Therefore, Figures 6, 7, and 8 may be considered as evidence for ANTs SST providing higher quality data than those provided by the other methods.

The variance ratio is a generic desideratum for a statistical assessment of performance over the set of possible use cases. Here we demonstrate two such possibilities involving prediction performance over the three longitudinal-specific cortical thickness pipelines: FSLong, ANTsNative, and ANTsSST. After estimating the regional cortical atrophy rates derived from the LME-derived slopes for each subject of each pipeline, we use those slope values to predict age and MMSE scores (cf Figure 10 for certain cortical regions. We predict age for the regions selected in [@Tustison:2014ab] (i.e., both left and right hemispheres for the pars opercularis (pOPER), pars triangularis (pTRI), posterior cingulate (PCC), precentral (PreC), and tranverse temporal (TT) cortical regions) since they demonstrated the largest age effects between both the FreeSurfer and ANTs cross-sectional results although, in this case, we are using rates of atrophy vs. actual thickness values for age prediction. Specifically, we test the linear model

$$Age_i \sim \Delta Y_i^k + Diagnosis_i \quad (3)$$

where  $i$  denotes the  $i^{th}$  subject,  $\Delta Y_i^k$  is the atrophy rate for the  $i^{th}$  subject in the  $k^{th}$  region of interest where the model is trained on 90% of the cohort and tested on the remaining 10%. This training/prediction scenario is repeated 100 times where the assignment to training or prediction data subsets is shuffled each time. The results of this predictive evaluation is shown in Figure 9.

In Figures 7 and 8, it is shown that the ANTsSST variance ratio is higher in most regions except for the left and entorhinal cortex where the FSLong values are slightly higher. Given the characteristics of the ADNI population and the fact that the entorhinal cortex is "ground zero" for AD pathology [70], we demonstrate that the higher variance ratio translates into better MMSE prediction values

for the FSLong pipeline. Thus, we evaluate the variance ratio in the context of the linear model

$$MMSE_i \sim \Delta Y_i^k + Age_i \quad (4)$$

where  $i$  denotes the  $i^{th}$  subject,  $\Delta Y_i^k$  is the atrophy rate for the  $i^{th}$  subject in the  $k^{th}$  region of interest where the model is trained similarly to that for age prediction.

## 4 Discussion

Herein we detailed the ANTs registration-based longitudinal cortical thickness framework which is 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 distributed between cognitively normal, MCI, LMCI, and AD were processed through the original ANTs cross-sectional framework [26] and two longitudinal variants. One of the variants, ANTs 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. ANTs Native, in contrast, estimates cortical thickness in the native space while also using tissue prior probabilities generated from the SST. All processing streams demonstrated feasibility of longitudinal cortical thickness quantification based on known relative cortical atrophy rates in ADNI sub-populations. AD patients exhibited increased decline in cortical thickness relative to LMCI and cognitively normal groups over the entire brain. These findings were consistent across all pipelines.

