

# **An open-science ADNI study using the ANTs longitudinal cortical thickness pipeline**

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### **Notes for discussion**

- change the title?
- ordering of authors?
- other people to include?

## **Abstract**

Alzheimers disease is terrible.

## Introduction

Quantification of brain morphology has proven invaluable in studying conditional abnormalities such as Huntington's disease [1–3], schizophrenia [4], bipolar disorder [5], Alzheimer's disease and frontotemporal dementia [6], Parkinson's disease [8], Williams syndrome [9], multiple sclerosis [10], autism [11], migraines [13], chronic smoking [14], alcoholism [15], cocaine addiction [16], marijuana use in adolescents [17], Tourette syndrome in children [18], scoliosis in female adolescents [19], heart failure [20], early-onset blindness [21], chronic pancreatitis [22], obsessive-compulsive disorder [23], ADHD [24], obesity [25], and heritable [26] and elderly [27] depression. Evidence of cortical thickness variation has also been found to be a function of age [28], gender [29], untreated male-to-female transsexuality [30], handedness [31], intelligence [32], athletic ability [33], meditative practices [34], musical ability [35], musical instrument playing [36], tendency toward criminality [37], childhood sexual abuse in adult females [38], and Tetris-playing ability in female adolescents [39]. Additionally, connectivity studies demonstrate structural relationships using cortical thickness measures [40].

Large neuroimaging datasets such as those provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI) are increasing the importance of fully automated and multiple modality brain mapping tools [41]. The scale of such datasets will only increase over time as international projects continue to build large-scale neuroimaging data resources. Currently, the National Institutes of Health (NIH) also mandates that any NIH-funded data resources, including MRI, must be released to the public. In contrast to ADNI, which provides standardized data acquisition protocols used across all sites, these smaller-scale projects are collected in an unstructured way. Therefore, neuroimage processing tools must reliably quantify even when there is a relative lack of quality control over the input data. While robustness is a goal shared by all software development targeted at neuroscience, very few methods have been thoroughly tested on large and unstructured neuroimaging datasets.

## Materials and Methods

### Imaging

#### Cortical thickness

##### Single time point processing

In [42] we introduced the ANTs cortical thickness processing pipeline using a large cohort of  $\sim 1200$  images taken from four popular, publicly available data sets with ages ranging from 4 to 97 years. The processing pipeline comprises the following four major steps (cf Figure 1 of [42]):

- N4 bias correction [43],
- brain extraction [44],
- Atropos six-tissue segmentation [45], and
- cortical thickness estimation [46]

which is enhanced by the use of optimal shape and intensity templates derived from the specific populations of study. Regional statistics were quantified by parcellating the cortex using a collection of 20 atlases from the OASIS test-retest data which were labeled using the Desikan-Killiany-Tourville (DKT) protocol [47] consisting of 31 labels per hemisphere (see Table 1). Consensus labelings in each subject were generated from the joint label fusion approach of [48]. A thickness-based evaluation with the well-known FreeSurfer algorithm demonstrated better predictive performance of age and gender. Since the original publication, we have added multi-modal capabilities and the optional inclusion of patch-based denoising based on an ANTs implementation of the patch-based denoising algorithm of [49]. The resulting regional statistics (including cortical thickness, surface area [50], volumes, and Jacobian determinant values) were posted online (<https://github.com/ntustison/KapowskiChronicles>). These include the corresponding FreeSurfer measurements which are also publicly available for research studies (e.g., [51]). Since publication, this pipeline has been used in a number of cross-sectional studies [52–54].

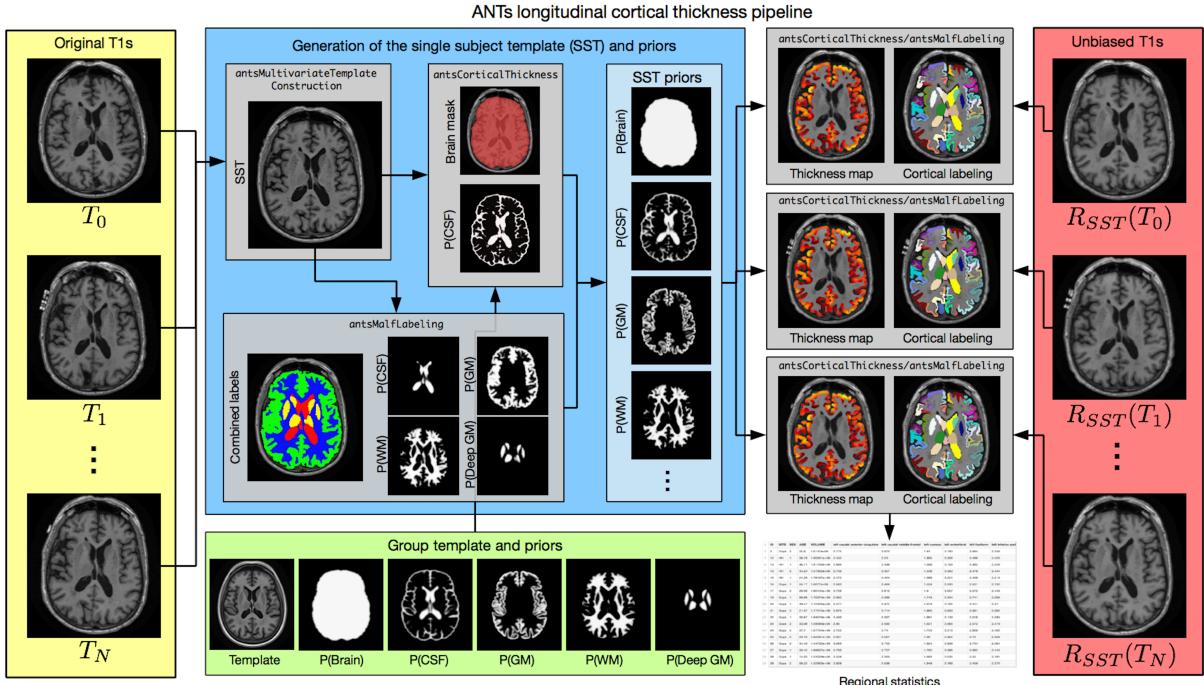
**Table 1:** The 31 cortical labels (per hemisphere) of the Desikan-Killiany-Tourville atlas.