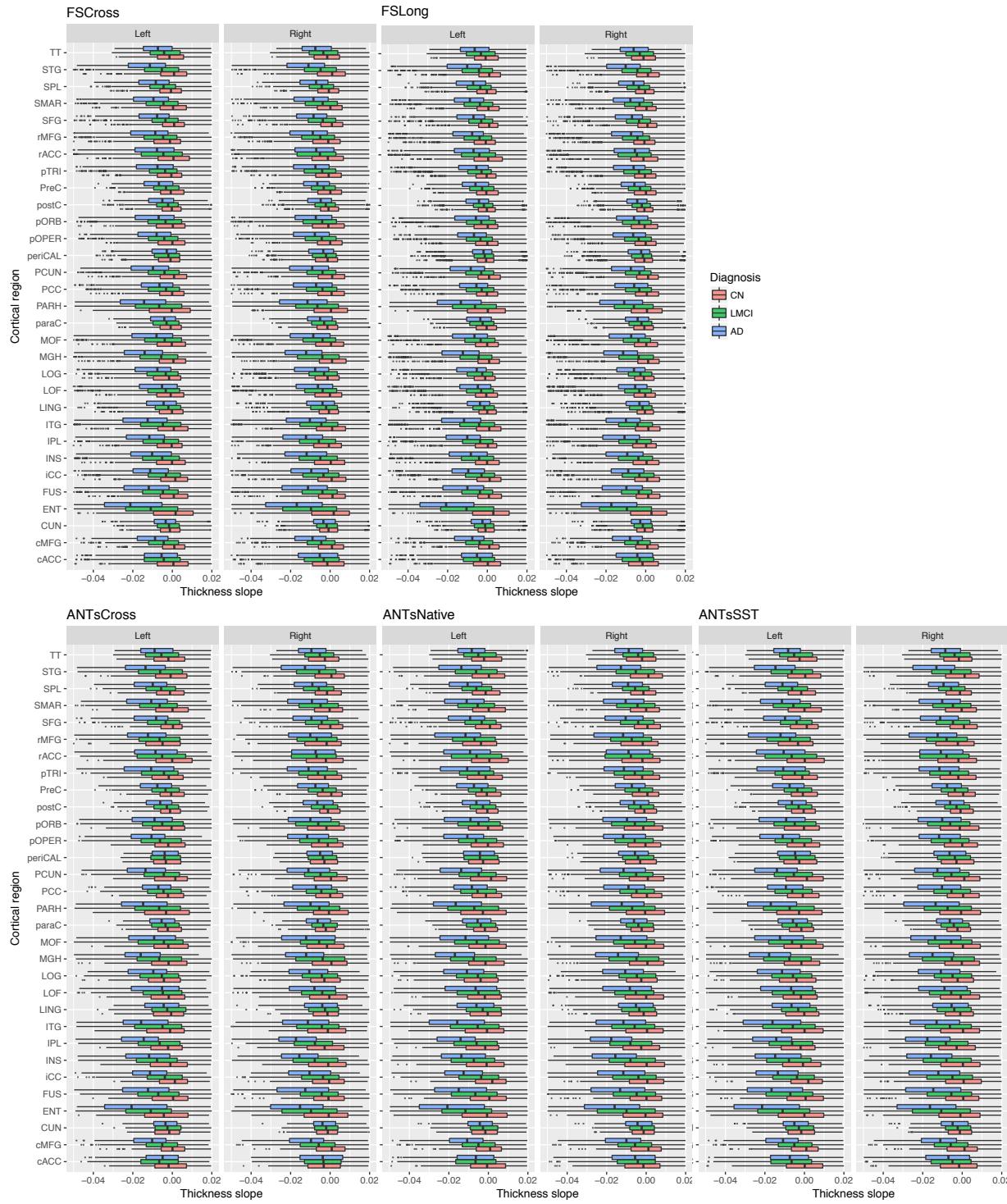
Comparative assessment utilized LME models to determine the between-subject to within-subject variance ratios over the 62 regions of the brain defined by the DKT parcellation scheme where higher values indicate greater discriminative capacity. In these terms, ANTs SST outperformed all other pipeline variants including both the FreeSurfer longitudinal and cross-sectional streams. Regional disparities between the ANTs SST and Native pipelines point to increases in both between-subject and within-subject variances which might be due to reorientation to a common space similar to other longitudinal strategies.

One very interesting finding was the superior performance of FS Long in the EC regions where the variance ratios was slightly larger than those of ANTs Native where the credible intervals have signifi-

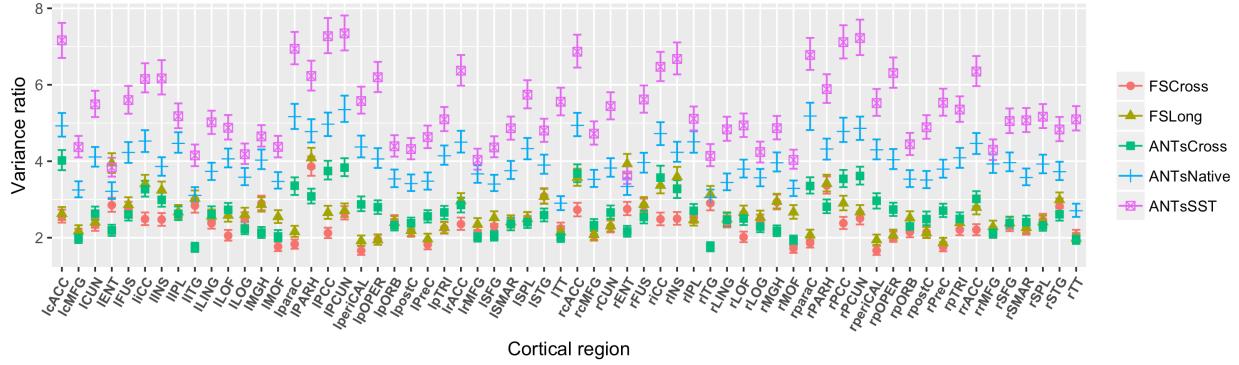
cant overlap. Given the small volume and indistinguishability from surrounding structures, segmentation of the EC can be relatively difficult [71]. This segmentation complexity has led to EC-specific [72] and related [73] strategies for targeted regional processing. For this work, we wanted to avoid such tuning and simply employ off-the-shelf input parameters and data. Future work will explore refining input template priors in these problematic regions for ANTs-based estimation of cortical thickness.

These findings promote longitudinal analysis considerations and motivates such techniques over cross-sectional methods for longitudinal data despite the increase in computational costs. While we focus on cortical thickness in this work, there are obvious limitations with the ANTs volume-based framework. Without a direct reconstruction of the cortical surfaces, many important cortical properties (e.g., surface area, cortical folding, sulcal depth, and gyration) [74] cannot be generated in a straightforward manner. Additional work will want to examine these features more closely working towards a more comprehensive idea of how structure changes. This will help determine the relative importance of such cortical features and will undoubtedly guide future methodological development. In addition, being voxel-based, the ANTs framework does have a couple of advantages not explored in this work but certainly to be utilized in future research. Specifically, the inherent voxel-based input/output processing is conducive to voxel-based analysis strategies (e.g., Eigenanatomy [75]) and straightforward extension to non-human research domains.

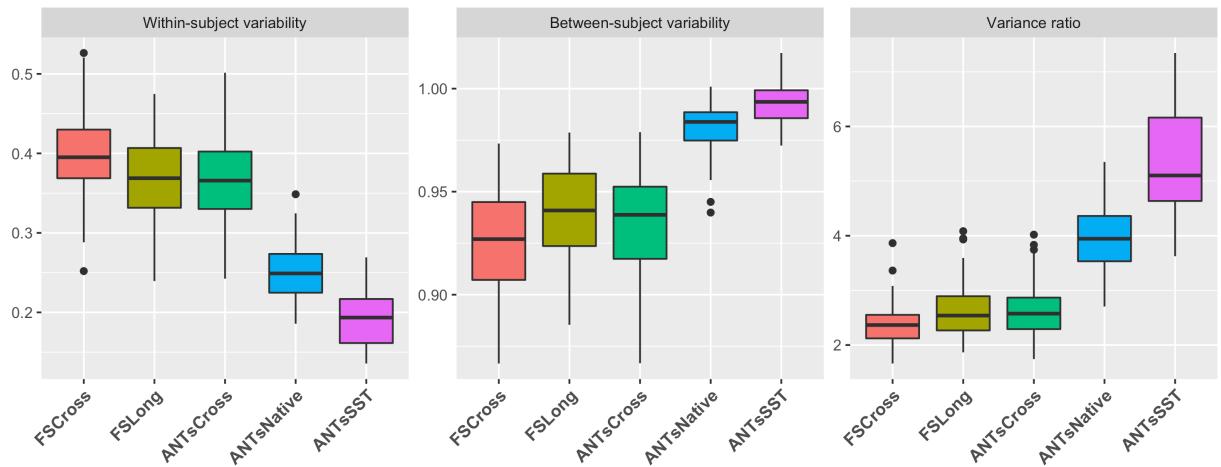
The longitudinal thickness framework is available in script form within the ANTs software library along with the requisite processing components (cf Appendix). All generated data used for input, such as the ADNI template and tissue priors, are available upon request. As previously mentioned, we also make available the csv files containing the regional thickness values for all three pipelines.