1) caudal anterior cingulate	17) pars orbitalis
2) caudal middle frontal	18) pars triangularis
3) cuneus	19) pericalcarine
4) entorhinal	20) postcentral
5) fusiform	21) posterior cingulate
6) inferior parietal	22) precentral
7) inferior temporal	23) precuneus
8) isthmus cingulate	24) rostral anterior cingulate
9) lateral occipital	25) rostral middle frontal
10) lateral orbitofrontal	26) superior frontal
11) lingual	27) superior parietal
12) medial orbitofrontal	28) superior temporal
13) middle temporal	29) supramarginal
14) parahippocampal	30) transverse temporal
15) paracentral	31) insula
16) pars opercularis	

### Unbiased longitudinal processing

*Overview.* See Figure 1. The ANTs longitudinal cortical thickness pipeline extends the ANTs cortical thickness pipeline for longitudinal studies which takes into account various bias issues which have been discussed in the literature [56]. Prior to the processing of any individual subjects a group template [59] and corresponding auxiliary images (i.e., six-tissue and brain extraction prior probability maps) are generated. This cohort is typically composed of a subset of the study subjects.

Following the offline construction of the group template and prior probability images, each subject under-



**Figure 1:** The ANTs longitudinal cortical thickness pipeline. The original T1-weighted images are used to generate an unbiased single-subject template (SST). The SST is then processed via the segmentation portion of the ANTs cross-sectional cortical thickness pipeline reported in [55] using the group template and tissue priors. This results in a probabilistic estimate of the CSF and the brain mask. Joint label fusion (JLF) of 20 atlases involving six labels (CSF, gray matter, white matter, deep gray matter, brain stem, and cerebellum) is used to get a probabilistic estimate of the six tissues. The latter five JLF probabilistic tissue estimates are used as the SST prior probabilities whereas the CSF SST prior probability is derived as a combination of the JLF and segmentation CSF estimates, i.e.,  $P(CSF) = \max(P_{Seg}(CSF), P_{JLF}(CSF))$ . The T1-weighted image at each time point is rigidly aligned to the template and processed through original cortical thickness pipeline using the SST template and auxiliary images (brain extraction mask and tissue priors). Cortical labelings obtained using JLF are then used to quantify ROI-based statistics.

goes similar processing. First, an average shape and intensity single subject template (SST) is created from all time point images [59]. Each time point image is then rigidly aligned to the SST. The SST prior probability maps are created using a protocol combining brain extraction and a six-tissue segmentation and a six-label joint label fusion processing of the SST. After the SST template priors are created, each time point image is rigidly aligned to the template to reduce the effect of coordinate system or interpolation bias.

Each rigidly-aligned time point image is processed using the ANTs original pipeline and the SST template and template priors resulting in a brain extraction mask, six-tissue segmentation, and a cortical thickness map for each time point image. The cortical ROIs from the DKT atlases are propagated to each time point using a “pseudo-geodesic” mapping and joint label fusion.

Subsequent processing segments the SST into six probabilistic tissue classes: cerebrospinal fluid (CSF), gray matter (GM), white matter (WM), deep gray matter (striatum + thalamus), brain stem, and cerebellum. This requires processing the SST through two parallel workflows. First, the SST proceeds through the standard ANTs cortical thickness pipeline which generates a brain extraction mask and the CSF posterior probability map. Second, using a data set of expert annotations [47], a class-leading multi-atlas joint label fusion step [48] is performed to create individualized probability maps for all tissue types. This final version of the SST enables unbiased mappings to the group template, subject-specific tissue segmentations, region of interest volumes and cortical thickness maps for each of the original time series images. The corresponding cortical labelings (generated using a multi-atlas label fusion approach and a selected cortical parcellation protocol) are then used to tabulate regional thickness and area values for statistical analysis. Other modalities are then mapped to the group template through these unbiased transformations, as in [55, 60]

*ADNI normal template.*

*“Cooking” the template priors.*

*Pseudo-geodesic for large cohort labeling.*

#### **Notes to self:**

- Add an image and discussion of the pseudo-geodesic for facilitating malf-labeling.
- Discuss the ants implementation (multi-threading, etc.)
- Discuss ADNI template

## **Statistical methods**

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

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

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

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

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

## Results

### Discussion

#### Subsection 1

And a sweet equation:

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

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