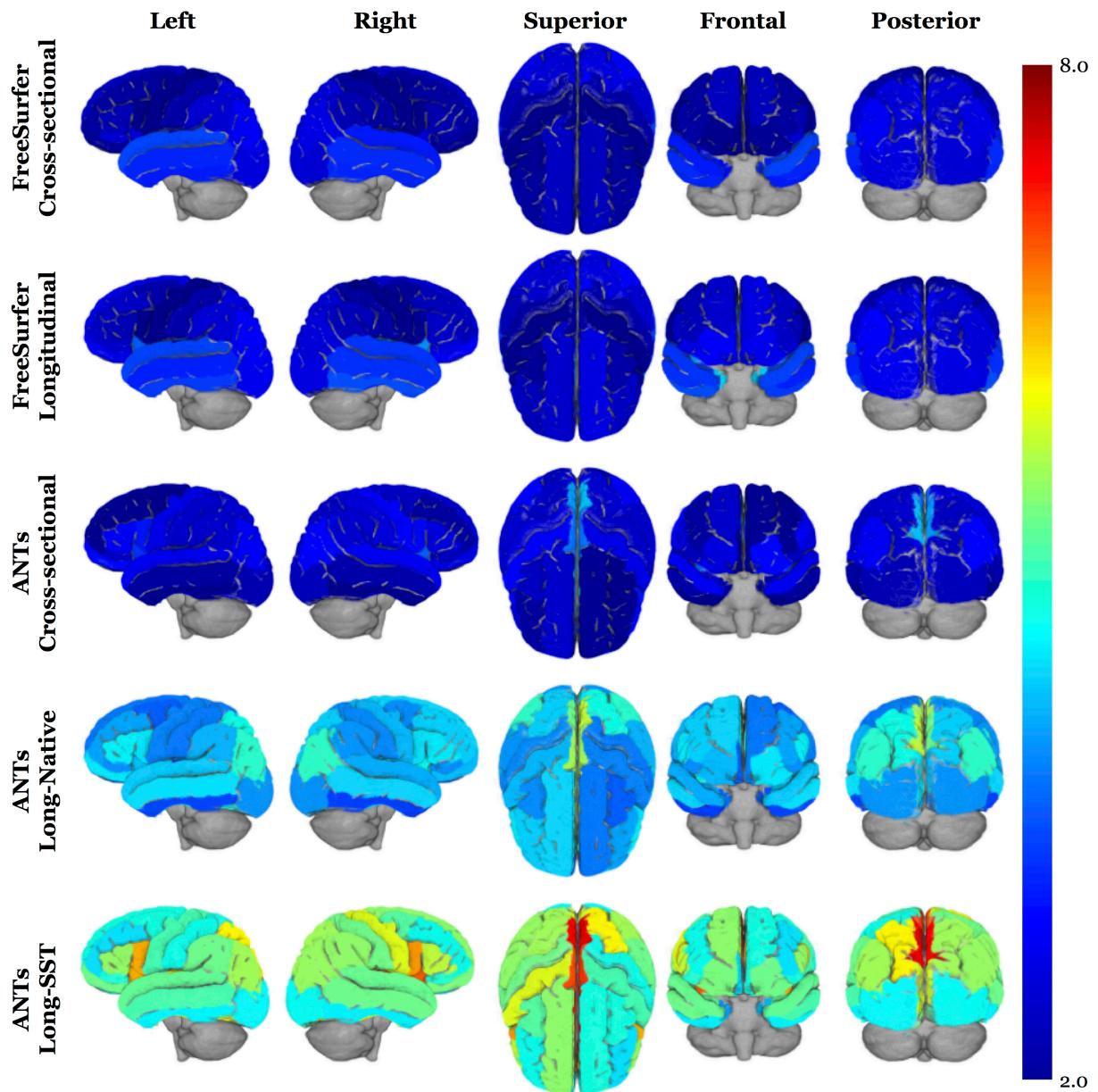
**Figure 5:** Box plots showing the distribution of cortical atrophy for each of the 62 DKT regions derived from the five different longitudinal processing streams. We subdivided each set of regional slope values based on diagnosis (i.e., CN vs. LMCI vs. AD) to illustrate the feasibility in derived cortical atrophy measures where those subjects with AD evince the steepest atrophy rates.



**Figure 6:** 95% credible intervals of the region-specific variance ratios  $r^k = \tau_k/\sigma_k$  are presented for each processing method. The ANTs Longitudinal-native method dominates the others across the majority of regions: its point estimates (posterior medians) are greater than those of the other processing methods except for the left and right EC values in FreeSurfer Long (although there is significant overlap in the credible intervals in those regions). These results also suggest that longitudinal processing is to be preferred for both packages.

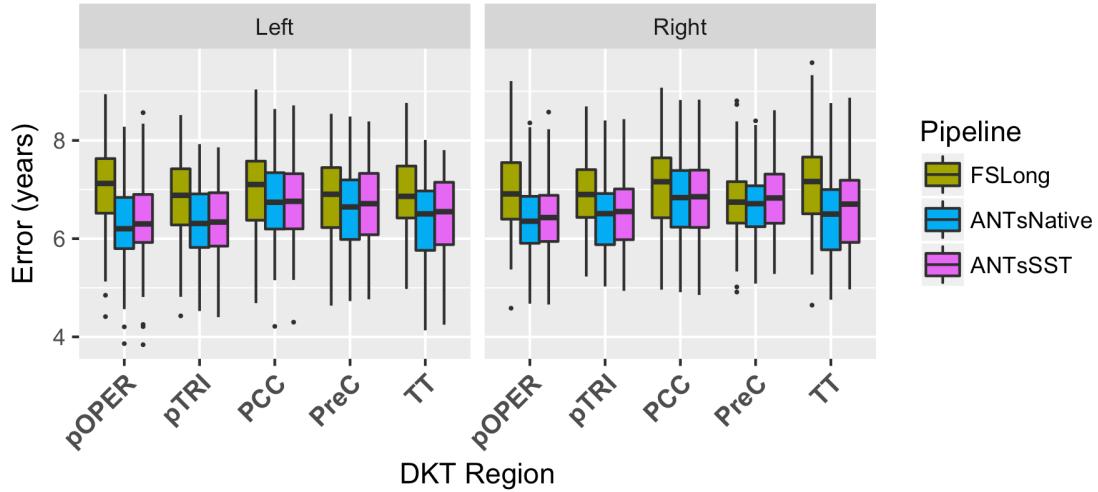


**Figure 7:** Box plots showing the distribution of the within-subject variability, between subject variability, and ratio of the between-subject variability and within-subject variability for each of the 62 DKT regions. Note that the “better” measurement maximizes this latter ratio.



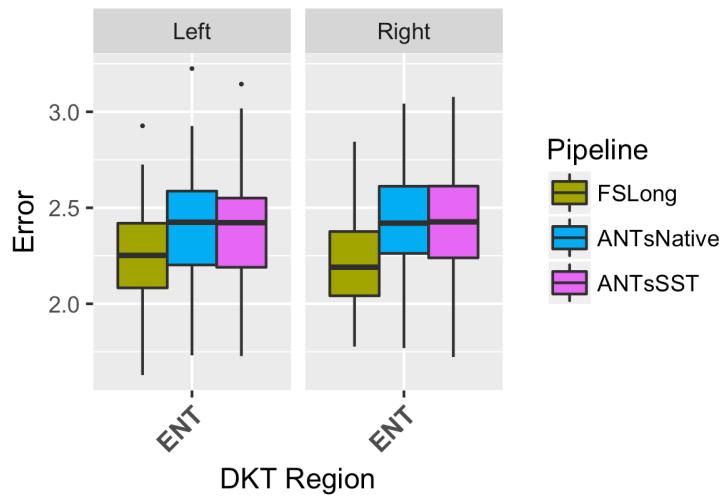
**Figure 8:** 3-D volumetric rendering of the regional variance ratio values on the generated ADNI template. The higher variance ratios indicate greater between-subject to within-subject variability.

## Age prediction



**Figure 9:** Age prediction error in years for each of the longitudinal processing pipelines over both left and right hemispheres for the pars opercularis (pOPER), pars triangularis (pTRI), posterior cingulate (PCC), pre-central (PreC), and tranverse temporal (TT) cortical regions. Consistent with the variance ratio comparison, the ANTs pipelines trend towards a lower relative prediction error.

## MMSE prediction



**Figure 10:** MMSE prediction error for each of the longitudinal processing pipelines in the left and right entorhinal cortex. Consistent with the variance ratio comparison, FSLong has a lower relative prediction error.

## 5 Appendix

### 5.1 Implementation overview

The script `antsLongitudinalCorticalThickness.sh` performs cortical thickness estimation for a longitudinal image series from a single subject. The following principal steps are performed:

1. A single-subject template (SST) is created from all the time point images.
2. The tissue prior probability images are generated for the SST. These six tissues are label 1: CSF, label 2: cortical gray matter, label 3: white matter, label 4: deep gray matter, label 5: brain stem, and label 6: cerebellum. Prior probability creation involves the following steps:
  1. The SST is passed through `antsCorticalThickness.sh`.
  2. The brain extraction posterior for the SST is created by smoothing the brain extraction mask created during 2a.
  3. If labeled atlases are not provided, we smooth the posteriors from 2.1 to create the SST segmentation priors, otherwise we use the `antsJointFusion` program to create a set of posteriors using the script `antsCookTemplatePriors.sh`.
3. Using the SST + priors, each subject is processed through the `antsCorticalThickness.sh` script.

A typical command line call is:

```
antsLongitudinalCorticalThickness.sh \
    -d ${imageDimension} \
    -e ${brainTemplate} \
    -m ${brainExtractionProbabilityMask} \
    -p ${brainSegmentationPriors} \
    -o ${outputPrefix} \
    ${anatomicalImages[@]}
```

## 5.2 Input parameters

- `imageDimension`: dimensionality of the input images. Can handle 2 or 3 dimensions.
- `brainTemplate`: the group template. We have made several publicly available along with the prior tissue and brain extraction images ([https://figshare.com/articles/ANTs\\_ANTsR\\_Brain\\_Templates/915436](https://figshare.com/articles/ANTs_ANTsR_Brain_Templates/915436)).
- `brainExtractionProbabilityMask`: prior probability image for the whole brain corresponding to the `brainTemplate`.
- `brainSegmentationPriors`: prior probability images for the six brain tissues mentioned above. These files are specified with the relevant labels, e.g., `prior1.nii.gz`, `prior2.nii.gz`, `prior3.nii.gz`, `prior4.nii.gz`, `prior5.nii.gz`, and `prior6.nii.gz`. The command line argument is specified in C-style formatting, e.g., `prior%d.nii.gz`.
- `anatomicalImages`: the time point images for a single subjects.
- other optional input parameters are available. `antsLongitudinalCorticalThickness -h` provides a listing of the full set of parameters, their descriptions, and other help information.

## 5.3 Output

In the specified output directory, the following subdirectories are created:

- `${outputPrefix}SST`
- `${outputPrefix} ${anatomicalImagesPrefix[0]}`
- `${outputPrefix} ${anatomicalImagesPrefix[1]}`
- `${outputPrefix} ${anatomicalImagesPrefix[2]}`
- ...

Each subdirectory contains the output of `antsCorticalThickness.sh` applied to the corresponding image. Output consists of the following files:

- `BrainExtractionMask`: Brain extraction mask in subject space.
- `BrainNormalizedToTemplate`: Extracted brain image normalized to the template space.
- `BrainSegmentationON4`: Input to the segmentation algorithm. It is not brain ex-

tracted, but is bias-corrected. If multiple images are used for segmentation, there will be `BrainSegmentation1N4` and so on. The brain extracted version of this is `ExtractedBrain0N4`.

- `BrainSegmentation`: Segmentation image, one label per tissue class. The number of classes is determined by the input priors.
- `BrainSegmentationPosteriors1`: Posterior probability of class 1. A similar image is produced for all classes. The numbering scheme matches the input priors.
- `CorticalThickness`: Cortical thickness image in subject space.
- `CorticalThicknessNormalizedToTemplate`: Cortical thickness image in template space.
- `ExtractedBrain0N4`: Brain-extracted version of `BrainSegmentation0N4`.
- `SubjectToTemplate1Warp`, `SubjectToTemplate0GenericAffine.mat`: Transforms to be used when warping images from the subject space to the template space.
- `SubjectToTemplateLogJacobian`: Log of the determinant of the Jacobian, quantifies volume changes in the subject to template warp.
- `TemplateToSubject0Warp`, `TemplateToSubject1GenericAffine.mat`: Transforms to be used when warping images from the template to the subject space.

In addition to these files, the `SST` subdirectory contains additional warps, suffixed `SubjectToGroupTemplateWarp` and `SubjectToTemplate0GenericAffine.mat`, that can be used to warp each time point image to the group template. These are a combination of the subject to `SST` warp, and the `SST` to group template warp. Also included are the `SST` brain and tissue prior probability images.

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